SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE	15	JUL	1957	58 Years	Male	Unk	19	JAN	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Hepatic cytolysis [Hepatic cytolysis]
Peak of arterial hypertension [Hypertension]
Renal failure [Renal failure]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) VALSARTAN (VALSARTAN)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 500 mg, 1x/day
#2) 160 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Bout of hypertension (Hypertension)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 16-DEC-2015 / 20-JAN-2016
#2) 21-NOV-2017 / Ongoing

19. THERAPY DURATION
#1) 36 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 2015 / Unknown
#2) BRILIQUE (TICAGRELOR) ; 2015 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event in first line	
Unknown	Past Drug Event in second line	

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016080618

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
09-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from contactable reporter(s) (Physician) from a sales representative and the European Medicines Agency (EMA) EudraVigilance-WEB for protocol B1871047. Other Case identifier(s): FR-IPSEN Group, Research and Development-2019-00181 (IPSEN), 10002708523 (Case identifier), 10002833680 (Case identifier).

A 58 year old, male subject started to receive the study drug bosutinib (BOSULIF) in fourth line at 500 mg once daily from 16Dec2015 to 20Jan2016, at dose of 400 mg daily from 11Feb2016 to 27Feb2016, at dose of 300 mg daily from 12Mar2016 to 20Jul2016 and 400 mg daily from 21Jul2016 and ongoing for chronic myeloid leukemia and valsartan via an unspecified route of administration form 21Nov2017 and ongoing at 160 mg daily for bout of hypertension. Relevant medical history included inflammatory rheumatism ongoing since 1999; pleural effusion ongoing since Jun2014 and myocardial infarction from Nov2015. Concomitant medications included acetylsalicylate lysine (KARDEGIC) from 2015, and ticagrelor (BRILIQUE) from 2015. The subject previously took imatinib in first line, dasatinib (SPRYCEL) in second line, and nilotinib hydrochloride (TASIGNA) in third line for chronic myeloid leukemia. On 19Jan2016, the subject experienced hepatic cytolysis (grade 3) which was reported as non-serious event. On that same day, aspartate aminotransferase (ASAT) was measured at 140 IU/l (N: 15-37) and alanine aminotransferase (ALAT) was 423 IU/l (N: 12-45). On 25Feb2016, ASAT was 81 IU/l and ALAT 239 IU/l. In response to the event, bosutinib was temporarily stopped on an unspecified date until the transaminases return to normal, then resumed at reduced dose of 400 mg daily from 11Feb2016 to 27Feb2016. Additional lab data was as follows (all in IU/L): Aspartate aminotransferase 66 on 28Jan2016, 51 on 04Feb2016, 43 on 11Feb2016, 61 on 18Feb2016, 50 on 03Mar2016, 33 on 10Mar2016, 49 on 15Mar2016 and 39 on 24Mar2016. Alanine aminotransferase 257 on 28Jan2016, 155 on 04Feb2016, 86 on 11Feb2016, 184 on 18Feb2016, 176 on 03Mar2016, 103 on 10Mar2016, 83 on 15Mar2016 and 120 on 24Mar2016. The last action taken in response to the event hepatic cytolysis for bosutinib was dose reduced to 300 mg. It was reported that as a result of the event hepatic cytolysis, the treatment with bosutinib was withdrawn from 20Jan2016 to 11Feb2016 then the dose was reduced to 400 mg. The treatment was again withdrawn from 27Feb2016 to 12Mar2016 then the dose was reduced to 300 mg. Bosutinib was resumed on 12Mar2016 at 300 mg once daily until 20Jul2016 and at dose of 400 mg once daily from 21Jul2016. Cytolysis returned to grade 1 on 11Feb2016, then grade 2 was recorded on 18Feb2016 and grade 3 on 25Feb2016. A grade 1 is acquired from 10Mar2016. On 21Nov2017, the subject presented with peak of arterial hypertension which was considered as non-serious and rated as grade 3. No action was taken with study drug in response to this event. Peak of arterial hypertension was not resolved. In Jan2018, the subject experienced renal failure which was considered as non-serious and rated as grade 1. No action was taken with study drug or with valsartan in response to this event. The subject recovered from renal failure on 08Mar2018, and hepatic cytolysis recovered on 23Jun2016. Bout of arterial hypertension was not resolved. The subject should be seen at the beginning of 2019.

According to the investigator, the event hepatic cytolysis and peak of arterial hypertension were related to study drug but not related to concomitant medication while the renal failure was unrelated to study drug and related to valsartan.

Follow-up (16Feb2016): New information reported includes: action taken: updated from temporarily withdrawn to dose reduced.

Follow-up (06Apr2016): Follow-up attempts completed. No further information expected.

Follow-up (19May2016): New information reported form the reporting physician via a company representative includes: reaction data (event onset date), patient data, product data, relevant medical history data, clinical details, lab data, and investigator causality (related, previously not provided).

Follow-up (12 Sep2016): Follow-up attempts completed. No further information expected.

Follow-up (16Oct2017): New information reported includes lab data and reaction data (updated outcome of event to recovered and added stop date of event).

Follow-up (11Dec2018): New information received from the study site includes concomitant drug, clinical course and two additional events Bout of arterial hypertension and renal failure.

Follow-up (12Dec2018): New information received from the Site includes clarification on bosutinib administrations, and additional concomitant medications.

Follow-up (29Jan2019): New information downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB, FR-IPSEN Group, Research and Development-2019-00181, is as follows:
Additional reference was FR-IPSEN Group, Research and Development-2019-00181.

SENDER COMMENT: Very suggestive temporal relationship, known mechanism of action and safety profile of the suspect drug argues in favor of causality. Considering above mentioned, the event renal failure is assessed as possibly related to the suspect drug. Lack of mechanism connecting use of suspect drug with the reported event arterial hypertension, therefore it is assessed as not related to suspect drug. However, role of patient's underlying condition of inflammatory rheumatism, myocardial infarction, pleural effusion and arterial hypertension cannot be underestimated either.

Follow-up (31Jan2019): New information received from the European Medicines Agency (EMA) EudraVigilance-WEB included EMA reference numbers FR-EMA-DD-20190118-sharma_d2-103724 and FR-EMA-DD-20190108-sharma_d2-101047, and sender

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

comment.

SENDER COMMENT: "This case is a master made from existing duplicates in EudraVigilance by the EMA duplicate management team. The case numbers of the underlying duplicates are in the Other Case Identifiers section" Based on the information provided, due to a partial dechallenge (event improvement after bosutinib dose decrease), considering the positive drugevent temporal association and the known safety profile of the suspect drug, the Company agrees with the investigator's opinion, considering the assessment of the hepatic cytolysis, arterial hypertension and renal failure as related to suspect drug bosutinib. The follow-up information received does not alter the previous company clinical evaluation. Very suggestive temporal relationship, known mechanism of action and safety profile of the suspect drug argues in favor of causality. Considering above mentioned, the events renal failure and hepatic cytolysis are assessed as possibly related to the suspect drug. Lack of mechanism connecting use of suspect drug with the reported event arterial hypertension, therefore it is assessed as not related to suspect drug. However, role of patient's underlying condition of inflammatory rheumatism, myocardial infarction, pleural effusion and arterial hypertension cannot be underestimated either.

Follow-up (12Mar2019): Follow-up attempts completed. No further information expected.

Follow-up (16Aug2019): New information received includes: Study drug data (drug withdrawal/dose reduction details for bosutinib).

Follow-up (01Feb2021): new information received includes: updated investigator causality of event renal failure (from related to unrelated).

Follow-up (09Oct2023): This is a non-interventional study report received from the investigational site via the CRO.
Updated information: patient data (patient initials updated); reaction data (verbatim for "bout of arterial hypertension" updated to "peak of arterial hypertension", event outcome updated for hepatic cytolysis to recovered on 23Jun2016) and clinical course details added.

Case Comment: The event hepatic cytolysis is unlisted in the SRSD of bosutinib and related per company assessment.

Based on the information provided, due to a partial dechallenge (event improvement after bosutinib dose decrease), considering the positive drug-event temporal association and the known safety profile of the suspect drug, the Company considers the hepatic cytolysis, arterial hypertension and renal failure as related to suspect drug bosutinib.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to RAs, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	19-JAN-2016	Alanine aminotransferase	423 IU/l	45 12
2	28-JAN-2016	Alanine aminotransferase	257 IU/l	45 12
3	04-FEB-2016	Alanine aminotransferase	155 IU/l	45 12
4	11-FEB-2016	Alanine aminotransferase	86 IU/l	45 12
5	18-FEB-2016	Alanine aminotransferase	184 IU/l	45 12
6	25-FEB-2016	Alanine aminotransferase	239 IU/l	45 12
7	03-MAR-2016	Alanine aminotransferase	176 IU/l	45 12
8	10-MAR-2016	Alanine aminotransferase	103 IU/l	45 12
9	15-MAR-2016	Alanine aminotransferase	83 IU/l	45 12
10	24-MAR-2016	Alanine aminotransferase	120 IU/l	45 12
11	19-JAN-2016	Aspartate aminotransferase	140 IU/l	37 15
12	28-JAN-2016	Aspartate aminotransferase	66 IU/l	37

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
				15
13	04-FEB-2016	Aspartate aminotransferase	51 IU/l	37 15
14	11-FEB-2016	Aspartate aminotransferase	43 IU/l	37 15
15	18-FEB-2016	Aspartate aminotransferase	61 IU/l	37 15
16	25-FEB-2016	Aspartate aminotransferase	81 IU/l	37 15
17	03-MAR-2016	Aspartate aminotransferase	50 IU/l	37 15
18	10-MAR-2016	Aspartate aminotransferase	33 IU/l	37 15
19	15-MAR-2016	Aspartate aminotransferase	49 IU/l	37 15
20	24-MAR-2016	Aspartate aminotransferase	39 IU/l	37 15
21		Transaminases	abnormal : hepatic cytolysis	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	11-FEB-2016 / 27-FEB-2016; 17 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	12-MAR-2016 / 20-JUL-2016; 131 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	21-JUL-2016 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event in first line	IMATINIB (IMATINIB); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia)
Unknown	Past Drug Event in second line	SPRYCEL (SPRYCEL); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia)
Unknown	Past Drug Event in third line	TASIGNA (TASIGNA); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia)
1999 to Ongoing	Relevant Med History	Inflammatory rheumatism (Rheumatic disorder);
JUN-2014 to Ongoing	Relevant Med History	Pleural effusion (Pleural effusion);
NOV-2015 to Unknown	Relevant Med History	Myocardial infarction (Myocardial infarction);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		NOV	1955	60 Years	Male	73.00 kg		NOV	2015

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
hypokalemia [Hypokalaemia]
Nausea (CTCAE grade 1) [Nausea]
Iron deficiency anemia, rated as grade 2 [Iron deficiency anaemia]
diarrhea [Diarrhoea]
diarrhea [Diarrhoea]
iron deficiency [Iron deficiency]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF® UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) KAYEXALATE (SODIUM POLYSTYRENE SULFONATE)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, 1x/day	#1) Oral
#2) 1 DF (1 mesuring spoon)	#2) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 30-OCT-2015 / Unknown	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CARDENSIEL (BISOPROLOL FUMARATE) ; Ongoing
#2) TRIATEC (CODEINE PHOSPHATE, PARACETAMOL) ; Ongoing
#3) ESIDREX (HYDROCHLOROTHIAZIDE) ; Ongoing
#4) ASPEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#5) CRESTOR (ROSUVASTATIN CALCIUM) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Angina pectoris (Angina pectoris)
Unknown	Relevant Med History	Myocardial infarction (Myocardial infarction)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016147105

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
29-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol B1871047.
A 60 years old male subject started to receive bosutinib (BOSULIF, film-coated tablet) orally on 30Oct2015 at 500 mg once daily for chronic myeloid leukemia. Co-suspect drug included acetylsalicylate lysine (KARDEGIC), route of administration, dose, start date and indication not provided and sodium polystyrene sulfonate (KAYEXELATE) was received at 1 a dose of one measuring spoon from unknown date, "depending of the laboratory analysis". Medical history included angina pectoris, myocardial infarction, sleep apnea syndrome, lower limb arterial occlusive disease, arterial hypertension (ongoing), hypercholesterolemia (ongoing), cervical artery atheroma, osteoarthritis of the spine, gastroesophageal reflux, hiatal hernia, surgery of knee and shoulder and obliterative arteriopathy (ongoing). Concomitant medications for myocardial infarction included: bisoprolol fumarate (CARDENSIEL) and codeine phosphate/ paracetamol (TRIATEC); all taken orally and ongoing. Additional ongoing concomitant medications from unknown dates included: hydrochlorothiazide (ESIDREX) via oral route for arterial hypertension, acetylsalicylate lysine (ASPEGIC) via oral route for obstructive arteriopathy of lower limbs, and rosuvastatin calcium (CRESTOR) via oral route for hypercholesterolemia. On 04Oct2016, the subject experienced anemia (grade 2) due to iron deficiency. The subject's hemoglobin was 9x10^9/L (grade 2) in Oct2016 leading to lower limbs and eyelids edema. Endoscopic work-up was normal, videocapsule was pending. In Nov2015, the subject experienced nausea (CTCAE grade 1). On 14Dec2016, the subject experienced diarrhea rated grade 1 and considered as non-serious. Potassium was 2,4 mmol/l on 26Dec2018 and 3,3 mmol/l on 31Dec2018. The dose was decreased to 400 mg once per day from 11Jan2017. In response to the event hypokalemia, sodium polystyrene sulfonate (KAYEXALATE) was temporarily stopped. The investigator assessed that the event nausea and iron deficiency anemia were non-serious, that hypokalemia was rated grade 4 but was non-serious (treated with a stop of sodium polystyrene sulfonate (KAYEXALATE)).
The last action taken in response to the event for bosutinib was dose not changed. The subject had recovered from the event nausea in Nov2015. The clinical outcome of the event diarrhea was recovered on 16Jan2017. The subject recovered from hypokalemia on Jan2019. The outcome of event Iron deficiency anemia was recovered on 01Mar2017.
The investigator considered that the event nausea was related to study drug bosutinib. According to the investigator, the event nausea was considered as unrelated to concomitant drug. The investigator considered that the event iron deficiency anemia was unrelated to study drug bosutinib. The investigator considered that there was a reasonable possibility that the event diarrhea was related to bosutinib and not to a concomitant drug. In 2018, the subject experienced diarrhea assessed grade 1 and considered non-serious. In response to diarrhea, no action was taken for bosutinib. The subject recovered on 22Jan2019. The investigator considered that there was a reasonable possibility that the event was related to bosutinib but unrelated to a concomitant drug. On 20Dec2018, the subject experienced iron deficiency assessed grade 1 and considered non-serious. In response to iron deficiency, no action was taken for bosutinib. The subject had not recovered. The subject recovered from hypokalemia on Jan2019. The investigator considered that there was not a reasonable possibility that the event iron deficiency was related to bosutinib or to a concomitant drug. On 20Dec2018, the subject experienced hypokalemia assessed grade 4 and considered non-serious. In response to hypokalemia, no action was taken for bosutinib and concomitant drug sodium polystyrene sulfonate (KAYEXALATE) was withdrawn. The subject recovered in Jan2019. The investigator considered that there was not a reasonable possibility that the event hypokalemia was related to bosutinib but related to concomitant drug sodium polystyrene sulfonate.
Investigator Initial Awareness Date of the event Iron deficiency anaemia was reported as 16Oct2016.
Investigator Initial Awareness Date of the event Diarrhoea (start: 14Dec2016) was reported as 16Jan2017.
Investigator Initial Awareness Date of the event Iron deficiency and Diarrhoea (start: 2018) was reported as 18Sep2018.

Follow-up (26Mar2016): New information received from the investigator includes: medical history, study drug data (added route of administration, start date, dosage regimen, and indication), lab data, and causality assessment (nausea updated from not specified to related to study drug bosutinib).

Follow-up (16Nov2016): New information received includes: Medical history, reaction data (added new event anemia), Action taken (bosutinib dose was reduced) and Laboratory data.

Follow-up (06Feb2017): New information received includes updated onset date of anemia (from 'Oct2016' to '04Oct2016') and updated causality assessment for anemia (from 'related' to 'unrelated').

Follow-up (13Feb2017): Follow-up attempts completed. No further information expected.

Follow-up (20Feb2017): New information received includes: Concomitant drug data and Reaction data (onset date of event iron deficiency anemia was updated to 10Oct2016).

Follow-up (30Jan2018): New information received from investigator includes: product data (updated dosing to 400 mg), medical history details, concomitant medications (added hydrochlorothiazide, acetylsalicylate lysine, and rosuvastatin calcium), reaction data (added diarrhea), and dose not changed (updated from dose reduced to dose not changed).

Follow-up (07May2019): New information received included bosutinib dose updated, added new events diarrhea, iron deficiency and hypokalemiam, and acetylsalicylate lysine upgraded to suspect drug.

Follow-up (20Apr2020): New information was received from the investigational site via the clinical team in response to query reporting: Bosutinib dose/dates of therapy and dose decrease/date of decrease, action taken with sodium polystyrene sulfonate in

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

response to the event, potassium levels.

Follow-up (06Jul2023): New information was received from CRO in a context of reconciliation between Safety and clinical database included: Outcome of the event iron deficiency anaemia.

Follow-up (19Sep2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the investigational site CRO for protocol B1871047. Updated information included: Investigator Initial Awareness Date of the events Iron deficiency anaemia, Diarrhoea (start: 14Dec2016), Iron deficiency and Diarrhoea (start: 2018).

Follow-up attempts completed. No further information expected.

Amendment: This follow-up report is being submitted to amend previously reported information: Event details (Iron deficiency anemia onset date and outcome updated).

Follow-up (29Nov2023): This is a non-interventional study follow-up report received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: detail for event Iron deficiency anemia.

Case Comment: The company considers nausea, diarrhea and anemia related to bosutinib. The events are consistent with the known toxicity profile of the suspect product. The event hypokalemia was unrelated to bosutinib but likely related to the concomitant medication acetylsalicylate lysine. Positive dechallenge with acetylsalicylate lysine was noted. The event iron deficiency was unrelated to bosutinib. The follow up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	26-DEC-2018	Blood potassium	2.4 mmol/L	
2	31-DEC-2018	Blood potassium	3.3 mmol/L	
3		Endoscopy	normal	
4	OCT-2016	Haemoglobin grade 2	9 x10 9/l	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, 1x/day; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	11-JAN-2017 / Ongoing; Unknown
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Regimen #1	UNK; Oral	myocardial infarction (Myocardial infarction)	Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Sleep apnea syndrome (Sleep apnoea syndrome);
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
Unknown to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
Unknown	Relevant Med History	Atherosclerosis (Arteriosclerosis);
Unknown	Relevant Med History	Spinal osteoarthritis (Spinal osteoarthritis);
Unknown	Relevant Med History	Gastroesophageal reflux (Gastrooesophageal reflux disease);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hiatal hernia (Hiatus hernia);
Unknown	Relevant Med History	Knee surgery NOS (Knee operation);
Unknown	Relevant Med History	Shoulder operation (Shoulder operation);
Unknown to Ongoing	Relevant Med History	Peripheral obliterative arteriopathy (Peripheral arterial occlusive disease);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1947	68 Years	Female	58.00 kg	06	MAR	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Worsening of general status [General physical health deterioration]
Vomiting [Vomiting]
Gout [Gout]
Purpura [Purpura]
Infectious episode [Infection]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF® UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) COLCHIMAX (FRANCE) (COLCHICINE, PAPAVER SOMNIFERUM **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Unknown
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) Gout (Gout) **(Continued on Additional Information Page)**

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 23-FEB-2016 / 01-MAR-2016	#1) 8 days
#2) 08-MAR-2016 / 21-MAR-2016	#2) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) HYDREA (HYDROXYCARBAMIDE) ; 02-MAR-2016 / Ongoing
#2) ALLOPURINOL (ALLOPURINOL) ; 07-MAR-2016 / 08-MAR-2016
#3) INIPOMP (PANTOPRAZOLE SODIUM SESQUIHYDRATE) ; Ongoing
#4) ULCAR /00434701/ (SUCRALFATE) ; Ongoing
#5) APROVEL (IRBESARTAN) ; Ongoing
#6) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing **(Continued on Additional Information Page)**

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016152270

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-AUG-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 68-year-old female subject of an unspecified ethnicity started to receive bosutinib (BOSULIF, film-coated tablet) via an unspecified route of administration, from 23Feb2016 at 300 mg daily, for an unspecified indication. Co-suspect drug included colchicine/papaver somniferum latex/tiemonium methylsulphate (COLCHIMAX) orally from 08Mar2016 to 21Mar2016 for gout and Hyperuricaemia. Medical history included ongoing hypertension arterial. Concomitant medications included hydroxycarbamide (HYDREA) orally for progression of chronic myeloid leukemia ongoing since 02Mar2016, ongoing allopurinol (trade name unspecified) orally, at unspecified dose for hyperuricemia from 07Mar2016 to 08Mar2016, diuretics (unspecified) by oral route for hyperuricemia ongoing since 07Mar2016, usual treatment including ongoing oral pantoprazole sodium sesquihydrate (INIPOMP), ongoing oral sucralfate (ULCAR), ongoing oral irbesartan (APROVEL), ongoing oral atorvastatin (TAHOR), ongoing oral levothyroxin sodium (LEVOTHYROX), and ongoing oral bisoprolol fumarate/ hydrochlorothiazide (LODOZ). The subject experienced vomiting (CTCAE grade 3) on Mar2016 and worsening of general status (CTCAE grade 3) on 06Mar2016 leading to hospitalization or prolongation of hospitalization. The subject was hospitalized for vomiting and hematemesis. She presented with repetitive episodes of rectorrhagia. After several investigations, vomits were considered as related to worsening of her general status, aggravation of the disease. On 08Mar2016, the subject developed gout CTCAE grade 2. On 10Mar2016, general pain increased, the subject was administered fentanyl (DUROGESIC). On 20Mar2016, she presented with repetitive episodes of epistaxis. Rectorrhagia, general pain increased, and epistaxis were not additional events but were manifestations of the worsening of the condition. And on 21Mar2016, she developed purpura CTCAE grade 2 Lab data included: On 05Mar2016, laboratory analysis was done and found white blood cells (range 3800-11000) at 220560 M/L with anaemia at 7.4 g/dl. It was reported that the hematemesis, anaemia at 7.4 g/dl and the WBC of 220560 should not be added as additional events but were considered as aggravation of disease. White blood cells decreased to 16000 (unit not provided). On 12Mar2016, hemoglobin was 8.8 g/dl. On an unspecified date (in Mar2016), an abdominopelvic CT scan was done: no occlusive syndrome was observed, a rectosigmoidoscopy was done: no mark of blood was found, hemoglobin was 10.7 g/dl, and colonoscopic and gastroscopic work-up was negative. The subject received blood transfusion. On 12Mar2016, the subject developed non serious event diarrhea rated grade 2. The event resolved on 15Mar2016. On 20Mar2016, white blood cells were 630, hemoglobin was 9.7 g/dl, platelets were 10000 (no unit provided). She received transfusion of platelet concentrate. On 22Mar2016, the subject developed non serious event infectious episode rated grade 2. The event resolved on 29Mar2016. On 23Mar2016, she experienced episodes of mouth bleeding. Hemoglobin was 6.7 g/dl, platelets were 44000 (no unit provided). She received transfusion of blood and platelet concentrate. Bosutinib was discontinued because of the exhausted condition, appearance of mutation T3T5I. Bosutinib was stopped before the event, therefore action taken with bosutinib in response to the event was post-therapy. Bosutinib was not reintroduced after it was stopped, the stop date was 01Mar2016. Action taken with colchicine/papaver somniferum latex/tiemonium methylsulphate was unknown. The clinical outcome of the event vomiting was recovered on 07Mar2016, and worsening of general status was recovered on 19Apr2016. There was therapeutic failure and palliative care ensued. She recovered from gout on 21Mar2016 and from purpura on 22Mar2016.
The subject had experienced disease progression which led to several hospitalizations and then, palliative care. The patient died on 23Jan2017 due to sepsis (reported under AER 202101865953). It was unknown if an autopsy was performed.

According to the investigator, the event vomiting was considered as unrelated to the suspect product bosutinib and unrelated to one concomitant drug. It was reported that there was no reasonable possibility that the event general physical health deterioration could be related to study drug bosutinib or to any concomitant drug. The investigator considered the events gout CTCAE grade 2 and purpura CTCAE grade 2 as unrelated to bosutinib and concomitant medications. The investigator considered this event diarrhea rated grade 2 as unrelated to study drug bosutinib and related to concomitant medication colchicine/papaver somniferum latex/tiemonium methylsulphate. It was reported that there was an infection by Pseudomonas aeruginosa and Streptococcus mitis that led to fever. The investigator considered this event infectious episode rated grade 2 as unrelated to study drug bosutinib and to concomitant medication.

Follow-up (22Mar2016): New information received from the site includes: Study drug data (stop date of bosutinib was updated from 01Mar2016 to 03Mar2016) and Clinical outcome (event vomiting updated from recovering to recovered).

Follow-up (31Mar2016): New information received from the investigator includes: study drug data (confirmed stop date of bosutinib was 03Mar2016), lab data, clinical course details, action taken (confirmed as unknown), reaction data (added general physical health deterioration), clinical outcome (confirmed vomiting was recovered on 07Mar2016), and treatment received (blood transfusions), and causality assessment.

Follow-up (18Apr2016): New information received from investigational site includes: reaction details (rectorrhagia, general pain increased, and epistaxis were not additional events) and action taken details (post therapy).

Follow-up (08Sep2016): New information received includes: concomitant medication details (start date for hydroxycarbamide corrected to 04Mar2016 from 02Mar2016, allopurinol was reported as ongoing (previously provided with a stop date of 08Mar2016); and additional concomitant medications were reported) and reaction details (out CTCAE grade 2 and purpura CTCAE grade 2).

Amendment: This follow-up report is being submitted to amend previously reported information: added additional events diarrhea and infectious, recoded colchicine/papaver somniferum latex/tiemonium methylsulphate as co-suspect drug. Additional information

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

received on 11Jan2018 included added new event fatal disease progression and outcome of event general physical health deterioration updated to death, death details.

Follow-up (09Jan2020): New information received from the CRO included: Confirmed the event worsening of general status was rated grade 5 (previously reported grade 3).

Follow-up (31Jan2022): This is a Non-Interventional Study follow-up report received from the CRO.
Updated information: Onset date of event vomiting update to Mar2016 from 06Mar2016. Event worsening of general status of 06Mar2016 was grade 3 (previously grade 5), hospitalisation or prolongation of hospitalisation, with outcome of recovered on 19Mar2016 (previously fatal).

Follow-up (14Mar2022). This is a non interventional study follow-up report received from the study coordinator.

Updated information: cause of death confirmed as sepsis only, non fatal disease progression deleted.

Follow-up (09Mar2023): This is a Non-Interventional Study follow-up report received from the investigational site via the CRO.
Updated information: updated outcome of the event Worsening of general status and Vomiting; Concomitant drug updated.

Follow-up (03Aug2023): new information received from the investigator via the CRO.
Patient's initials updated and start date of Colchimax from 08Mar2016 (previously 09Mar2016).

Case Comment: Based on the additional information received, this patient appears in a deteriorated clinical condition characterized by disease progression, likely with related complications of vomiting, hematemesis, rectorrhagia and epistaxis. In agreement with the reporter, the company considers the reported events, vomiting, general physical health deterioration, gout, purpura, infectious episode, and diarrhea unrelated to suspect drug bosutinib.
The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	MAR-2016	Colonoscopy	negative	
2	MAR-2016	Colonoscopy	no mark of bleeding	
3	MAR-2016	Computerised tomogram	no occlusive syndrome	
4	MAR-2016	Endoscopy upper gastrointestinal tract	negative	
5	05-MAR-2016	Haemoglobin	7.4 g/dl	15 11.5
6	12-MAR-2016	Haemoglobin	8.8 g/dl	15 11.5
7	MAR-2016	Haemoglobin	10.7 g/dl	15 11.5
8	20-MAR-2016	Haemoglobin	9.7 g/dl	15 11.5
9	23-MAR-2016	Haemoglobin	6.7 g/dl	15 11.5
10	20-MAR-2016	Platelet count	10000	
11	23-MAR-2016	Platelet count	44000	
12	05-MAR-2016	White blood cell count	220560	11000 3800
13	10-MAR-2016	White blood cell count	16000	11000 3800
14	20-MAR-2016	White blood cell count	630	11000 3800

Mfr. Control Number: 2016152270

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#2) COLCHIMAX (FRANCE) (COLCHICINE, PAPAVER SOMNIFERUM LATEX, TIEMONIUM METHYLSULPHATE) ; Regimen #1	UNK; Oral	Gout (Gout) HYPERURICEMIA (Hyperuricaemia)	08-MAR-2016 / 21-MAR-2016; 14 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing

#8) LODOZ (BISOPROLOL FUMARATE, HYDROCHLOROTHIAZIDE) ; Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		FEB	1935	81 Years	Female	50.00 kg	13	APR	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Anemia [Anaemia]
Deterioration of general physical health [General physical health deterioration]
Hypokalemia [Hypokalaemia]
Fever [Pyrexia]
Paranoid attack [Paranoia]
Head trauma [Head injury]
Lower limb oedema [Oedema peripheral]
Urinary infection [Urinary tract infection]
Constipation [Constipation]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 29-JUL-2016
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) CIFLOX [CIPROFLOXACIN] (CIPROFLOXACIN)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 200 mg, daily
#2)

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 26-MAR-2016 / 29-JUL-2016
#2) Unknown

19. THERAPY DURATION
#1) 126 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown		

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016239426

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Pubis rash [Rash]
Insomnia [Insomnia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol B1871047.
An 81-year-old female subject started to receive bosutinib (BOSULIF, film-coated tablet) via an unspecified route of administration, from 26Mar2016, at 200 mg daily, for an unspecified indication. Medical history was not reported. Concomitant drug included CIFLOX.The subject experienced anemia and fever (CTCAE grade 2), and lower limb oedema (CTCAE grade 1) on 13Apr2016. According to the investigator, anemia was considered as serious event and led the subject to hospitalization or prolongation of hospitalization, whereas fever and lower limb oedema were considered non-serious events. On 14Apr2016, the subject experienced insomnia (CTCAE grade 1), which was reported as non-serious. On 19Apr2016, she experienced paranoid attack and then on 21Apr2016, she experienced head trauma (CTCAE grade 1). These two last events were considered non-serious. The subject experienced urinary infection (CTCAE grade 2) on 26Apr2016 and pubis rash on 11May2016, and then she experienced constipation (CTCAE grade 1) on 22May2016. These three events, urinary infection (CTCAE grade 2), pubis rash, and constipation, were reported as non-serious. No modification was taken with bosutinib in response to the events. On 15Apr2016, the subject experienced hypokalemia (CTCAE grade 1) assessed as non-serious by the investigator. On unspecified date, potassium was at 3.2 mmol/L, grade 1 (normal range: 3.4 -4.5 mmol/L). No action was taken with bosutinib in response to the event. The last action taken with bosutinib in response to the events was dose not changed. The study drug had never been discontinued. Urinary infection recovered on 25May2016, constipation recovered on 22May2016, anemia recovered on 13Jul2016, fever recovered on 17Apr2016, head trauma recovered on 21Apr2016, paranoid attack recovered on 25May2016, lower limb oedema recovered in 2016 and rash recovered on 24May2016. The subject recovered from the events hypokalemia on 22Apr2016 and insomnia on 18Jun2016. On 26Jul2016 the patient experienced deterioration of general physical health(CTCAE grade 5), assessed as serious. Then, she died at home on 29Jul2016 due to progressive deterioration of general physical health with voluntary relief of care. Last available biological work-up performed on 25Jul2016 did not allow to directly relating the patient's death to the hematological disease evolution because the patient was in complete hematologic response at this same date. Bosutinib was stopped on 29Jul2016. The action taken was not applicable. The outcome of the deterioration of general physical health was fatal. It was unknown if an autopsy was performed.

The reporter considered anemia related to bosutinib.

The investigator considered there was not a reasonable possibility that the events fever, head trauma, insomnia, lower limb oedema, and hypokalemia were related to the study medication bosutinib and concomitant drug.

The investigator considered there was not a reasonable possibility that the event paranoid attack was related to the study medication bosutinib Paranoid attack was related to concomitant drug CIFLOX.

The investigator assessed the events urinary infection, pubis rash, and constipation as unrelated to the study drug bosutinib or to another product. According to the investigator, the event urinary infection was not considered related to concomitant drugs.

The investigator considered there was no reasonable possibility that the fatal event deterioration of general physical health was related to study drug bosutinib or to concomitant drug.

Follow-up (10Jun2016 and 13Jun2016): New information reported includes: reaction data (added non-serious events lower limb oedema, insomnia, urinary infection, pubis rash, and constipation), outcome data, action taken, and causality.

Follow-up (12Aug2016): Follow-up attempts completed. No further information expected.

Follow-up (05Sep2016): New information received from the investigator includes: reaction data (added hypokalemia), clinical course details, and causality assessment.

Follow-up (23Sep2016): New information reported includes: investigator aware date, lab data, and causality (updated hypokalemia from related to unrelated to bosutinib).

Follow-up (30Sep2016): New information reported from the investigator includes: clinical outcome (insomnia updated from not recovered to recovered) and causality assessment (lower limb oedema unrelated).

Follow-up (31Oct2016): Follow-up attempts are completed. No further information is expected.

Follow-up (30Nov2016): New information reported includes: reaction data (added Fatal event Deterioration of general physical health) and clinical details.

Follow-up (14Nov2023): This is a non-interventional study follow-up report received from investigational site via clinical team for protocol B1871047. Updated information included: anemia causality assessment changed to related, updated outcome and recovery

Mfr. Control Number: 2016239426

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

dates, CIFLOX added as suspect drug.

Case Comment: Based on available information and known safety profile, a possible contributory role of the subject drug cannot be excluded for the reported event Anemia. Based on available information and on the investigator's assessment, the company considers all the other reported events unrelated to suspect drug bosutinib. Elderly age and underlying malignancy may play a contributory role.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Blood potassium grade 1	3.2 mmol/L	4.5 3.4
2	25-JUL-2016	Investigation did not allow to directly relating the patient's death to the hematological disease evolution because the patient was in complete hematologic response at this same date.	results	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1939	76 Years	Female	58.00 kg	20	APR	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 19-APR-2016 / 25-APR-2016

19. THERAPY DURATION
#1) 7 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☒ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016241628

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
25-APR-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 76-year-old female subject started to receive bosutinib (BOSULIF, film-coated tablet), via an unspecified route of administration, from 19Apr2016 to 25Apr2016 at 500 mg once a day, for an unspecified indication. The patient had no relevant medical history. There were no concomitant medications. The subject experienced diarrhea (CTCAE grade 2) on 20Apr2016. The action taken in response to the event for bosutinib was permanently withdrawn on 25Apr2016, on subject's request. The event diarrhea recovered on 26Apr2016.

The event was non-serious. The investigator considered that the event was related to bosutinib and unrelated to any concomitant drug.

Follow-up (25Apr2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site via the CRO for protocol B1871047.
Updated information includes: investigator aware date, reporter and patient details, and outcome of the event.

Case Comment: By close temporal relationship and absence of factors which may provide an alternative cause, the event diarrhea may be attributed to the suspect drug bosutinib, the event is compatible with the safety profile of the suspect drug.

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		SEP	1941	74 Years	Male	81.00 kg	02	MAY	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

aggravation of carotid stenosis [Carotid artery stenosis]
Hepatic cytolysis [Hepatic cytolysis]
Benign mucinous tumor of the head of the pancreas [Benign pancreatic neoplasm]
Laryngitis [Laryngitis]
uveitis [Uveitis]
epistaxis [Epistaxis]
right index and last phalanx panaritium [Paronychia]
Not well balanced dyslipidemia [Dyslipidaemia]
Thoracic pain [Chest pain]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) KARDEGIC (ACETYLSALICYLATE LYSINE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) atheroma (Arteriosclerosis)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☒ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 21-MAR-2016 / 13-APR-2016	#1) 24 days
#2) Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) FRACTAL (FLUVASTATIN SODIUM) ; 1990 / Ongoing
#2) COVERSYL [PERINDOPRIL ARGININE] (PERINDOPRIL ARGININ
#3) HEXOMEDINE [HEXAMIDINE ISETIONATE] (HEXAMIDINE ISETI

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1990 to Ongoing	Relevant Med History persistent	Hypercholesterolemia (Hypercholesterolaemia)
APR-2014 to APR-2014	Relevant Med History	Prostate cancer (Prostate cancer)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016257514

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

ocular herpes [Herpes ophthalmic]
Achilles tendinitis [Tendonitis]
Under left mandibular hypoesthesia [Hypoaesthesia]
high blood pressure [Hypertension]
renal cyst [Renal cyst]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 74-year-old male patient received bosutinib (BOSULIF), first regimen from 21Mar2016 to 13Apr2016 at 100 mg 1x/day, second regimen from 14Apr2016 to 03May2016 at 300 mg 1x/day, third regimen from 04May2016 to 16Jun2016 at 100 mg 1x/day and fourth regimen since 17Jun2016 (ongoing) at 200 mg 1x/day; acetylsalicylate lysine (KARDEGIC), (ongoing) (Batch/Lot number: unknown), oral for arteriosclerosis. The patient's relevant medical history included: "hypercholesterolemia", start date: 1990 (ongoing), notes: persistent; "prostate cancer", start date: Apr2014, stop date: Apr2014; "atheroma", start date: 09Apr2015 (ongoing), notes: persistent; "Dyslipidemia" (ongoing). Concomitant medication(s) included: FRACTAL oral taken for hypercholesterolaemia, start date: 1990 (ongoing); COVERSYL [PERINDOPRIL ARGININE] oral taken for hypertension, start date: 25May2018 (ongoing); HEXOMEDINE [HEXAMIDINE ISETIONATE] topical taken for paronychia, start date: 28Mar2018 (ongoing).
On 02May2016, the subject experienced hepatic cytolysis (CTCAE grade 2), assessed as non-serious. On the same day, the subject underwent lab tests and procedures which revealed hepatic cytolysis, aspartate aminotransferase (ASAT, normal between 5-34) was at 118 IU/L, and alanine aminotransferase (ALAT, normal between 0-55) was at 271 IU/L. The patient had recovered from this event on 24Jun2016. As a result of this event, dose of bosutinib was reduced. The subject developed intolerance to bosutinib on 04May2016. This event was considered as not serious and rated grade 1. The subject again developed intolerance to bosutinib on 17Jun2016. This event was considered as not serious and rated grade 1. The events intolerance of bosutinib (onset 04May2016), resolved on 17Jun2016, and the second occurrence (onset 17Jun2016) resolved on 02Jul2016. On 15Dec2016, the subject experienced laryngitis grade 1 considered as non-serious event. As a result of the event, action taken with bosutinib was ongoing. The event laryngitis grade 1 resolved on 12Jan2017. On 31Aug2017, the subject experienced uveitis rated grade 1 considered as non-serious event. No action was taken in response to the event for bosutinib. The subject received prednisolone (CORTANCYL) oral from 31Aug2017 to 31Oct2017 for uveitis. Uveitis resolved on 31Oct2017. On 08Nov2017, the subject experienced epistaxis rated grade 1 considered as non-serious event. No action was taken in response to the event for bosutinib. The event was resolved on 05Apr2018. On 28Mar2018, the subject experienced right index and last phalanx panaritium rated grade 3 considered as non-serious event. No action was taken in response to the event for bosutinib. The patient had recovered from the event on 29May2018. The subject started to receive hexamidine isethionate (HEXOMEDINE) for local application from 28Mar2018 and ongoing for panaritium. On 08Mar2018, the subject experienced benign mucinous tumor of the head of the pancreas (exact diagnosis), grade 2, reported as a non-serious event and from which the patient had not recovered. No action was taken in response to the event for bosutinib. The event had not recovered at the report time. No action was taken in response to the event for bosutinib. On 05Mar2018, the subject experienced aggravation of carotid stenosis, which led to hospitalization. The event was assessed of grade 4. As a result of the event, no action was taken regarding bosutinib. The subject underwent surgery in Jan2019. On 05Apr2018, the subject experienced renal cyst, grade 1. The event was assessed as non-serious. The investigator considered the event was unrelated to the study drug. The action taken for bosutinib was dose not changed. On 29May2018, the subject experienced not well balanced dyslipidemia and thoracic pain, both rated as grade 1. No action was taken in response to the event for bosutinib. The subject started to receive perindopril (COVERSYL) by oral route ongoing from 25May2018 for hypertension; fluvastatin sodium (FRACTAL) orally ongoing from 1990 for hypercholesterolemia. In Jul2018, the subject experienced ocular herpes, which was assessed as non-serious and grade 3. As a result of the event, no action was taken regarding bosutinib. In Oct2018, the subject experienced achilles tendinitis which was rated grade 1 and considered non serious. On 29Jan2019, the subject experienced under left mandibular hypoesthesia which was rated grade 1 and high blood pressure which was rated grade 3, considered non-serious events. The action taken for bosutinib in response to hepatic cytolysis was temporarily withdrawn; for acetylsalicylate lysine in response to event epistaxis was dosage not changed. On 10Jan2019, the event aggravation of carotid stenosis had resolved. The event high blood pressure resolved on 29Jan2019. The event under left mandibular hypoesthesia resolved in Feb2019. The event ocular herpes had resolved on 05Apr2019. The outcome of event thoracic pain was resolved on 16Nov2018. The outcome of events achilles tendinitis and balanced dyslipidemia was not resolved.

The investigator considered there was a reasonable possibility that the event hepatic toxicity could be related to the study drug bosutinib. The investigator considered both events of intolerance of bosutinib (onset dates 04May2016 and 17Jun2016) as possibly related to study drug bosutinib and not related to concomitant medications. The investigator considered the event laryngitis, uveitis, epistaxis, benign mucinous tumor of the head of the pancreas (exact diagnosis), right index and last phalanx panaritium, aggravation of carotid stenosis, ocular herpes, achilles tendinitis, under left mandibular hypoesthesia, high blood pressure as not related to study drug bosutinib and concomitant medications. The investigator considered there was not a reasonable possibility that the events not well balanced dyslipidemia and thoracic pain could be related to the study drug bosutinib. Event epistaxis assessed as possibly related to concomitant drug KARDEGIC.

Follow-up (06Jun2016): New information received includes: Concomitant drug data, Reaction data (CTCAE grade of the event

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

hepatic toxicity was updated from grade 4 to grade 2), Action taken (updated to temporarily withdrawn for bosutinib), Clinical outcome (updated to not recovered for event hepatic toxicity) and Causality assessment per investigator (related to study drug bosutinib; previously not reported).

Follow-up (14Dec2016): New information reported includes: suspect product regimen data, reaction data (added non-serious events intolerance of bosutinib (onset dates 04May2016 and 17Jun2016)), clinical course, action taken, and causality.

Follow-up (20Feb2017): New information received from the investigator includes new adverse event laryngitis grade 1 (non-serious).

Follow-up (26Jun2018): New information received from the investigator includes new adverse event uveitis, epistaxis, pancreas mucinous tumor, right index and last phalanx panaritium.

Follow-up (02Jul2018): New information received from clinical team includes: the action taken with bosutinib in response to the event with onset date 17Jun2016 was temporary withdrawal.

Follow-up (04Jul2018) New information received included: new events (not well balanced dyslipidemia and thoracic pain); bosutinib dosage; fluvastatin sodium was deleted from concomitant drugs.

Follow-up (11Sep2018 and 13Sep2018): New information received included event epistaxis outcome updated and recovery date provided.

Amendment: This follow-up report is being submitted to amend previously reported information: added second primary malignancy before event term 'Pancreas mucinous tumor'.

Follow-up (13Jun2019): New information received from the CRO included dosage regimen of bosutinib, new events(imputable evolutive carotid stenosis, ocular herpes, achilles tendinitis, under mandibular hypoesthesia and increase of arterial hypertension).

Follow-up (25Jun2019): New information received from the CRO incudes seriousness and causality for the events tendonitis of the Achilles, under mandibular hypoesthesia, and arterial tension increase.

Follow-up (22Jul2019): New information received from the CRO included the subject's initials provided, and dosage regimen for bosutinib updated.

Follow-up attempt completed. No further information expected.

Follow-up (01Oct2019): New information received from the CRO includes reaction data (event verbatim "increase of arterial hypertension" changed to "high blood pressure", and event verbatim "under mandibular hypoesthesia" changed to "under left mandibular hypoesthesia").

Follow-up (03Dec2019): New information received from the investigator includes: dose regimens of bosutinib updated, outcome of event thoracic pain updated as resolved (previously not resolved), and grade of events under left mandibular hypoesthesia and high blood pressure added.

Amendment: This follow-up is being submitted to amend previously reported information. The event term "Second primary malignancy" has been deleted, since the pancreas mucinous tumor was described as non serious (so presumably a benign tumor).

Follow-up (06Jan2020): New information received from the investigator included: new event (secondary cancer), dosage of bosutinib, start date of fluvastatin sodium, outcome of event, updated events (from hepatic toxicity to hepatic cytolysis; from pancreas mucinous tumor to pancreas tumor), action taken.

Amendment: This follow-up is being submitted to amend previously reported information. The event "Neoplasm progression" has been deleted and "Second primary malignancy" added, since the event term "Pancreas mucinous tumor" was updated to "Pancreas tumor" and also specified as patient presented with secondary cancer.

Follow-up (23Jan2020): New information received includes: The event pancreas tumor is confirmed as benign. Previously reported event 'Pancreas tumor' has therefore been re-coded to benign neoplasm of pancreas.

Follow-up (14May2023): This is a non-interventional study report (Post Authorization Safety Study) received from the investigator for protocol B1871047. Updated information: suspect product data (new suspect concomitant product KARDEGIC, additional dosage regimen of bosutinib), concomitant medication data (start date of FRACTAL, additional concomitant treatment perindopril arginine (COVERSYL)), causality and action taken of KARDEGIC.

Follow-up (18Jul2023, 18Jul2023, 18Jul2023): This is non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047 received from Clinical Team and via investigator site via the CRO: Updated information includes: suspect drug data (bosutinib dosing regimens), event data (event pancreas tumor was updated to Benign mucinous tumor of the head of the pancreas (exact diagnosis), non-serious and event evolutive carotid stenosis was updated to aggravation of carotid stenosis with onset date updated to 05Mar2018), new event added (renal cyst), new concomitant medication added (Hexomedine), confirmed

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

event hepatic cytolysis was not serious and the event did not reccur upon bosutinib dose resumption.

Follow-up (07Sep2023): This is a non-interventional study report received from clinical team. Updated information: concomitant medication data.

Amendment: This follow-up report is being submitted to amend previously reported information: Concomitant drug Coversyl was received as an antihypertensive.

Follow-up (23Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: action taken with bosutinib in response to hepatic cytolysis.

Case Comment: Considering a positive drug-event temporal association, the company attributes the hepatic cytolysis to bosutinib. The events laryngitis, uveitis, epistaxis, benign neoplasm of pancreas, right index and last phalanx panaritium, not well balanced dyslipidemia, thoracic pain, imputable evolutive carotid stenosis, ocular herpes, achilles tendinitis, high blood pressure, under mandibular hypoesthesia and renal cyst are considered unrelated to bosutinib. The event increase of arterial hypertension, started and resolved on the same day, was likely attributed to the intercurrent medical condition in this elderly subject and unrelated to bosutinib. The non-specific drug intolerance (not reportable as event) is still unspecified by the investigator with the last follow-up. The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02-MAY-2016	Alanine aminotransferase hepatic toxicity	271 IU/l	55 0
2	02-MAY-2016	Aspartate aminotransferase hepatic toxicity	118 IU/l	34 5

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, 1x/day; Unknown	Unknown	14-APR-2016 / 03-MAY-2016; 20 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	100 mg, 1x/day; Unknown	Unknown	04-MAY-2016 / 16-JUN-2016; 1 month 13 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, 1x/day; Unknown	Unknown	17-JUN-2016 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#2) COVERSYL [PERINDOPRIL ARGININE] (PERINDOPRIL ARGININE) ; 25-MAY-2018 / Ongoing

#3) HEXOMEDINE [HEXAMIDINE ISETIONATE] (HEXAMIDINE ISETIONATE) ; 28-MAR-2018 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
09-APR-2015 to Ongoing	Relevant Med History	Atheromatosis (Arteriosclerosis);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
	persistent	
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		APR	1938	78 Years	Female	82.00 kg		MAY	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Acute bronchitis [Bronchitis]
Urticarial rash [Urticaria]
Diarrhea [Diarrhoea]
Vomiting [Vomiting]
Nausea [Nausea]
BOSULIF misuse [Intentional product misuse]
Dental infection [Tooth infection]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

15. DAILY DOSE(S)
#1) 300 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 19-MAY-2016 / 22-JUN-2016

19. THERAPY DURATION
#1) 35 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Iodine allergy (Iodine allergy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016317562

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
29-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047. A 78-year-old female subject started to receive bosutinib (BOSULIF, film-coated tablet), via an unspecified route of administration from 19May2016 to 22Jun2016 at 300 mg once a day, from 27Jun2016 to an unspecified date in 2018 at 300 mg daily, from 01Sep2018 at an unknown dose, and ongoing from Oct2018 at 500 mg daily for an unspecified indication. Medical history included ongoing iodine allergy. The subject did not have concomitant medications.
The subject experienced vomiting grade 1 on unspecified date in May2016, which was considered non-serious. The subject reported several vomiting at the beginning of the treatment (dates unknown). No action was taken with study drug in response to the event vomiting. No treatment was taken. The subject experienced diarrhea (CTCAE grade 1) on an unspecified date in May2016, which was considered non-serious. The subject experienced nausea grade 1 on unspecified date in Jun2016, which was considered non-serious. No action was taken with study drug in response to this event. The subject experienced urticarial rash (CTCAE grade 1) on 17Jun2016, which was considered non-serious. The reporter specified that from 17Jun2016, the subject experienced the urticarial rash (grade 1) associated with a mild pruritus and some diarrhoea since the beginning of bosutinib (exact dates unknown) required a corrective therapy with loperamide hydrochloride (IMODIUM). The action taken in response to the event urticarial rash for bosutinib was temporarily withdrawn on 23Jun2016 to 26Jun2016, with the last intake was on 22Jun2016. Later, the drug was re-administered on 27Jun2016 at the dosage of 300 mg daily. The subject recovered from the vomiting on unspecified date in May2016. The outcome of the event diarrhea was recovered on 15Jun2016 and the event urticarial rash was recovered on 29Aug2016. The event nausea was not recovered. In 2018 on an unknown date, the subject misused bosutinib, details not provided. The event was considered as non serious. The event resolved on 01Sep2018. The investigator considered the event as unrelated to study drug bosutinib. The subject decided not to take bosutinib during an unknown duration. Bosutinib was administered at that time at the dose of 300 mg daily. BCR-ABL increased. Bosutinib was resumed on 01Sep2018. In Oct2018, the subject developed acute bronchitis, rated grade 2 and considered as a medically important event. The event resolved in Dec2018. No action was taken with bosutinib in response to the event. The bronchitis had led to fatigue, dyspnea, water overload and pericardial effusion. The subject went to the Emergency unit on 16Nov2018. In Mar2019, the subject developed dental infection, rated grade 1 and considered as non serious. No action was taken with bosutinib in response to the event. The event resolved in Apr2019.

The investigator considered there was a reasonable possibility that the events vomiting, nausea, diarrhea and urticarial rash was related to the study medication bosutinib and not related to concomitant drugs. The investigator considered the event bronchitis and dental infection were not related to bosutinib.

Follow-up (01Aug2016): New information received includes: reaction data (onset date of diarrhea updated from Jun2016 to May2016), action taken (confirmed temporarily withdrawn), and outcome (diarrhea was recovered in Jun2016).

Follow-up (09Sep2016 and 13Sep2016): New information reported includes: suspect product data (start date updated from 17May2016 to 19May2016; dose updated from 500mg to 300mg), medical history, concomitant medication (none), and reaction data (added vomiting and nausea).

Follow-up (23Jan2017): New information received includes: product data (updated dating and dosing), and clinical course details.

Follow-up (02Jul2019): New information received includes additional events (drug misuse, acute bronchitis, dental infection) and additional dosage regimens of bosutinib. The case is now serious.

Follow-up (10Jul2019): New information received from the investigational site includes: updated start date of bisutinib 500 mg dosage regimen.

Follow-up (08Feb2023): This is a follow-up report from the investigator via CRO. New information received included: The action taken in response to the event vomiting was dosage not changed.

Amendment: This follow-up report is being submitted to amend previously reported information: event diarrhea stop date 15Jun2016; for event Urticarial rash recovered on 29Aug2016 instead of recovering.

Case Comment: Diarrhea, urticaria rash, vomiting and nausea are expected events in the safety profile of the suspect drug, and a plausible drug-events temporal relationship cannot be excluded. In agreement with the reporter, the company considers diarrhea, urticaria rash, vomiting and nausea related to bosutinib, and acute bronchitis and dental infection unrelated to bosutinib. The underlying malignancy could be contributory to the infectious events in the context of immunosuppression.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	2018	Philadelphia chromosome positive	increased	

Mfr. Control Number: 2016317562

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Unknown	27-JUN-2016 / 2018; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	UNK; Unknown	Unknown	01-SEP-2018 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	500 mg, daily; Unknown	Unknown	OCT-2018 / Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE	15	APR	1946	69 Years	Male	90.00 kg	22	MAR	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Aggravation of tremors [Tremor]
Intercapsular pain [Pain]
Arrhythmia [Arrhythmia]
Asthenia [Asthenia]
Asthenia [Asthenia]
Vertigo [Vertigo]
Vertigo [Vertigo]
Vomiting [Vomiting]
Diarrhea [Diarrhoea]
Diarrhea [Diarrhoea]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) Lyrica (PREGABALIN) Unknown

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Unknown
#2) 150 mg, 2x/day	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) Pruritus (Pruritus)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 21-MAR-2016 / 22-AUG-2016	#1) 155 days
#2) 25-MAY-2017 / Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TAREG (VALSARTAN) ; MAY-2016 / Ongoing
#2) AERIUS [DESLORATADINE] (DESLORATADINE) ; 16-DEC-2016 / Ongoing
#3) MODOPAR (BENSERAZIDE HYDROCHLORIDE, LEVODOPA) ; 04-MAY-2018 / Ongoing
#4) DOMPERIDONE (DOMPERIDONE) ; 04-MAY-2018 / Ongoing
#5) PONATINIB (PONATINIB) ; 09-MAR-2018 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2001 to Ongoing	Relevant Med History	Essential tremor (Essential tremor)
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016339215

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Eructations [Eructation]
Abdominal pain [Abdominal pain]
Scratch lesions [Scratch]
Chronic pruritus [Pruritus]
Intercostal pain [Musculoskeletal chest pain]
Headaches [Headache]
Headaches [Headache]
melanic skin lesion [Skin lesion]
Nausea [Nausea]
joint pains [Arthralgia]
Constipation [Constipation]
Irritability [Irritability]
Allergic reaction [Hypersensitivity]
Testicular pain [Testicular pain]
Sweats [Hyperhidrosis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) from License Party for protocol B1871047. Other Case identifier(s): 2022FR0690028 (Unknown), 2023/529 (Viatric local reference).

A 69-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration at 300 mg daily from 21Mar2016 to 22Aug2016 then at 200mg daily from 23Aug2016 to 19May2017 for an unspecified indication, pregabalin (LYRICA) orally at 150mg twice a day from 25May2017 to unspecified date in 2017 for pruritus, and ponatinib hydrochloride (ICLUSIG). Medical history included essential tremors ongoing from 2001, ongoing arterial hypertension, and cholecystectomy from 2014. Concomitant medications included valsartan (TAREG) ongoing from May2016 for arterial hypertension, desloratadine (AERIUS) from 16Dec2016 and ongoing for itching, benserazide hydrochloride/levodopa (MODOPAR) from 04May2018 and ongoing for neurologic disorder, domperidone from 04May2018 and ongoing for neurologic disorder, and ponatinib from 09Mar2018 to 16Mar2018 and ongoing from 16Mar2018. On 17May2016, the subject experienced scratch lesions grade 1 (non-serious). No action was taken for bosutinib in response to the event. On 22Mar2016, the subject developed non-serious events vomiting (grade 1), diarrhea (grade 1), and eructations (grade 1). Event diarrhea grade 1 on 22Mar2016 recovered on 23Aug2016. In response to the event diarrhea, bosutinib dose was reduced. On 04May2016, the subject developed allergic reaction (grade 1). In Aug2016, the subject developed non-serious events asthenia (grade 1), vertigo (grade 1), abdominal pain (grade 1), and aggravation of tremors (grade 2). The event Aggravation of tremors required hospitalization. Patient hospitalized for deep bilateral intervertebral stimulation placement on 27Nov2018 followed by 2 hospitalizations from 05 to 13Dec2018 then from 25 to 26Feb2019 for follow-up workups. Investigator awareness date for allergic reaction due to after shave on 17May2016 and for tremors on 23Aug2016. In response to the event abdominal pain, bosutinib dose was reduced. The investigator acknowledged the allergic reaction on after shave on 17May2016 and for tremors on 23Aug2016 (as reported). On 23Aug2016, the subject experienced non-serious event constipation grade 1. No action was taken for bosutinib in response to constipation. On 10Dec2016, the subject experienced testicular pain grade 1, non-serious. No action was taken for bosutinib in response to testicular pain. On 16Dec2016, the subject developed non-serious chronic pruritus, rated grade 2. Action taken with bosutinib in response to the events vomiting grade 1, diarrhea grade 1, eructations grade 1, asthenia grade 1, vertigo grade 1 and abdominal pain grade 1 was not applicable. Action taken with study drug bosutinib in response to the events aggravation of tremors grade 2, and allergic reaction grade 1 was dose not changed. In response to event chronic pruritus on 16Dec2016, bosutinib was withdrawn. The chronic pruritus grade 2 was persistent despite intake of anti-histamines. There were no suspect skin lesion. On 16Dec2016, the subject experienced nausea grade 2, non-serious. No action was taken for bosutinib in response to nausea. In Mar2017, the subject experienced joint pain grade1, non-serious. No action was taken for bosutinib and for concomitant drug pregabalin (LYRICA) in response to joint pain. In May2017, the subject experienced intercostal pain and arrhythmia which were stated as non-serious. Intercostal pain was described as peri thoracic, mainly after passage to orthostatism. Action taken with study drug bosutinib in response to the events intercostal pain and arrhythmia was dose not changed. In May2017, the subject experienced diarrhea grade 2, recovered on 01Dec2017. In response to diarrhea bosutinib dose was reduced. The event was considered as related to bosutinib and unrelated to a concomitant drug. In May2017, the subject experienced vertigo grade 1. On 19May2017, the subject experienced loss of bosutinub efficacy grade 1 assessed as non-serious event. Action taken for bosutinib in response to the event loss of bosutinub efficacy was dose increased. Loss of bosutinib efficacy was resolved on 12Oct2017. Loss of bosutinub efficacy as related to study drug bosutinib and unrelated to concomitant medication. On 01Dec2017, the subject experienced irritability considered non-serious and rated grade 1. No action was taken for bosutinib in response to irritability. In Feb2018, the subject experienced headaches grade 2, non-serious. In response to the event bosutinib was withdrawn. In Mar2018, the subject experienced headaches grade 2. In response to the event bosutinib was withdrawn. The event recovered in Mar2018, ponatinib hydrochloride dose was reduced. On 09Mar2018, the subject experienced melanic skin lesion grade 1, non-serious. No action was taken for bosutinib in response to event melanic skin lesion. In Mar2018, the subject experienced sweats grade 1, non-serious. No action was taken for bosutinib in response to sweats and ponatinib hydrochloride (ICLUSIG) dose was reduced. In Mar2018, the subject experienced asthenia grade 1, recovered in Mar2018, and ponatinib hydrochloride dose was reduced. On 09Mar2018, the subject started to experience lack of efficacy of suspect drug bosutinib. This event was rated grade 3 and non-serious. As a result of

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

this event, bosutinib was withdrawn temporarily or permanently. In Mar2018, the subject experienced intercapsular pain, serious as medically significant. As a result, ponatinib hydrochloride dose was reduced. On 21Mar2018, ECG, lung X-ray and blood tests returned all normal results. On the same day, intercapsular pain resolved. In response to vertigo bosutinib dose was reduced. On 04May2018, the subject started to receive levodopa/ benserazide hydrochloride (MODOPAR) and domperidone (unspecified trade name), both by oral route for neurologic disorder. On 18Jan2019, the event neoplasm progression recovered. The outcome of vomiting grade 1 was resolved in Apr2016, diarrhea grade 1 (22Mar2016) was resolved on 23Aug2016, diarrhea grade 2 (May2017) was resolved on 01Dec2017, eructations grade 1 was resolved in 23Aug2016, allergic reaction grade 1 was resolved on 23Aug2016, aggravation of tremors was resolved on 26Feb2019, asthenia grade 1 (Aug2016) was resolved on 16Dec2016, asthenia (Mar2018) was resolved on Mar2018, vertigo (Aug2016) recovered on 09Mar2018, vertigo (May2017) was resolved on 10Aug2017, abdominal pain grade 1 was resolved on 16Dec2016, scratch lesions was resolved on 23Aug2016, bosutinib lack of efficacy was resolved on 11May2018, chronic pruritus grade 2 was recovered on 11May2018, headaches (Feb2018) was resolved on 09Mar2018, headaches (Mar2018) was resolved on Mar2018, melanic skin lesion grade 1 was resolved on 11May2018, joint pain was resolved on 19May2017, nausea was resolved on 19May2017, testicular pain was resolved on 19May2017, sweats grade 1 was resolved in Mar2018, constipation was resolved on 16Dec2016, irritability was resolved on 09Mar2018. The clinical outcome of the events intercostal pain and arrhythmia were both resolved on 01dec2017. The last action taken for bosutinib was permanently withdrawn, for pregabalin was dose not changed, and for ponatinib hydrochloride was dose reduced.

The investigator considered that the events vomiting grade 1, diarrhea grade 1, diarrhea grade 2, eructations grade 1, asthenia grade 1 (Aug2016), vertigo grade 1 (Aug2016), abdominal pain grade 1, headache (Feb2018) were related to study drug bosutinib.

The investigator considered the events chronic pruritus grade 2, nausea grade 2, constipation as related to study drug bosutinib and unrelated to concomitant medication.

The investigator considered the events intercapsular pain and headache (Mar2018) as unrelated to the study drug bosutinib; asthenia grade 1 (Mar2018) and headache (Feb2018) as related to the concomitant medication ponatinib hydrochloride.

The investigator considered that the events aggravation of tremors grade 2, allergic reaction grade 1, intercostal pain and arrhythmia, scratch lesions, melanic skin lesion grade 1, joint pain grade1, testicular pain grade 1, irritability were unrelated to study drug bosutinib and concomitant drugs.

The events sweats grade 1 was unrelated to bosutinib and related to concomitant drug ponatinib hydrochloride (ICLUSIG). The event vertigo (May2017) was unrelated to study drug bosutinib, related to pregabalin. The events asthenia (both Aug2016 and Mar2018), headache (both Feb2018 and Mar2018), testicular pain, sweats and irritability were unrelated to pregabalin. The events diarrhea (May2017), nausea and constipation were related to pregabalin. The reporter's considered the event lack of efficacy as related to the suspect and unrelated to concomitant medication.

Reporter comments: The events asthenia (both Aug2016 and Mar2018), headache (both Feb2018 and Mar2018), testicular pain, sweats and irritability were unrelated to pregabalin. According to the reporter, headaches were not related to Bosulig but could be related to Iclusig

Follow-up (20Sep2016 and 22Sep2016): New information received from CRO includes: new non-serious events (vomiting grade 1, diarrhea grade 1, eructations grade 1, asthenia grade 1, vertigo grade 1, abdominal pain grade 1, aggravation of tremors grade 2 and allergic reaction grade 1), study drug regimen data, medical history, concomitant medications, action taken data, and causality assessment. Follow-up attempts completed. No further information expected.

Follow-up (23Feb2017): New information received from the CRO includes: clinical course details, reaction data (added chronic pruritus), treatment received (antihistamines), and causality assessment (chronic pruritus considered related).

Follow-up attempts completed. No further information expected. Follow-up (06Jun2017): New information received as follows: concomitant medication (added pregabalin) and reaction data (added intercostal pain and arrhythmia).

Follow-up (10Aug2017): New information received from the investigational site includes: action taken for bosutinib in response to events intercostal pain and arrhythmia (no action taken), and causality of events intercostal pain and arrhythmia with bosutinib (unrelated, previously not provided). Follow-up attempts completed. No further information expected. Follow-up (08Jan2018): New information received included clinical course "loss of response to treatment".

Follow-up (11Jan2018): New information received from the investigator includes: reaction data (loss of bosutinib efficacy), outcome (recovered from loss of bosutinib efficacy), and seriousness and causality assessment (loss of bosutinub efficacy grade 1 assessed as non-serious event; related to study drug bosutinib and unrelated to concomitant medication).

Follow-up (14Aug2018): New information received included: additional event (intercapsular pain) and details (onset date, stop date, seriousness criterion, causality assessment), medical history, concomitant medication, lab data, case upgrade to serious, additional suspect product ponatinib hydrochloride, subject's age updated.

Follow-up (28Feb2019): New information received from the study coordinator outcome of chronic pruritus (recovered on 11May2018). Follow-up (26Mar2019) New information received from the CRO included new event lack of efficacy, action taken with bosutinib updated Follow-up (28Aug2019): New information received via the CRO includes: updated outcome of the events lack of efficacy,

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

diarrhea on 22Mar2016, and abdominal pain; new events (asthenia, vertigo, diarrhea, headache, skin lesion, joint pain, vertigo, nausea, testicular pain, sweats, constipation, and irritability); updated start date and seriousness of event intercapsular pain (from hospitalization to medically significant); updated stop date of events loss of bosutinub efficacy on 19May2017 and eructation; additional concomitant drugs; updated start date of valsartan and essential tremors; upgrade pregabalin (LYRICA) as suspect drug; and clinical course.

Follow-up (02Sep2019): New information received from the CRO includes: route of administration of ponatinib updated, and events asthenia (09Mar2018) and headache (09Mar2018) as unrelated to bosutinib. Follow-up (18Sep2019): New information received from the CRO includes: the causality of the event headache (Feb2018) updated as related to study drug bosutinib (instead of unrelated as previously reported), and event skin lesion (09Mar2018) updated to event term "benign skin lesion".

Follow-up (02Oct2019): New information received from the investigational site included: dosage regimens of suspect drugs pregabalin and bosutinib; start date of concomitant drug valsartan. Follow-up (13Nov2019): New information includes: updated onset date for scratch lesions. Follow-up (30May2022): New information received from CRO includes seriousness of event Aggravation of tremors updated, outcome of Aggravation of tremors updated, hospitalization details, event term benign skin lesion was changed for "melanic skin lesion", onset date for event scratch lesions updated to 17May2016, onset date for event headache, asthenia, sweats updated from 09Mar2018 to Mar2018, causality for event arrhythmia (related to bosutinib).

Follow-up information was received by Viatris on 14-Apr-2023 (Reference number: 2022FR0690028) Providing an updated company comment.

Follow-up (28Apr2023): New information was received from Viatris providing an updated company comment.

Amendment: Case is being re-submitted to add a follow-up statement for information received on 28Apr2023.

Amendment: this follow-up is submitted to amend previously reported information: to update arrhythmia and intercapsular pain captured non serious as reported by the investigator.

Pregabalin is under agreement with Viatris.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the clinical team for protocol B1871047.

Updated information includes that the event "transit disorder" in Aug2016 was deleted since it was regarding the "diarrhea" event already recorded.
No follow-up attempts are needed. No further information is expected.
Pregabalin is under agreement with Viatris.

Case Comment: Tremor is unlisted in the SRSD of bosutinib and related per company.

Tremor, pain, asthenia(two episodes), vertigo (AUG2016), vomiting, diarrhea (two episodes), eructation, abdominal pain, scratch, pruritus, intercostal pain, headache(two episodes), & nausea are related to bosutinib based on temporal association and product profile. Hypersensitivity, vertigo(May2017), skin lesion, testicular pain, sweats, constipation, irritability, arrhythmia, intercapsular pain & NP were unrelated to bosutinib. Vertigo(May2017) was related to pregabalin; other events are unrelated to pregabalin.

The impact of this report on the b/r profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for AEs. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to RA, ECs and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	21-MAR-2018	Blood test	within normal limits	
2	21-MAR-2018	Chest X-ray	within normal limits	
3	21-MAR-2018	Electrocardiogram	within normal limits	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet;	200 mg, daily; Unknown	Unknown	23-AUG-2016 /

Mfr. Control Number: 2016339215

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #2			19-MAY-2017; 270 days
#3) ICLUSIG (PONATINIB HYDROCHLORIDE) ; Regimen #1	UNK; Unknown	Unknown	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2014 to Unknown	Relevant Med History	Cholecystectomy (Cholecystectomy);
Unknown to Ongoing	Relevant Med History	Neurologic disorder NOS (Nervous system disorder);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		NOV	1938	77 Years	Male	64.00 kg	24	MAY	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol B1871047.

A 77-year-old male subject started to receive bosutinib (BOSULIF) via

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 23-MAY-2016 / 13-JUN-2016	#1) 22 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1998 to Ongoing	Relevant Med History angioplasty	Coronary insufficiency (Coronary artery insufficiency)
2015 to Unknown	Relevant Med History	Angioplasty (Angioplasty)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016341715

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2016341715

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

an unspecified route of administration from 23May2016 to 13Jun2016 at 200 mg and then at 100 mg daily from 20Jun2016 to 27Jun2016 for an unspecified indication. Medical history included coronary insufficiency ongoing since 1998 for which he underwent an angioplasty in 2015 and sigmoid diverticulitis ongoing since 1998. Concomitant medications were not reported. On 24May2016, the subject experienced diarrhea (grade 2) which was stated as non-serious. It was reported that diarrhea appeared the day after taking bosutinib, on 24May2016, despite a reduced dosage (200 mg). The subject was treated at home with loperamide (unspecified trade name) as needed, up to 6 dosage forms daily. This symptomatic treatment was ineffective. The study drug was temporarily withdrawn on 13Jun2016 for 7 days, then it was decided to reintroduce it at 100 mg daily from 20Jun2016. The subject experienced another occurrence of diarrhea and it was decided to permanently stop the study drug bosutinib on 27Jun2016. The clinical outcome of the event diarrhea was recovered on 27Jun2016.

According to the investigator, the study drug bosutinib was considered related to the event but unrelated to concomitant drug.

Follow-up (03Oct2023). This follow-up is received from the investigational site via CRO. Updated information: additional dosage regimen.

Case Comment: By close temporal relationship and absence of factors which may provide an alternative cause, the event diarrhea may be attributed to suspect drug bosutinib, the event is compatible with the safety profile of the suspect drug.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, daily; Unknown	Unknown	20-JUN-2016 / 27-JUN-2016; 8 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1998 to Ongoing	Relevant Med History	Sigmoid diverticulitis (Diverticulitis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1947	69 Years	Male	84.00 kg	02	JUN	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Cephalgia [Headache]
Dyslipidemia increased [Dyslipidaemia]
Dyslipidemia increased [Condition aggravated]
Slight aggravation of renal failure [Renal failure]
Bronchitis grade 2 [Bronchitis]
Thyroid nodule recurrence grade 1 [Thyroid mass]
diarrhea [Diarrhoea]
benign hypertrophy of prostate [Benign prostatic hyperplasia]
Vitamin D deficiency [Vitamin D deficiency]
Lumbar pain [Back pain]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) LASILIX (FUROSEMIDE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown
#2) 330 mg, daily	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) Cardiopathy (Cardiac disorder)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 31-MAY-2016 / 06-JUN-2016	#1) 7 days
#2) Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) SOTALOL (SOTALOL) ; Ongoing
#2) AMLOR (AMLODIPINE BESILATE) ; Ongoing
#3) CREON (PANCREATIN) ; Ongoing
#4) ZOPHREN (ONDANSETRON) ; Unknown
#5) DIFFU K (POTASSIUM CHLORIDE) ; Unknown
#6) INEXIUM (ESOMEPRAZOLE MAGNESIUM) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Hypertrophic cardiomyopathy (Hypertrophic cardiomyopathy)
2000 to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016398918

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 69-year-old male patient received bosutinib (BOSULIF), first regimen from 31May2016 to 06Jun2016 at 100 mg 1x/day, second regimen from 07Jun2016 to 13Jun2016 at 200 mg 1x/day, third regimen from 14Jun2016 to 12Jun2019 at 300 mg 1x/day and fourth regimen since 13Jun2019 at 200 mg daily; furosemide (LASILIX), (ongoing) (Batch/Lot number: unknown) at 330 mg daily, oral for cardiac disorder. The patient's relevant medical history included: "hypertrophic cardiopathy", start date: 2013 (ongoing); "type 2 diabetes", start date: 2000 (ongoing); "Hypertension arterial", start date: 1986 (ongoing); "adenocarcinoma of pancreas", start date: 04Aug2015 (ongoing), notes: currently monitored by MRI, operated in 2015; "operation of adenocarcinoma of pancreas", start date: 2015, stop date: 2015; "coronopathy", start date: 2013 (ongoing), notes: with stent in 2013 (coronary and femoral); "stent insertion", start date: 2013 (ongoing), notes: coronary and femoral; "rheumatoid arthritis" (ongoing); "Widal's disease" (ongoing); "cardiac arrhythmia by atrial fibrillation", start date: Apr2016 (ongoing); "cardiac arrhythmia by atrial fibrillation", start date: Apr2016 (ongoing); "pulmonary aterial hypertension" (ongoing); "unilateral renal artery stenosis" (ongoing); "left urothelial lesion" (ongoing); "dyslipemia" (ongoing); "asthenia" (ongoing); "chronic renal failure" (ongoing); "polyuria" (unspecified if ongoing); "fatigue" (ongoing). Concomitant medication(s) included: SOTALOL oral taken for hypertension (ongoing); AMLOR oral taken for hypertension (ongoing); CREON oral taken for pancreatic disorder (ongoing); ZOPHREN; DIFFU K; INEXIUM.
The following information was reported: HEADACHE (non-serious) with onset 02Jun2016, outcome "recovered" (13Dec2016), described as "Cephalgia"; THYROID MASS (non-serious) with onset 04Nov2016, outcome "not recovered", described as "Thyroid nodule recurrence grade 1"; BRONCHITIS (non-serious) with onset 13Dec2016, outcome "recovered" (18Dec2016), described as "Bronchitis grade 2"; DYSLIPIDAEMIA (non-serious) with onset Mar2017, outcome "recovered" (31Aug2017), CONDITION AGGRAVATED (non-serious) with onset Mar2017, outcome "recovered" (31Aug2021) and all described as "Dyslipidemia increased"; RENAL FAILURE (non-serious) with onset Mar2017, outcome "not recovered", described as "Slight aggravation of renal failure"; DIARRHOEA (non-serious) with onset 11Apr2017, outcome "recovered" (08Aug2017), described as "diarrhea"; BENIGN PROSTATIC HYPERPLASIA (non-serious) with onset 2017, outcome "not recovered", described as "benign hypertrophy of prostate"; VITAMIN D DEFICIENCY (non-serious) with onset Aug2017, outcome "recovered" (29Mar2018); BACK PAIN (non-serious) with onset Feb2018, outcome "recovered" (Feb2018), described as "Lumbar pain". The action taken for bosutinib and furosemide was dosage not changed. Therapeutic measures were taken as a result of dyslipidaemia, condition aggravated, bronchitis.

Additional information: On 02Jun2016 the subject experienced fatigue grade 2 and cephalgia grade 2 which were considered non-serious and on 02Jun2016 polyuria grade 1 which was considered non-serious. No action was taken with study drug bosutinib and suspect concomitant treatment furosemide in response to the events fatigue, cephalgia, and polyuria. As of 14Nov2023, it was confirmed that event fatigue should be deleted as site staff answered to query and replied that AE fatigue was already ongoing when patient was enrolled.

The investigator considered there was a reasonable possibility that fatigue grade 2 and cephalgia grade 2 were related to the study medication bosutinib but not related to concomitant treatment.
The investigator considered there was a reasonable possibility that the event polyuria grade 1 was related to the study medication bosutinib and to suspect concomitant treatment furosemide. Slight aggravation of renal failure was related to study drug but not related to concomitant therapy.
The reporter considered "bronchitis grade 2", "thyroid nodule recurrence grade 1", "diarrhea", "benign hypertrophy of prostate", "vitamin d deficiency" and "lumbar pain" not related to bosutinib.

Follow-up (27Jan2017). Follow-up attempts completed. No further information expected.

Follow-up (11Sep2017): New information includes: previously reported medical history were updated: hypertrophic cardiopathy, type 2 diabetes, adenocarcinoma of pancreas operated in 2015. Additional ongoing medical history included coronaropathy with stent in 2013 (coronary and femoral), rheumatoid arthritis, Widal's disease, cardiac arrhythmia by atrial fibrillation in Apr2016, arterial pulmonary hypertension, unilateral renal artery stenosis, left urothelial lesion, dyslipemia, asthenia, and chronic renal failure. The subject received study drug bosutinib at 100 mg once daily from 31May2016 to 06Jun2016, at 200 mg once a day from 07Jun2016 to 13Jun2016 and at 300 mg once a daily ongoing since 14Jun2016. Additional non-serious events were reported: on 04Nov2016, the subject developed thyroid nodules recurrence rated grade 1. In response to this event, dose of bosutinib was not changed. The event did not resolve. The investigator considered this event as unrelated to study drug bosutinib and to concomitant medications. On 13Dec2016, the subject developed bronchitis rated grade 1. In response to this event, dose of bosutinib was not changed. Bronchitis was treated by amoxicillin (unspecified trade name) during 5 days from 13Dec2016 to 18Dec2016. Follow-up information received on 10Jun2022 reported "renal failure", which was updated to "slight aggravation of renal failure", rated as grade 2 (no action taken in response to this event),

The event resolved on 18Dec2016. The investigator considered this event thyroid nodules grade 1 and bronchitis, grade 1 as unrelated to study drug bosutinib and to concomitant medications.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (28Sep2017): New information received from the CRO includes: an additional non-serious event was reported: on 06Jul2017, the subject developed hyperkalemia which was rated grade 1. In response to the event, the subject received sodium polystyrene sulfonate (KAYEXALATE) and the dose of bosutinib was not changed. The event resolved on 07Jul2017. The investigator considered this event as unrelated to study drug bosutinib and as unrelated to concomitant medications. The event was not considered as significant by the investigator and this was the reason why the investigator did not declare it earlier.

Follow-up (12Oct2017): New information includes: polyuria onset date and seriousness assessment.

Follow-up (13Sep2018): New information received from the investigator via the CRO is as follows: The previously reported event of polyuria was removed by the investigator. Polyuria was part of the subject's medical history. Bronchitis was rated grade 2 and not grade 1. The subject experienced diarrhea on 11Apr2017, and benign hypertrophy of prostate in 2017, both assessed as non-serious and rated grade 1. No action was taken with bosutinib in response to diarrhea and benign hypertrophy of prostate. At the time of the report, the subject had not recovered yet from diarrhea and benign hypertrophy of prostate. On 23Apr2018, the subject presented with exertional dyspnea reported as probably related to heart failure. Exertional dyspnea was not considered as an adverse event by the investigator. The investigator considered the events diarrhea and benign hypertrophy of prostate as unrelated to bosutinib and unrelated to a concomitant medication.

Follow-up(16Jan2020): New information received from the clinical team was as follows: Event hyperkalemia was deleted from the e-CRF.

Follow-up (12Feb2021) : New information received from the study site includes: the event diarrhea resolved on 08Aug2017.

Follow-up (12Feb2021): New information received from the study site includes: Cephalgia resolved on 13Dec2016.

Follow-up (18Feb2021): New information received from the study site via clinical team upon monitoring included: additional events dyslipidemia increased, Vitamin D deficiency, renal failure increased and lumbar pain (grade 1).

In Mar2017, dyslipidemia increased and required atorvastatin (TAHOR) introduction. This event was rated as grade 2 and considered as related to bosutinib. Outcome was unknown.
In Mar2017, the patient also presented with renal failure increased which was rated as grade 2 and related to bosutinib. This event was ongoing.
In Aug2017, the patient presented with Vitamin D deficiency rated as grade 2 and considered as unrelated to bosutinib. Outcome was unknown.
In Feb2018, the patient experienced lumbar pain which was rated as grade 1 and considered as unrelated to bosutinib. The event resolved in Feb2018.

Follow-up (17Nov2021): New information received from the study site via CRO includes: Outcome of dyslipidemia increased updated to resolved (31Aug2017) and vitamin D deficiency outcome updated to resolved (29Mar2018).
The patient received bosutinib (BOSULIF) until 12Jun2019 at 300 mg 1x/day then since 13Jun2019 (Batch/Lot number: unknown) at 200 mg daily. No action was taken with bosutinib in response to these events.

Follow-up (10May2022): This is a follow-up report combining information from duplicate reports 2016398918 and 202101617893. The current and all subsequent follow-up information will be reported under manufacturer report number 2016398918. New information updated the event term "renal failure" to "slight aggravation of renal failure", provided action taken in response to this event, provided causality, and reported lumbar pain as grade 1.

Follow-up (14Nov2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from the clinical team in the context of reconciliation for protocol B1871047.
Updated information included: Ongoing fatigue was added as medical history.

Case Comment: Based on the information available, the Company (Pfizer) is in agreement with the investigator that there was a reasonable possibility that fatigue grade 2 and cephalgia grade 2 were related to the study medication bosutinib. Similarly, the Company cannot completely exclude the possible causality between the reported dyslipidemia increased, Vitamin D deficiency, renal failure increased and the administration of bosutinib. Conversely, there was not a reasonable possibility that the events thyroid nodules (grade 1), bronchitis (grade 1), diarrhea, benign hypertrophy of prostate, lumbar pain, and vitamin D deficiency were related to the study medication bosutinib. This case will be re-assessed should additional information become available.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet;	200 mg, 1x/day; Unknown	Unknown	07-JUN-2016 /

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #2			13-JUN-2016; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	Unknown	14-JUN-2016 / 12-JUN-2019; 2 years 11 months 30 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Unknown	Unknown	13-JUN-2019 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1986 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
04-AUG-2015 to Ongoing	Relevant Med History	Adenocarcinoma pancreas (Adenocarcinoma pancreas); currently monitored by MRI, operated in 2015
2015 to 2015	Relevant Med History	Cancer surgery (Cancer surgery);
2013 to Ongoing	Relevant Med History	Coronaropathy (Coronary artery disease); with stent in 2013 (coronary and femoral)
2013 to Ongoing	Relevant Med History	Stent insertion NOS (Stent placement); coronary and femoral
Unknown to Ongoing	Relevant Med History	Rheumatoid arthritis (Rheumatoid arthritis);
Unknown to Ongoing	Relevant Med History	Widal syndrome (NSAID exacerbated respiratory disease);
APR-2016 to Ongoing	Relevant Med History	Cardiac arrhythmia (Arrhythmia);
APR-2016 to Ongoing	Relevant Med History	Atrial fibrillation (Atrial fibrillation);
Unknown to Ongoing	Relevant Med History	Hypertension pulmonary (Pulmonary hypertension);
Unknown to Ongoing	Relevant Med History	Unilateral renal artery stenosis (Renal artery stenosis);
Unknown to Ongoing	Relevant Med History	Urothelium erosion (Urothelium erosion);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);
Unknown to Ongoing	Relevant Med History	Asthenia (Asthenia);
Unknown to Ongoing	Relevant Med History	Chronic renal failure (Chronic kidney disease);
Unknown	Relevant Med History	Polyuria (Polyuria);
Unknown to Ongoing	Relevant Med History	Fatigue (Fatigue);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1942	74 Years	Male	82.00 kg	03	JUN	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Acute renal failure (on pre-existing chronic renal failure) [Acute kidney injury]
Acute renal failure [Acute kidney injury]
Decompensation cardiac with two episodes of pleural effusion [Cardiac failure]
Decompensation cardiac [Cardiac failure]
Decompensation cardiac with pleural effusion [Cardiac failure]
cardiac decompensation [Cardiac failure]
left ear hearing loss [Deafness unilateral]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) SPRYCEL (DASATINIB MONOHYDRATE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 200 mg, 1x/day
#2) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 03-JUN-2016 / 09-JUN-2016
#2) Unknown

19. THERAPY DURATION
#1) 7 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ELIQUIS (APIXABAN) ; 10-APR-2016 / Ongoing
#2) BISOPROLOL (BISOPROLOL) ; 01-JUN-2005 / Ongoing
#3) SPIRONOLACTONE (SPIRONOLACTONE) ; 2014 / Ongoing
#4) TAHOR (ATORVASTATIN CALCIUM) ; 26-OCT-2015 / Ongoing
#5) NOVONORM (REPAGLINIDE) ; 25-JAN-2010 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1995 to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus)
2001 to Ongoing	Relevant Med History	Cardiac arrhythmia (Arrhythmia)
	Cardioversions in 2001, 2013, 2014 and 2015	

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016399142

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

anorexia [Decreased appetite]
fatigue [Fatigue]
hyperthermia [Hyperthermia]
cephalgia [Headache]
diarrhea [Diarrhoea]
Nausea [Nausea]
Bronchial infection [Bronchitis]
Bronchial infection [Bronchitis]
Otitis media acute [Otitis media acute]
Several palpitations [Palpitations]
Dyspnea [Dyspnoea]
Dysphonia [Dysphonia]
lower limbs oedema [Oedema peripheral]
lower limbs oedema [Oedema peripheral]
dyspnea [Dyspnoea]
onychomycosis of the hallux [Onychomycosis]
vitamin D deficiency [Vitamin D deficiency]
back pain [Back pain]
VESTIBULAR SYNDROME [Vestibular disorder]
fatigue [Fatigue]
appetite decrease [Decreased appetite]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 74-year-old male patient received bosutinib (BOSULIF), first regimen from 03Jun2016 to 09Jun2016 at 200 mg 1x/day, second regimen from 10Jun2016 to 16Jun2016 at 300 mg 1x/day, third regimen from 17Jun2016 to 12Jul2016 at 400 mg 1x/day, fourth regimen from 13Jul2016 to 31Jul2016 at 300 mg 1x/day and fifth regimen from 01Aug2016 to 02Aug2016 at 100 mg 1x/day; dasatinib monohydrate (SPRYCEL), first regimen (Batch/Lot number: unknown) at 100 mg daily and second regimen since 26Oct2016 (Batch/Lot number: unknown) at 70 mg daily; candesartan (CANDESARTAN), from 02Jun2016 (Batch/Lot number: unknown) to 14Apr2017, oral for hypertension. The patient's relevant medical history included: "Type 2 diabetes mellitus", start date: 1995 (ongoing); "cardiac arrhythmia by atrial fibrillation", start date: 2001 (ongoing), notes: Cardioversions in 2001, 2013, 2014 and 2015; "cardiac arrhythmia by atrial fibrillation", start date: 2001 (ongoing), notes: Cardioversions in 2001, 2013, 2014 and 2015; "dilated cardiomyopathy", start date: 2000 (ongoing); "arterial hypertension", start date: 2002 (ongoing); "chronic renal failure", start date: 2010 (ongoing); "Hodgkin's lymphoma", start date: 1999 (unknown if ongoing); "Non-ischaemic cardiomyopathy", start date: 2000 (ongoing); "Dyslipidemia" (ongoing). Concomitant medication(s) included: ELIQUIS oral taken for arrhythmia, atrial fibrillation, start date: 10Apr2016 (ongoing); BISOPROLOL oral taken for cardiomyopathy, start date: 01Jun2005 (ongoing); SPIRONOLACTONE oral taken for hypertension, start date: 2014 (ongoing); TAHOR, start date: 26Oct2015 (ongoing); NOVONORM, start date: 25Jan2010 (ongoing).
On 03Jun2016, the subject experienced anorexia grade 3, fatigue grade 2, hyperthermia grade 1, cephalgia grade 1, and diarrhea grade 2. All the events were assessed as non-serious by the investigator except fatigue for which the investigator did not provide seriousness criterion. The subject presented with anorexia associated with weight loss, and persistent diarrhea despite modification of dose affecting the subject's weight. No action was taken with bosutinib in response to hyperthermia and cephalgia. Bosutinib was withdrawn on 03Aug2016 in response to diarrhea. As a result of the events anorexia and fatigue the study drug bosutinib was withdrawn. On 03Jun2016, the subject experienced nausea grade 2, assessed as non-serious. In response to the event, bosutinib was withdrawn temporarily. On 05Jun2016, the subject was hospitalized for planned insertion of cardiac defibrillator insertion for treatment of cardiac arrhythmia by atrial fibrillation. The same day, a grade 2 acute renal failure on pre-existing chronic renal failure was discovered. The investigator considered this event acute renal failure (on pre-existing chronic renal failure) as unrelated to both bosutinib and concomitant medications. This event acute renal failure (on pre-existing chronic renal failure) was related to dehydration. The subject was treated by rehydration as corrective treatment leading to subject recovery on 06Jun2016. The subject was discharged the same day. The cardiac defibrillator insertion was then rescheduled on 27Jun2016. On 13Jul2016, the subject experienced dysphonia grade 1, assessed as non-serious. As a result of this event study drug was withdrawn. The investigator initial aware date for the event dysphonia was 13Jul2016. The Investigator considered this event as clinically non-significant. No action was taken on bosutinib as a result of this event. On 01Oct2016, the subject experienced fatigue assessed of grade and considered non-serious. The event recovered on 30Oct2016. On 11Oct2016, the subject experienced bronchial infection grade 2, assessed as non-serious. The subject received amoxicillin, clavulanic acid (AUGMENTIN) as corrective treatment. In response to the event, dasatinib monohydrate (SPRYCEL) daily dose was reduced, and not applicable for BOSULIF. On an unspecified date in Dec2016, the subject experienced another episode of bronchial infection grade 2, assessed as non-serious. The subject received amoxicillin, clavulanic acid (AUGMENTIN) as corrective treatment. On 26Oct2016, the subject experienced appetite decrease assessed of grade 1 and considered non-serious. The event recovered on 03Jan2017. The event related to dasatinib monohydrate and dasatinib monohydrate dose was reduced from 100mg daily to 70mg daily on 26Oct2016. On 14Dec2016, the subject experienced cardiac

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

decompensation grade 2 with two episodes of pleural effusion on 21Dec2016 and 24Dec2016 (considered symptoms of the event cardiac decompensation), which required hospitalization on 24Dec2016 and was considered as medically significant. Despite the event, dasatinib monohydrate was ongoing. Following this event, furosemide (LASILIX) 60 mg was added to subject's treatment. On an unspecified date laboratory analysis was done and found brain natriuretic peptide at 900 ng/ml and left ventricular ejection fraction at 20-25%. On 12Feb2017, the subject experienced another episode of cardiac decompensation with pleural effusion grade 2 which lead to hospitalization the same day and was considered as medically significant. As a result of the event, the dose of dasatinib monohydrate was reduced. On 01Apr2017, the subject experienced otitis media acute grade 1, assessed as non-serious. Action taken on study drug as a result of the event was reported as not applicable. On 10Apr2017, the subject experienced acute renal failure grade 2 leading to hospitalization and was considered as medically significant, the subject was also hospitalized for diabetes and thyroid checkup. Then, potassium chloride (DIFFU K), warfarin (COUMADINE), tinzaparin (INNOHEP), amoxicillin, clavulanic acid (AUGMENTIN) and paracetamol (DOLIPRANE) were added to subject's treatment. In response to the event acute renal failure, candesartan was discontinued on 14Apr2017. On 10Apr2017, the subject experienced vitamin D deficiency assessed of grade 1 and considered non-serious and was treated (unspecified treatment). The event recovered on 14Apr2017. On 12Apr2017, the subject experienced vestibular syndrome assessed of grade 2 and considered non-serious. The event had not recovered. On 13Apr2017, the subject experienced another episode of cardiac decompensation with pleural effusion grade 2 which required hospitalization or prolongation of hospitalization and was considered as medically significant. As a result of the event, dasatinib monohydrate was temporarily or permanently withdrawn. In Apr2017, the subject experienced onychomycosis of the hallux assessed of grade 1 and considered non-serious. The event recovered in Apr2017. On 26Jul2017, the subject experienced back pain assessed of grade 1 and considered non-serious. The event recovered on 02Oct2017. On 23Aug2017, the subject experienced several palpitations grade 1 and dyspnea grade 1, assessed as non-serious. The subject consulted a cardiologist at emergency department the same day. Action taken on study drug as a result of the events was reported as not applicable. On 23Aug2017, the subject experienced lower limbs oedema assessed of grade 1 and considered non-serious. The event recovered on 02Oct2017. In 2017, the subject experienced left ear hearing loss assessed of grade 2 and considered non-serious. The event was not resolved. On 15Mar2018, the subject experienced lower limbs oedema assessed of grade 1 and considered non-serious. The event recovered on 20Jul2018. On 29Mar2018, the subject experienced cardiac decompensation assessed grade 2, which required hospitalization and was considered as medically significant. The subject was hospitalized from 29Mar2018 to 30Mar2018 for decompensation cardiac and the subject had sodium and water retention depletion. The event recovered on 30Mar2018. In 2018, the subject experienced dyspnea assessed of grade 1 and considered non-serious. The investigator reported dyspnea rather nocturnal for many months with normal cardio-pulmonary auscultation without other signs of cardiac insufficiency and balanced cardio treatment. The event recovered on 20Jul2018. On 13Jul2016, the subject had fully recovered from hyperthermia and cephalgia. At the reporting time, the subject had not recovered yet from fatigue. The subject recovered from event Diarrhea on 12Sep2016. The subject recovered from the event anorexia on 12Sep2016. The outcome of the event acute renal failure (on pre-existing chronic renal failure) (onset date 05Jun2016) was recovered on 06Jun2016. The event nausea recovered on 12Sep2016. The event bronchial infection (onset date 11Oct2016) recovered with sequelae on Dec2016. The event bronchial infection (onset date Dec2016) recovered on 03Jan2017. The event "cardiac decompensation with two episodes of pleural effusion" (onset date 21Dec2016) recovered on 03Jan2017. The event "cardiac decompensation with pleural effusion" (onset date 12Feb2017) recovered with sequelae on 21Feb2017. The event cardiac decompensation with pleural effusion (onset date 13Apr2017) recovered with sequelae on 13Apr2017. The event otitis media acute recovered on Apr2017. On 14Apr2017, the subject recovered from the event acute renal failure (onset date10Apr2017). The events several palpitations and dyspnea recovered on 23Aug2017. The event dysphonia recovered on 03Aug2016. On 24Apr2023, the outcome of the event fatigue with start date of 03Jun2016 was recovered on 12Sep2016. Unspecified treatment was received for the event onychomycosis. It was also reported that the subject experienced rather nocturnal dyspnea (reported under dyspnea) for several months with normal cardiopulmonary auscultation without other signs of heart failure. Cardio balance treatment. Dysphonia was considered not clinically significant by doctor (privacy). Bosutinib from 13Jul2016 at 300 mg, (AE - diarrhea), from 01Aug2016 at 100 mg (AE - anorexia, diarrhea, asthenia, nausea), permanently withdrawn (intolerance) on 02Aug2016.

The investigator considered there was a reasonable possibility that the events anorexia, fatigue, hyperthermia, cephalgia and diarrhea, nausea were related to the study medication bosutinib, but unrelated to a concomitant medication. According to the Investigator, the events bronchial infection, otitis media acute, several palpitations, dyspnea and dysphonia were not related to study drug bosutinib or concomitant medication. According to the investigator, the event "cardiac decompensation with pleural effusion" was not related to study drug bosutinib but related to dasatinib monohydrate. According to the Investigator, the event acute renal failure was not related to study drug bosutinib but related to candesartan. The investigator considered that there was not a reasonable possibility that the event lower limb oedema (23Aug2017), cardiac decompensation (29Mar2018), lower limbs oedema (15Mar2018), dyspnea (2018), left ear hearing loss (13Dec2017), onychomycosis of the hallux (Apr2017), vitamin D deficiencys (10Apr2017), back pain (26Jul2017) was related to study drug or to concomitant drug. The investigator considered that there was not a reasonable possibility that the event fatigue (01Oct2016), appetite decrease (26Oct2016) was related to study drug but related to concomitant drug dasatinib monohydrate (SPRYCEL).

The reporter considered "acute renal failure (on pre-existing chronic renal failure)", "acute renal failure", "decompensation cardiac with two episodes of pleural effusion", "decompensation cardiac", "decompensation cardiac with pleural effusion", "cardiac decompensation", "left ear hearing loss", "bronchial infection", "otitis media acute", "several palpitations", "dyspnea", "dysphonia", "lower limbs oedema", "dyspnea", "onychomycosis of the hallux", "vitamin d deficiency", "back pain", "vestibular syndrome", "fatigue" and "appetite decrease" not related to bosutinib. The reporter considered "anorexia", "fatigue", "hyperthermia", "cephalgia", "diarrhea" and "nausea" related to bosutinib.

Follow-up attempts are completed. No further information is expected.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (11Oct2017): New information received included: drug data, new event acute renal failure (on pre-existing chronic renal failure), concomitant medication and medical history.

Follow-up (12Oct2017): This is a follow-up report combining information from duplicate reports 2017420358 and 2016399142. The current and all subsequent follow-up information will be reported under manufacturer report number 2016399142.
The new information reported from a CRO and Clinical team included: medical history information updated; lab data; dosage regimens updated; new events (acute kidney injury; decompensation cardiac with pleural effusion; nausea; bronchial infection; otitis media acute; Several palpitations; dyspnea; dysphonia); new suspect drugs (candesartan; dasatinib monohydrate); events outcome.

Follow-up (04Dec2017): No follow-up attempts completed. No further information expected.

Follow-up (09Nov2018): New information received includes: new events lower limb oedema (23Aug2017), cardiac decompensation (29Mar2018), lower limbs oedema (15Mar2018), dyspnea (2018), left ear hearing loss (13Dec2017), onychomycosis of the hallux (Apr2017), vitamin D deficiency (10Apr2017), back pain (26Jul2017), dizziness (12Apr2017), fatigue (01Oct2016), appetite decrease (26Oct2016) added.

Follow-ups (17Nov2021): New information received from investigational site via CRO included: updated stop date for the event bronchial infection which occurred on 11Oct2016, action taken of SPRYCEL and BOSULIF regarding the event bronchial infection which occurred on 11Oct20216, updated verbatim, onset date, stop date for the event Decompensation cardiac on 12Feb2017.

Follow-up (24Apr2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site CRO.
Updated information: event details (outcome of the event 'Fatigue' with onset date 03Jun2016 updated from not recovered to recovered), treatment received for the event 'Onychomycosis'), new event of 'Nocturnal dyspnea', suspect drug details (dosing regimen of Bosulif), and event course details.

Follow-up (19Jun2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site CRO.
Updated information: Bosulif dosage details and events details.

Amendment: This follow-up report is being submitted to amend previously reported information: update recovery date of otitis media acute from 21Apr2017 to Apr2017; start date of decompensation cardiac from 21Dec2016 to 14Dec2016; start date of left ear hearing loss grade 2 from 13Dec2017 to 2017, outcome to not recovered; and verbatim and coding of dizziness grade 1 to vestibular syndrome grade 2.

Amendment:This follow-up report is being submitted to amend previously reported information: to amend outcome and recovery date of the event "Diarrhea" from not recovered to recovered on 12Sep2016.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from clinical team following reconciliation between clinical and safety databases. Updated information: the events "nocturnal dyspnea" and all the events "pleural effusion" were removed from events tab.

Case Comment: Based upon FU the events nocturnal dyspnea and pleural effusion were removed.

Based on available information, the events acute renal failure (on pre-existing chronic renal failure), cardiac failure, bronchitis, otitis media acute, dyspnea, dysphonia, palpitations, lower limb oedema, cardiac decompensation, lower limbs oedema, dyspnea, left ear hearing loss, onychomycosis of the hallux, vitamin D deficiency, back pain, vestibular syndrome, fatigue (onset 01Oct20216) and appetite decrease (onset 26Oct20216) are assessed as unrelated to bosutinib (BOSULIF). The rest of the events are assessed as related to bosutinib based on temporal association and the suspect drug's safety profile. This case will be reassessed should additional information becomes available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Auscultation	NORMAL	
2		Brain natriuretic peptide	900 ng/ml	
3		Ejection fraction	20 - 25 %	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION

Mfr. Control Number: 2016399142

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, 1x/day; Unknown	Unknown	10-JUN-2016 / 16-JUN-2016; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, 1x/day; Unknown	Unknown	17-JUN-2016 / 12-JUL-2016; 26 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	300 mg, 1x/day; Unknown	Unknown	13-JUL-2016 / 31-JUL-2016; 19 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	100 mg, 1x/day; Unknown	Unknown	01-AUG-2016 / 02-AUG-2016; 2 days
#2) SPRYCEL (DASATINIB MONOHYDRATE) ; Regimen #2	70 mg, daily; Unknown	Unknown	26-OCT-2016 / Unknown; Unknown
#3) CANDESARTAN (CANDESARTAN) ; Regimen #1	UNK; Oral	arterial hypertension (Hypertension)	02-JUN-2016 / 14-APR-2017; 317 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2001 to Ongoing	Relevant Med History	Atrial fibrillation (Atrial fibrillation); Cardioversions in 2001, 2013, 2014 and 2015
2000 to Ongoing	Relevant Med History	Dilated cardiomyopathy (Dilated cardiomyopathy);
2002 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
2010 to Ongoing	Relevant Med History	Chronic renal failure (Chronic kidney disease);
1999 to Unknown	Relevant Med History	Hodgkin's lymphoma (Hodgkin's disease);
2000 to Ongoing	Relevant Med History	Non-ischaemic cardiomyopathy (Cardiomyopathy);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE	16	APR	1977	39 Years	Female	70.00 kg	01	JUN	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Threat of premature delivery [Complication of pregnancy]
Flatulence grade 1 [Flatulence]
Diarrhea grade 1 [Diarrhoea]
Diarrhea [Diarrhoea]
Gastroesophageal reflux disease [Gastrooesophageal reflux disease]
Left hypochondrial pain [Abdominal pain upper]
Throat pain [Oropharyngeal pain]
Dizziness [Dizziness]
night sweats [Night sweats]
pregnancy by implantation [Maternal exposure during pregnancy] **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 14-APR-2016 / 48 days

19. THERAPY DURATION
#1) 48 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; FEB-2015 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown		Date of LMP for pregnancy
JAN-2001 to JAN-2001	Relevant Med History	Pneumopathy (Lung disorder)
FEB-2015 to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016418217

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician) for protocol B1871047.

A 39-year-old female patient (pregnant) received bosutinib (BOSULIF), first regimen since 14Apr2016 for 48 days at 100 mg 1x/day, second regimen from May2016 to 31May2016 at 200 mg 1x/day, third regimen since 01Jun2016 at 300 mg 1x/day, fourth regimen from 23Mar2017 to 06May2017 at 200 mg daily, fifth regimen from 15Feb2018 to 24Feb2018 at 100 mg 1x/day, sixth regimen from 25Feb2018 to 04Apr2018 at 200 mg 1x/day and seventh regimen since 05Apr2018 (ongoing) at 300 mg 1x/day. The patient's relevant medical history included: "Pneumopathy", start date: Jan2001, stop date: Jan2001; "hypothyroidism", start date: Feb2015 (ongoing); "Uterus conization", start date: Aug2011, stop date: Aug2011, notes: for intraepithelial lesions and endometriosis; "endometriosis" (unspecified if ongoing); "pre-menopause" (unspecified if ongoing); "gravida 3" (unspecified if ongoing); "parity 2" (unspecified if ongoing), notes: 2 vaginal deliveries in 2002 and 2004; "chronic myeloid leukemia" (unspecified if ongoing); "Parity", start date: 2002, stop date: 2002; "intraepithelial lesions" (unspecified if ongoing), notes: for intraepithelial lesions and endometriosis; "Parity", start date: 2004, stop date: 2004. Concomitant medication(s) included: LEVOTHYROX oral taken for hypothyroidism, start date: Feb2015 (ongoing).
On 01Jun2016, the subject experienced flatulence grade 1 and diarrhea grade 1, which were assessed as non-serious by the investigator. In Feb2018, the subject experienced gastroesophageal reflux disease which considered as non-serious by the investigator. Action taken in response to diarrhea (01Jun2016) was dose reduced. Therapeutic measures were taken as a result of the diarrhea which included loperamide hydrochloride (IMODIUM) via oral route on 01Jun2016 and ongoing; and for the gastroesophageal reflux disease, pantoprazole (INIPOMP) and sodium alginate/sodium bicarbonate/calcium carbonate (GAVISCON) were given orally from Feb2018 to 05Apr2018. The outcome of the events gastroesophageal reflux disease grade 2 was not recovered, flatulence grade 1 was recovered on 30Jun2016, diarrhea grade 1 was recovered on May2017.
As of 09Jun2017, she was recently treated by bosutinib 200 mg per day. The subject became pregnant following in vitro fecondation with re-implantation on 15May2017. Bosutinib was already stopped 15 days prior to the re-implantation, i.e over than 5 half-lives of the study drug as the subject had stopped bosutinib in mid Apr2017. Pregnancy end date was 21Jan2018. The outcome of maternal exposure during pregnancy was recovered on 21Jan2018.
The investigator reported that there was then no exposure of the embryon because it was an in vitro fecondation with re-implantation. The investigator considered that no safety notification was therefore needed. The clinical team considered that given that the embryon was developing in the mother's uterus previously exposed within the 28-day time limit after bosutinib withdrawal, a safety notification was needed.
However, the investigator reported that the 28 days were related to the uncertainty on the real onset date of pregnancy but reportedly, it was not the case here. Then, the investigator declined to notify the pregnancy to safety department.
In Jul2017, the subject presented with dizziness which was considered as non-serious and grade 1. Dizziness resolved in Nov2017.
In Oct2017, the subject experienced throat pain which was considered as non-serious and grade 1. Antibiotics drugs were introduced via oral route in from Oct2017 to 18Oct2017 for throat pain. The throat pain was resolved in Nov2017.
On 29Nov2017, the subject experienced left hypochondrial pain which was considered as non-serious and grade 2. She also presented with threat of premature delivery on the same day which required hospitalization and was considered as grade 2.
From 29Nov2017 to 01Dec2017, intramuscular corticosteroids therapy was taken for fetal pulmonary maturation and nifepine (ADALATE) tocolysis was done for threat of premature delivery. She recovered from left hypochondrial pain and threat of premature delivery on 04Dec2017. The action taken with study drug in response to these events was reported as not applicable.
It was reported that a full term normal baby was born on 21Jan2018 at 37 weeks of amenorrhea and 6 days. The doctor reported that the mother gave birth in the hematology unit on 21Jan2018. Current pregnancy was obtained by oocyte donation. This pregnancy was marked by a threat of preterm birth at 30 weeks of amenorrhea who succumbed after tocolysis by nifedipine (ADALATE). The pregnancy finally continued to 37 weeks of amenorrhea and 6 days when the water pocket was broken. The mother did not start labour spontaneously, she was triggered by prostine (gel) 24 hours after the water pocket break. The mother gave birth to a male baby. The baby's weight was 2660 g and APGAR Score at 1 min was 10 and APGAR Score at 5 min was 10 (APGAR 10/10/10), PH was 7.26 and lactate was 2.
The subject presented with night sweats in Dec2018, which rated grade 2. The action taken with study drug in response to the event was not reported. It was also specified that the subject was considering an in vitro pregnancy, the investigator indicated that bosutinib would be stopped 15 days before ovarian stimulation. In response to the event night sweats, no action was taken with bosutinib. The outcome of night sweats was resolved on 04Apr2019.
On an unspecified date in Apr2019, the subject developed diarrhea, rated grade 1 and considered as not serious. No action was taken with bosutinib in response to the event diarrhea. The diarrhea was not yet resolved. The last action taken for bosutinib in response to events was dosage reduced.

The reporter considered "flatulence grade 1", "diarrhea grade 1" and "diarrhea" (both episodes) related to bosutinib but not related to concomitant treatment. The reporter considered "threat of premature delivery", "gastroesophageal reflux disease", "left hypochondrial pain", "throat pain", "dizziness" and "night sweats" not related to bosutinib or to concomitant treatment.

Follow-up (09Jun2017): New information received from the clinical team includes: The complete birthdate of the subject was provided, medical history, new event 'the mother's uterus previously exposed' added.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (27Jun2017): New information received from the CRO includes: suspect product data (frequency), reaction data (previously reported event 'uterus previously exposed' deleted and reported in fetal case).

Follow-up (27Jun2018): New follow-up information was received from the study site includes: product data (additional dosage regimens), new events (gastroesophageal reflux disease, nausea, aliementary pseudoblocking feeling) and causality for new events.

Follow-up (04Jul2018): New information received from the study sites includes: Subject's height and weight, new events (Pruritus, Threat of premature delivery, Left hypochondrial pain, Throat pain, Dizziness).

Follow-up (13Jun2019): New information received from the study sites includes: new events (night sweats and Diarrhea).

Follow-up (01Oct2019 and 08Oct2019): This is a follow-up report combining information from duplicate reports AER 2017287694 (fetus case) and AER 2016418217 (mother case). The current and all subsequent follow-up information will be reported under manufacturer report number AER 2016418217. New information included medical history, concomitant medication and neonates' information. Additional information received on 01Oct2019 from the investigational included outcome of events Flatulence and diarrhea updated from not recovered to recovered and recovery date, action taken in response to diarrhea was dose reduced (previously dose not changed), pregnancy end date was 21Jan2018.

No follow-up attempt needed. No further information expected.

Follow-up (03Dec2019): New information received included: dosage regimens and action taken of bosutinib; outcome, stop date and causality of event night sweats; new event (diarrhea on Apr2019).

No follow-up attempt needed. No further information expected.

Follow-up (20Dec2019): New information reported from CRO stated that in response to the event night sweats, no action was taken with bosutinib.

Amendment: This follow-up report is being submitted to amend previous information: Outcome and recovery date of maternal exposure during pregnancy (resolved on 21Jan2018).

Follow-up (06Sep2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician) for protocol B1871047.
Upadted information includes: administration date of Bosutinib at 200 mg, 1x/day was from May2016 to 31May2016; event term "maternal exposure during pregnancy" was updated to "pregnancy by implantation", events pruritus, nausea and alimentary pseudoblocking feeling were removed, night sweats was rated grade 2; treatment of IMODIUM was ongoing since 01Jun2016.

Follow-up (03Oct2023): This is a non-interventional study follow-up report received from the clinical team in response to query;) for protocol B1871047. Updated information includes: fourth dosing regimen details confirmed as 200 mg, daily received from 23Mar2017 to 06May2017. Confirmed also that nausea and alimentary pseudoblocking feeling were symptoms of Gastroesophageal reflux disease.

Case Comment: Based on the information currently provided, the Company concurs with the causality assessment provided by the investigator, considering there was a reasonable possibility that the events flatulence grade 1 and diarrhea grade 1 (both episodes) was related to the study medication bosutinib given the known suspect drug profile and/or plausible temporal association. Conversely, the reported gastroesophageal reflux disease, threat of premature delivery, left hypochondrial pain, throat pain and dizziness are considered unlikely related to the study drug, bosutinib, but most likely related to the current onset of pregnancy. The event night sweats is assessed as unrelated to bosutinib based on the limited information and known product safety profile.
The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	Unknown	MAY-2016 / 31-MAY-2016; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	Unknown	01-JUN-2016 / Unknown; Unknown

Mfr. Control Number: 2016418217

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Unknown	Unknown	23-MAR-2017 / 06-MAY-2017; 1 month 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	100 mg, 1x/day; Unknown	Unknown	15-FEB-2018 / 24-FEB-2018; 10 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	200 mg, 1x/day; Unknown	Unknown	25-FEB-2018 / 04-APR-2018; 39 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	300 mg, 1x/day; Unknown	Unknown	05-APR-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
AUG-2011 to AUG-2011	Relevant Med History	Cervical conization (Cervical conisation); for intraepithelial lesions and endometriosis
Unknown	Relevant Med History	Endometriosis (Endometriosis);
Unknown	Relevant Med History	Premenopause (Menopause);
Unknown	Relevant Med History	Multiparous (Multiparous);
Unknown	Relevant Med History	Parity 2 (Multiparous); 2 vaginal deliveries in 2002 and 2004
Unknown	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);
2002 to 2002	Relevant Med History	Parity (Parity);
Unknown	Relevant Med History	Cervical intraepithelial neoplasia (Cervical dysplasia); for intraepithelial lesions and endometriosis
2004 to 2004	Relevant Med History	Parity (Parity);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		DEC	1980	35 Years	Female	92.00 kg		JUN	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Sleep apnea syndrome [Sleep apnoea syndrome]
Tumefaction of the right eye [Eye swelling]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 18-APR-2016 / 01-MAY-2016	#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) IMODIUM (LOPERAMIDE HYDROCHLORIDE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
14-DEC-1980 to Ongoing	Relevant Med History pituitary insufficiency	Pituitary insufficiency (Hypopituitarism)
2004 to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016418238

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional clinical study case reporting non-serious events only. A 35-year-old female subject started to receive bosutinib (BOSULIF), via oral route of administration, on 18Apr2016 through 01May2016, at 100 mg daily, then 200 mg daily from 02May2016 to 15May2016, then at 300 mg daily since 16May2016 to 20Apr2017, and then from 21Apr2017 to 30Jun2017 at 400 mg daily for chronic myeloid leukemia. Relevant medical history included pituitary insufficiency ongoing since 14Dec1980; diabetes since 2004 and ongoing; right tibia and fibula fracture in 1996; cholecystectomy on 08Feb2016. Concomitant medications included loperamide hydrochloride (IMODIUM) at 1 dosage form thrice daily from an unspecified date. In Jun2016, the subject started to experience 3 daily episodes of diarrhea. On 30Jun2016, she developed hematomas on lower limbs while platelet count was normal at 167 x10^9/L (N: 150-400). The event hematoma was assessed by the investigator as non-clinically significant, thus not graded. The subject underwent lab tests and procedures which included on 30Jun2016: white blood cell count 9.7 x10^9/L (N: 4.0 -10.0), red blood cell count 4.64 x10^12/L (N: 4.1 - 5.2), hemoglobin 13.1 g/dl (N: 12.0 - 16.0), hematocrit 41.5 % (N: 36-45), mean corpuscular volume 89.5 fl (N: 85 - 95), mean corpuscular hemoglobin 28.2 pg (N: 28 - 32), mean corpuscular hemoglobin concentration 31.6 g/dl (N: 32 -36), red blood cell distribution width 12.8 (N: 11.5 -18.0), mean platelet volume 5.9 fl (N: 6.4 - 12.0), neutrophil count 6.00 x10^9/L (N: 1.7 -7.0), lymphocyte count 3.00 x10^9/L (N: 1.5 - 4.0), monocyte count 0.57 x10^9/L (N: 0.1 -1.0), eosinophil count 0.06 x10^9/L (N < 0.5) and basophil count 0.07 x10^9/L (N < 0.1). Both events were assessed as non-serious by the investigator. On 01Apr2017, the subject started to experienced Sleep apnea syndrome grade 2 which was considered as non-serious event. On 30Jun2017, loss of efficacy was observed. This event was considered as non-serious (grade 1). Additional non-serious event occurred in Jul2017: the subject developed tumefaction of the right eye. Action taken with study drug was reported as not applicable. The last action taken with bosutinib in response to the events diarrhea, hematomas and Sleep apnea syndrome was dose not changed. The subject discontinued study drug on 30Jun2017 due to loss of efficacy. The subject had not recovered yet from hematomas. The subject recovered from diarrhea on 01Mar2017. The event tumefaction of the right eye resolved on 10Aug2017. The subject did not recover from the event Sleep apnea syndrome. The outcome of the event loss of efficacy was unknown.

According to the investigator, the event diarrhea was considered unrelated to a concomitant medication, but related to bosutinib.
The investigator considered there was not a reasonable possibility that the event hematomas was related to bosutinib.
The investigator assessed the event Sleep apnea syndrome as unrelated to bosutinib.
The investigator considered there was a reasonable possibility that loss of efficacy was related to study drug but not related to concomitant medication.
The investigator considered the event tumefaction of the right eye as unrelated to study drug bosutinib and to concomitant medications.

Follow-up (12Sep2016): New information received from the investigator includes: product data (route and indication), concomitant medication data, clinical details, lab data, and causality of event hematomas (unrelated to bosutinib, previously not reported).

Follow-up attempts are completed. No further information is expected.

Follow-up (02May2017): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. New information reported includes: reaction data (added non-serious event somnolence) and outcome of previously reported event diarrhea (from not recovered to recovered on 01Mar2017).

Follow-up (27Jun2017): New information received includes: action taken (updated from unknown to dose not changed), causality (investigator provided causality for event somnolence), and clinical outcome (somnolence updated from unknown to recovered).

Follow-up (04Jul2017): New information received from clinical team includes: the recovery date for the event somnolence.

Follow-up (07May2018): New information received from clinical team includes: reasons for study drug discontinuation.

Follow-up (15May2018): New information received from clinical team includes study drug (date and dosage).

Follow-up (26Jun2018): New information received from the CRO includes: the end date of the bosutinib cycle at 300 mg once a day was 20Apr2017 then the end date of the bosutinib cycle at 400 mg once a day was on 30Jun2017. Additional non-serious event occurred in Jul2017: the subject developed tumefaction of the right eye. The event resolved on 09Aug2017. The action taken with bosutinib was not applicable. The investigator considered the event as unrelated to study drug bosutinib and to concomitant medications.

Follow-up attempts completed. No further information expected.

Follow-up (01Oct2019): New information received from the CRO included: sleep apnea was diagnosed in Dec2017. The event tumefaction of the right eye resolved on 10Aug2017 (instead of 09Aug2017 as previously reported).

Follow-up (18Jul2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: New reporter added (other HCP). Event description updated from "somnolence" to "Sleep apnea syndrome" with outcome updated to "not recovered".

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (07Sep2023): This is a follow-up report received from the CRO.
Updated information included: classification, suspect drug Bosulif details (stop date for 100 mg, start date for 200 mg).

Follow-up (14Nov2023): New information received from Clinical team following reconciliation included: The event Hematoma (30Jun2016) has been removed.

Case Comment: In agreement with the investigator, the event diarrhea was considered related to bosutinib. In addition, the company cannot completely exclude that the event Sleep apnea syndrome was related to suspect drug bosutinib. Event Eye swelling represents an intercurrent medical condition and unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	30-JUN-2016	Basophil count	0.07 x10 9/l	0.1
2	30-JUN-2016	Eosinophil count	0.06 x10 9/l	0.5
3	30-JUN-2016	Haematocrit	41.5 %	45 36
4	30-JUN-2016	Haemoglobin	13.1 g/dl	16.0 12.0
5	30-JUN-2016	Lymphocyte count	3.00 x10 9/l	4.0 1.5
6	30-JUN-2016	Mean cell haemoglobin	28.2 pg	32 28
7	30-JUN-2016	Mean cell haemoglobin concentration	31.6 g/dl	36 32
8	30-JUN-2016	Mean cell volume unit: fl	89.5	95 85
9	30-JUN-2016	Mean platelet volume unit: fl	5.9	12.0 6.4
10	30-JUN-2016	Monocyte count	0.57 x10 9/l	1.0 0.1
11	30-JUN-2016	Neutrophil count	6.00 x10 9/l	7.0 1.7
12	30-JUN-2016	Platelet count	167 x10 9/l	400 150
13	30-JUN-2016	Red blood cell count	4.64 x10 12/l	5.2 4.1
14	30-JUN-2016	Red cell distribution width	12.8	18.0 11.5
15	30-JUN-2016	White blood cell count	9.7 x10 9/l	10.0 4.0

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	02-MAY-2016 / 15-MAY-2016; 14 days

Mfr. Control Number: 2016418238

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	16-MAY-2016 / 20-APR-2017; 340 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	21-APR-2017 / 30-JUN-2017; 71 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
08-FEB-2016 to 08-FEB-2016	Relevant Med History	Cholecystectomy (Cholecystectomy);
1996 to Unknown	Relevant Med History right tibia fracture	Tibia fracture (Tibia fracture);
1996 to Unknown	Relevant Med History	Fibula fracture (Fibula fracture);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE	21	MAY	1959	57 Years	Female	86.00 kg	03	SEP	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Sepsis [Sepsis]
Thyroidectomy [Thyroidectomy]
Hepatic cytolysis [Hepatic cytolysis]
Sleep apnea [Sleep apnoea syndrome]
Eyelid oedema (insect bite) [Eyelid oedema]
Mosquito bite [Arthropod bite]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 300 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 21-AUG-2016 / 04-SEP-2016

19. THERAPY DURATION
#1) 15 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) GLUCOPHAGE (METFORMIN HYDROCHLORIDE) ; Ongoing
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#3) NORSET (MIRTAZAPINE) ; 21-NOV-2016 / Ongoing
#4) LIPANTHYL (FENOFIBRATE) ; 21-NOV-2016 / Ongoing
#5) PRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE] (INDAPAMI
#6) ATARAX [HYDROXYZINE] (HYDROXYZINE) ; Unknown

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus)
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016421841

24c. DATE RECEIVED BY MANUFACTURER
21-FEB-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a report from a Pfizer Sponsored Non-Interventional Study source for Protocol B1871047.

A 57-year-old female subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 21Aug2016 to 04Sep2016 at 300 mg once daily, via an unspecified route of administration from 29Nov2016 to 31Dec2016 at 300 mg daily, via an unspecified route of administration from 01Jan2017 to 31Jan2017 at 400 mg daily, then via an unspecified route of administration from 01Feb2017 and ongoing at 500 mg daily for chronic myeloid leukemia. Medical history included ongoing type 2 diabetes, ongoing hypertension arterial, ongoing chronic obstructive pulmonary disease (COPD) and ongoing obesity, liver steatosis, hypercholesterolemia and depression. Concomitant medications included ongoing metformin hydrochloride (GLUCOPHAGE), ongoing acetylsalicylic acid (KARDEGIC), ongoing mirtazapine (NORSET) from 21Nov2016, ongoing fenofibrate (LIPANTHYL), perindopril arginine, indapamide (PRETERAX), hydroxyzine (ATARAX), alprazolam (unspecified trade name) and pregabalin (LYRICA).
On 04Sep2016, the subject experienced hepatic cytolysis (CTCAE grade 3) which assessed as non-serious. On the same day, laboratory analysis was done and found alanine aminotransferase (normal range: 9 - 52 IU) at 325 IU and aspartate aminotransferase (normal range: 14 - 36 IU) at 478 IU. As a result of the event, bosutinib was temporarily withdrawn the same day. The subject experienced sepsis (CTCAE grade 3) on 03Sep2016, which led to hospitalization. The conclusion of hospitalization was respiratory distress and hypercapnic coma on bilateral interstitial pneumonia without found bacteria. The subject was then transferred in another hospital for recovery phase from 13Sep2016 to 14Oct2016. On an unspecified date in Sep2016, the subject experienced sleep apnea (CTCAE grade 2) which assessed as non-serious. The subject developed eyelid oedema (insect bite) on 26Nov2017 which was considered as a non-serious event. There was no modification of bosutinib dose in response to this event. Additional event was reported as 'thyroidectomy' with onset date (reportedly) on 10Dec2017, which required hospitalization from 10Dec2017 to 13Dec2017. The subject had a multiple heterogenous nodular goiter since 2014 which progressively became uncomfortable. Surgery was planned and performed on 11Dec2017. There was no modification of bosutinib dose in response to this event. Discharge treatment included cholecalciferol, calcium carbonate (CALCIDOSE D3) 500 mg once a day for 10 days and levothyroxin sodium (LEVOTHYROX) 75 ug once a day for 10 days then 100 ug. Additional lab data included on 08Aug2016, AST was 23 IU/l, ALT was 23 IU/l (the normal values for AST were LT 32 IU/l and for ALT were LT 33 IU/l); on 24Aug2016, AST was 37 IU/l, ALT was 35 IU/l; on 04Sep2016, AST was 281 IU/l, ALT was 274 IU/l, and bilirubin was 9 mg/l; on 15Oct2016, AST was 22 IU/l, ALT was 20 IU/l. In Aug2018 the subject experienced fever following the insect bite, grade 1, assessed as non-serious. Action taken with study drug was reported as NA. The subject was transferred to the center 48. As of 22Feb2023 it was reported that the mosquito bite was rated grade 2. The last action taken in response to the events for bosutinib was dose not changed. The outcome of events 'sepsis' and 'sleep apnea' was not recovered, the outcome of event 'hepatic cytolysis' was recovered on 09Sep2016, event 'eyelid oedema (insect bite)' was recovered on 28Nov2017, event 'thyroidectomy' was recovered on 13Dec2017, event 'fever following the insect bite' was recovered in Aug2018. The outcome of events 'sleep apnea' was not recovered, the outcome of event 'sepsis' was recovered on 13Sep2016, 'hepatic cytolysis' was recovered on 09Sep2016, event 'eyelid oedema (insect bite)' was recovered on 28Nov2017, event 'thyroidectomy' was recovered on 13Dec2017, event 'Mosquito bite' was recovered in Aug2018.

The investigator considered the event sepsis as not related to the study drug bosutinib and not related to concomitant medication. The investigator considered that there was a reasonable possibility that the event hepatic cytolysis was related to study drug bosutinib, but not related to concomitant drugs. The investigator considered that there was not a reasonable possibility that the event sleep apnea was related to study drug bosutinib or concomitant drugs. The investigator considered 'thyroidectomy' as unrelated to study drug bosutinib and unrelated to concomitant drugs. The investigator considered the event eyelid oedema (insect bite) as unrelated to study drug bosutinib and unrelated to concomitant drugs. According to the investigator the event ' Mosquito bite ' was not related to study drug or to concomitant treatment.

Follow-up (01Dec2016): New information received includes the subject's age and gender, updated start date of study drug, action taken with the study drug (withdrawn).

Follow-up (10Oct2017): New information reported includes: lab data, product information, and reaction data (added events 'hepatic cytolysis' and 'sleep apnea').

Follow-up (25Jan2018): New information reported includes: subject gender updated, medical history information, concomitant medications information, product information and reaction data (add 'thyroidectomy' and 'eyelid oedema (insect bite)').

Follow-up (11Apr2018): Follow-up attempts completed. No further information expected.

Follow-up (04Jun2018): New information received from clinical team includes: additional lab data, medical history and concomitant medication. It was also confirmed that the event hepatic cytolysis was a new event. The subject did not present with any symptoms.

Follow-up (15Nov2018). New information received from the site via CRO includes: new event (Fever following the insect bite).

Follow-up (05Feb2021): New information received from clinical team in the context of reconciliation includes: bosutinib indication.

Follow-ups (21Feb2023, 22Feb2023 and 22Feb2023): This is a non-interventional study Follow-up reports (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Updated information included: Investigator Initial Aware Date updated, event of 'fever following the insect bite' was recoded to 'Mosquito bite', onset date for the event Sepsis updated to 03Sep2016, stop date added (13Sep2016) and outcome updated to Recovered. Event of thyroidectomy was added.

Case Comment: Based on the clinical information currently provided, the company concurs with the causality assessment expressed by the investigator, considering there is not a reasonable possibility that the event sepsis is related to the suspect, study drug bosutinib. Based on temporal association, there was a reasonable possibility that the event hepatic cytolysis was related to study drug bosutinib, but not related to concomitant drugs. There was not a reasonable possibility that the event sleep apnea was related to study drug bosutinib or concomitant drugs but likely due to intercurremt condition. Event Eyelid oedema (insect bite) and Fever are due to insect bite and unrelated to study drug.
The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	08-AUG-2016	Alanine aminotransferase	23 IU/l	33
2	24-AUG-2016	Alanine aminotransferase	35 IU/l	33
3	04-SEP-2016	Alanine aminotransferase	325 iU	52 9
4	04-SEP-2016	Alanine aminotransferase	274 IU/l	33
5	15-OCT-2016	Alanine aminotransferase	20 IU/l	33
6	08-AUG-2016	Aspartate aminotransferase	23 IU/l	32
7	24-AUG-2016	Aspartate aminotransferase	37 IU/l	32
8	04-SEP-2016	Aspartate aminotransferase	281 IU/l	32
9	04-SEP-2016	Aspartate aminotransferase	478 iU	36 14
10	15-OCT-2016	Aspartate aminotransferase	22 IU/l	32
11	04-SEP-2016	Blood bilirubin	9 mg/l	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	29-NOV-2016 / 31-DEC-2016; 33 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	01-JAN-2017 / 31-JAN-2017; 31 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	500 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	01-FEB-2017 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#5) PRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE] (INDAPAMIDE, PERINDOPRIL ARGININE) ; Unknown

#7) ALPRAZOLAM (ALPRAZOLAM) ; Unknown

Mfr. Control Number: 2016421841

ADDITIONAL INFORMATION

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#8) LYRICA (PREGABALIN) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	COPD (Chronic obstructive pulmonary disease);
Unknown to Ongoing	Relevant Med History	Obesity (Obesity);
Unknown	Relevant Med History	Steatosis hepatic (Hepatic steatosis);
Unknown	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
Unknown	Relevant Med History	Depression (Depression);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1946	70 Years	Female	90.00 kg		MAR	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Arthrosis/Arthrosis worsened [Osteoarthritis]
Diarrhea [Diarrhoea]
Anaemia CTCAE grade 2 [Anaemia]
Digestive disorders [Gastrointestinal disorder]
fatigue [Fatigue]
TSH increased [Blood thyroid stimulating hormone increased]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 17-MAR-2016 / Unknown	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) METFORMIN (METFORMIN) ; 2011 / Unknown
#2) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2011 to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
2012 to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016421941

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
04-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 70-year-old female patient received bosutinib (BOSULIF), first regimen since 17Mar2016 at 500 mg 1x/day, second regimen till Sep2016 at 500 mg 1x/day and third regimen since 28Nov2016 (ongoing) at 500 mg alternate day (500 mg, alternate day (every other day)). The patient's relevant medical history included: "Diabetes", start date: 2011 (ongoing); "Hypothyroidism", start date: 2012 (ongoing); "Cerebrovascular accident", start date: 2011, stop date: 2011; "Hypertension arterial" (ongoing); "Arthrosis" (ongoing). Concomitant medication(s) included: METFORMIN oral taken for diabetes mellitus, start date: 2011; LEVOTHYROX oral taken for hypothyroidism (ongoing). Past drug history included: Sprycel, reaction(s): "pulmonary toxicity ".
On an unknown date in Mar2016, the subject experienced digestive disorders, grade 2, considered as non-serious. The event was described as slight digestive disorders, not specified and discreet unspecified digestive disorders leading to interruption temporary BOSULIF. To note, the investigator also reported that was not an event, there was no clinically significant (NCS) back pain. In response to the event digestive disorders, bosutinib was temporarily stopped on an unspecified date. The event resolved on an unknown date in Mar2016. Bosutinib was resumed on an unspecified date without recurrence of the event. The subject experienced diarrhea in Sep2016, stated as non-serious event. Bosutinib was stopped in Sep2016. The subject decreased dose of bosutinib at 500 mg every other day from 28Nov2016 to ongoing. Dose was not changed on 29Nov2016. The patient had diarrhea, she modified her treatment by herself but her physician made her resume the treatment at full dose during the consultation. The patient reported that she reduced the dose of Bosulif by herself since 3 months at 1 intake every 2 days due to diarrhea. Which was obviously induced by the drug, the diarrhea was ongoing at the beginning of treatment, but recovered on 02May2017 under symptomatic treatment prescribed by a physician, drug that she did not renew until recent recurrence of digestive disorders. The physician had knowledge of this on 28Nov2016.
On an unspecified date in 2017, the subject was hospitalized for knee prosthesis insertion (CTCAE grade 2) because of arthrosis/ arthrosis worsened assessed as serious. Following the surgery, on an unspecified date in 2017, the subject experienced anaemia (CTCAE grade 2) assessed as non-serious. The placement of a knee prosthesis on arthrosis anemia after surgery was known on 02May2017, however onset date provided as only 2017. The action taken in response to these events for bosutinib was dose not changed. The outcome of both events was reported as recovered on an unspecified date in 2017. The subject developed fatigue rated grade 1 on 12Apr2018 which was reported as non-serious. No action was taken with bosutinib in response to the event. The event resolved on 01Aug2018. According to the reporter, the event was unrelated to study drug and to concomitant drug. The subject developed TSH increased, rated grade 1 in Apr2018 which was reported as non-serious. No action was taken with bosutinib in response to the event. The outcome of this event was unknown. According to the reporter, the event was unrelated to study drug and to concomitant drug.
The last biological workup showed complete blood count normal, creatinine and hepatic workup not disturbed. However, BCR ABL was positive again at 0.015 %. The physician insisted on the necessity of perfect observance, only susceptible to preserve on long-term the induced benefit by the treatment. There are few alternative to Bosulif, in a patient who experienced pulmonary toxicity under Sprycel, and who had a contraindication of her cerebrovascular accident under Glivec, drug however less effective and usually much less tolerated that the tyrosine kinase inhibitors of new generation. Of immediate, the patient prefers to continue her treatment with Bosulif at full dose and should consult a physician to resume a symptomatic treatment of diarrhea which allowed a good monitoring. A new monitoring of BCR ABL will be performed in December.
The investigator considered the event digestive disorders as unrelated to bosutinib or to concomitant drugs. The investigator considered the event diarrhea as related to bosutinib and unrelated to concomitant drug. The investigator considered that there was not a reasonable possibility that the events arthrosis/ arthrosis worsened and anaemia were related to study drug bosutinib or concomitant drugs.

Follow-up (20Feb2017 and 20Feb2017): New information received includes: Initial investigator awareness date, new event (diarrhea), medical history, concomitant medication, action taken (updated to dose reduced), therapeutic measures, and clinical course.

Follow-up (10Oct2017): New information was received from CRO on new adverse events knee prosthesis insertion and anemia. The first was assessed as serious and the second and non serious. Both were considered unrelated. New medical history added. Action taken updated. The case become serious with this follow up.

Follow-up (13Feb2019): New information received from CRO includes: new events (fatigue and TSH increased) added.

Follow-up (14Mar2022): This is a non-interventional study follow-up report for protocol B1871047. Updated information included: outcome of event TSH increased updated to unknown.

No follow-up attempt initiated. No further information expected.

Follow-up (25Apr2023, 25Apr2023, and 25Apr2023): This is a non-interventional study follow-up report for protocol B1871047. Updated information included: reaction data (updated stop date of event diarrhea updated from 10Jan2017 to 02May2017), product data, and clinical details on previously reported events digestive disorders and knee prosthesis insertion.

Follow-up (16May2023 and 16May2023): This is a non-interventional study follow-up report for protocol B1871047 and received from the investigational site via the CRO.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Updated information included: event 'knee prosthesis insertion' was updated to 'arthrosis worsened' and 'arthrosis', seriousness, causality assessment were unchanged, 'back pain NCS' previously mentioned was not an event.

Follow-up attempts are completed. No further information is expected.

Follow-up (30May2023): This is a non-interventional study follow-up report for protocol B1871047 and received from the investigational site via the CRO.
Updated information includes additional medical history (arthrosis).

No follow-up attempts are needed. No further information is expected

Follow-up (09Jun2023): This is a non-interventional study follow-up report for protocol B1871047 and received from the investigational site.
Updated information included: past drug (Sprycel), lab data, recurrence of event digestive disorders and rationality of the use of bosutinib.

Follow-up (04Jul2023): This is a non-interventional study follow-up report for protocol B1871047 and received from the investigational site via the CRO.
Updated information included: confirmed medical history arthrosis was ongoing at the event time.

No follow-up attempts are needed. No further information is expected.

Case Comment: A contribution of bosutinib to the event diarrhea is possible based on temporal association and product safety profile. The events arthrosis/arthrosis worsened, anaemia, fatigue, digestive disorder and TSH increased are unlikely related to the suspect drug and can be explained as intercurrent or underlying medical conditions

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Cytogenetic analysis	BCR ABL was positive again at 0.015 %	
2		Full blood count	normal	
		creatinine and hepatic workup not disturbed		

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	500 mg, 1x/day; Unknown	Unknown	Unknown / SEP-2016; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	500 mg, alternate day (every other day); Unknown	Unknown	28-NOV-2016 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2011 to 2011	Relevant Med History	Cerebrovascular accident (Cerebrovascular accident);
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
Unknown to Ongoing	Relevant Med History	Arthrosis (Osteoarthritis);
Unknown	Past Drug Event	Sprycel (SPRYCEL); Drug Reaction: Pulmonary toxicity (Pulmonary toxicity)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE	12	APR	1951	65 Years	Male	80.00 kg		AUG	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Facial neuralgia [Trigeminal neuralgia]
Bronchial superinfection [Bronchitis]
diarrhea [Diarrhoea]
DIARRHEA [Diarrhoea]
ARTHRITIS [Arthritis]
Hands and feet cramps [Muscle spasms]
Dorsopathy [Back disorder]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

15. DAILY DOSE(S)
#1) 300 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 05-AUG-2016 / 17-AUG-2016

19. THERAPY DURATION
#1) 13 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KARDEGIC (ACETYLSALICYLATE LYSINE) ; MAR-2015 / Unknown
#2) URBANYL (CLOBAZAM) ; 27-JUL-2016 / Ongoing
#3) KEPPRA (LEVETIRACETAM) ; 27-JUL-2016 / Ongoing
#4) DAFALGAN (PARACETAMOL) ; Ongoing
#5) OXYNORMORO (OXYCODONE HYDROCHLORIDE) ; Ongoing
#6) LAMICTAL (LAMOTRIGINE) ; 16-SEP-2016 / Unknown **(Continued on Additional Information Page)**

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
10-MAR-2015 to Ongoing	Relevant Med History with sequelae	Stroke (Cerebrovascular accident)
27-JUL-2016 to Ongoing	Relevant Med History with sequelae	Stroke (Cerebrovascular accident)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016459635

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
02-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 65-year-old male subject started to receive bosutinib from 05Aug2016 to 17Aug2016 at 300 mg once daily and then on 23Aug2016 and ongoing, at 100mg once daily for an unspecified indication. Medical history included stroke on 10Mar2015 and on 27Jul2016 with ongoing sequelae, and ongoing epilepsy since 27Jul2016, cervicarthrosis, Arnold neuralgia from Jan2014. Concomitant medications included oral acetylsalicylate lysine (KARDEGIC) from Mar2015 and from 04Aug2016 for stroke, oral clobazam (URBANYL) ongoing since 27Jul2016 for epilepsy, oral levetiracetam (KEPPRA) ongoing since 27Jul2016 for epilepsy, oral paracetamol (DAFALGAN) ongoing for arthralgia, and oral oxycodone hydrochloride (OXYNORMORO) ongoing for arthralgia, lamotrigine (LAMICTAL) by oral route since 16Sep2016 for epilepsy, rosuvastatin (CRESTOR) by oral route since Mar2015 for stroke.
On 17Aug2016, the subject developed diarrhea grade CTCAE 3, which was considered a non-serious event. In response to the event, bosutinib was temporarily stopped on 17Aug2016. Event diarrhea resolved on 23Aug2016 and bosutinib was resumed on the same day. The subject experienced diarrhea again in Aug2016 assessed as a non-serious event grade 1. No action was taken with the study drug in response to this event and it recovered in Nov2016.
On 16Oct2016, the subject experienced bronchial superinfection, grade CTCAE 2, considered as medically significant. For the event 'bronchial superinfection', the subject was hospitalized from 17Oct2016 to 17Oct2016. No action was taken with bosutinib in response to the event and was ongoing. The late action taken in response to the event bronchial superinfection for bosutinib dose was not changed. The event 'bronchial superinfection' resolved on 27Oct2016. Resumption of bosutinib was well tolerated.
In Apr2017, the subject experienced arthritis assessed as a non-serious event grade 2. The investigator reported that it was a post traumatic arthritis. No action was taken with bosutinib in response to the event arthritis. On 20Jul2017 the event recovered.
On 07Aug2017, the subject experienced facial neuralgia and was hospitalized from 07Aug2017 to 08Aug2017. The event facial neuralgia was assessed as a grade 2 event. No action was taken with bosutinib in response to the event facial neuralgia. On 08Aug2017, the event recovered. The event did not reappear at the treatment reintroduction.
On 07Sep2017, the subject experienced dorsopathy and assessed as a non-serious event grade 2. The investigator described the event as dorsopathy at the cervical area. Action taken with the study drug was reported as 'dose not changed' (according to treatment reintroduction, last action taken was retained as temporarily withdrawn). The event did not reappear after the treatment reintroduction. The event was resolved on 19Oct2017.
In Nov2018, the subject experienced hands and feet cramps, rated grade 1 and not serious. No action was taken with bosutinib in response to this event. The event was resolving at the report time.

According to the investigator, there was a reasonable possibility that the event 'diarrhea' could be related to study drug bosutinib but not to concomitant drug.
The investigator considered the event hands and feet cramps as related to study drug bosutinib and unrelated to concomitant medications.
The investigator considered events (bronchial superinfection, dorsopathy, facial neuralgia and arthritis) to be unrelated to study drug bosutinib and to concomitant medications.

Follow-up (18Oct2016 and 18Oct2016): New information received from a contactable physician includes: new event (bronchial superinfection), patient's data (date of birth), medical history, concomitant medications (added paracetamol (DAFALGAN) and oxycodone hydrochloride (OXYNORMORO)), action taken (updated to dose not changed from temporarily withdrawn), clinical course details, causality assessment (bronchial superinfection unrelated).

Follow-up (14Nov2016): New information received includes: the outcome of events 'diarrhea' and 'bronchial superinfection' (updated to recovered) and recovered date, hospitalization period and subject's clinical course.

Follow-up (06Dec2017 and 07Dec2017): New information received includes: medical history, action taken updated to temporarily withdrawn, new events 'dorsopathy', 'arthritis' and 'right temporo- facio-cervical pain' and 'diarrhea' added.

Follow-up (06Mar2018): Follow-up attempts completed. No further information expected.

Follow-up (12Dec2019): New information received from CRO is as follows: updated the outcome of the event dorsopathy (resolved on 19Oct2017), and updated the reported action taken in response to the event dorsopathy ('dose not changed').

Follow-up (17Dec2019): New information received from the CRO includes: the previously reported event "right temporo- facio-cervical pain" was updated to "facial neuralgia"; causaity for event facial neuralgia; concomitant drugs (lamotrigine, rosuvastatin, acetylsalicylic acid); new event (hands and feet cramps).

Follow-up (02Oct2023): This is a non-interventional study report (Post Authorization Safety Study) received from the investigator site via the CRO for protocol B1871047.
Updated information: onset date of event dorsopathy updated, event arthritis considered unrelated to study drug bosutinib and concomitant medications, and seriousness criterion of hospitalization was removed for event bronchial superinfection.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up attempts completed. No further information expected.

Case Comment: Upon FU information the event arthritis was considered unrelated to bosutinib (post-traumatic arthritis).

By close temporal relationship and absence of factors which may provide an alternative cause, the event diarrhea may be attributed to suspect drug bosutinib, the event is compatible with the safety profile of the suspect drug. A possible contributory role of suspect drug bosutinib to the reported events hands and feet cramps cannot be excluded based on the temporal association. Conversely, bronchial superinfection, facial neuralgia and dorsopathy are assessed as unrelated to suspect drug bosutinib, in agreement with the reporter.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, once daily; Unknown	Unknown	23-AUG-2016 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) CRESTOR (ROSUVASTATIN CALCIUM) ; MAR-2015 / Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
27-JUL-2016 to Ongoing	Relevant Med History	Epilepsy (Epilepsy);
JAN-2014 to Unknown	Relevant Med History	Arnold neuralgia (Occipital neuralgia);
Unknown	Relevant Med History	Spinal osteoarthritis (Spinal osteoarthritis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		APR	1951	65 Years	Male	80.00 kg		OCT	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Dysuria [Dysuria]
Sleepiness [Somnolence]
hands and feet cramps [Muscle spasms]
hands and feet cramps [Muscle spasms]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) URBANYL (CLOBAZAM)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 300 mg, 1x/day
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) Epilepsy (Epilepsy)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 05-AUG-2016 / 17-AUG-2016
#2) 27-JUL-2016 / Ongoing

19. THERAPY DURATION
#1) 13 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 04-AUG-2016 / Unknown
#2) KEPPRA (LEVETIRACETAM) ; 27-JUL-2016 / Ongoing
#3) DAFALGAN (PARACETAMOL) ; Ongoing
#4) OXYNORMORO (OXYCODONE HYDROCHLORIDE) ; Ongoing
#5) LAMICTAL (LAMOTRIGINE) ; 16-SEP-2016 / Unknown
#6) CRESTOR (ROSUVASTATIN CALCIUM) ; MAR-2015 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
10-MAR-2015 to Ongoing	Relevant Med History with sequelae	Stroke (Cerebrovascular accident)
27-JUL-2016 to Ongoing	Relevant Med History with sequelae	Stroke (Cerebrovascular accident)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016491009

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
02-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2016491009

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 65-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 05Aug2016 to 17Aug2016 at 300mg once a day, then from 23Aug2016 and ongoing at 100mg once a day for an unspecified indication. The subject also started to receive clobazam (URBANYL) orally on 27Jul2016 and ongoing at an unspecified dose and frequency for epilepsy.
Medical history included stroke with sequelae on 10Mar2015 and 27Jul2016, and epilepsy since 27Jul2016; all ongoing.
Concomitant medications included acetylsalicylate lysine (KARDEGIC) for stroke since 04Aug2016, levetiracetam (KEPPRA) for epilepsy since 27Jul2016, paracetamol (DAFALGAN) for arthralgia and oxycodone hydrochloride (OXYNORMORO) for arthralgia; all taken orally and ongoing, lamotrigine (LAMICTAL) orally from 16Sep2016 for epilepsy, rosuvastatin calcium (CRESTOR) for stroke from Mar2015.
The subject developed dysuria in Oct2016 and sleepiness on 16Oct2016; both grade CTCAE 2 and considered medically significant.
In Aug2018, the subject experienced hands and feet cramps considered non-serious and rated grade 1. No action was taken for bosutinib in response to the event.
The action taken in response to the events for suspect concomitant clobazam was dose not changed. The outcome of the event sleepiness resolved on 17Oct2016 and the outcome of dysuria was resolved on 14Nov2016. The event hands and feet cramps was recovering.

The investigator considered that the event hands and feet cramps was related to bosutinib and unrelated to any concomitant drug.
The investigator considered the events dysuria and sleepiness as unrelated to study drug bosutinib but related to concomitant drug clobazam.

Follow-up (23Jun2020): New information received from the investigational site via the CRO included new event hands and feet cramps, concomitant drug updated

Follow-up (02Oct2023): This is a non-interventional study report (Post Authorization Safety Study) received from the investigator site via the CRO for protocol B1871047.
Updated information: outcome of event dysuria updated from resolving to resolved and stop date added.

Follow-up attempts are completed. No further information is expected.

Case Comment: In agreement with the reporter, the company does not attribute dysuria, sleepiness to suspect drug bosutinib. Both events are more likely related to concomitant drug clobazam. Based on the available information, the company considers that a causal relationship between hands and feet cramps and bosutinib cannot be excluded due to plausible temporal association.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, 1x/day; Unknown	Unknown	23-AUG-2016 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
27-JUL-2016 to Ongoing	Relevant Med History	Epilepsy (Epilepsy);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		OCT	1930	86 Years	Female	66.00 kg	20	OCT	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Multi-metastatic undifferentiated adenocarcinoma [Second primary malignancy]
Multi-metastatic undifferentiated adenocarcinoma [Adenocarcinoma metastatic]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 02-NOV-2016
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosutinib (BOSUTINIB) Unknown
#2) PREVISCAN /00789001/ (FLUINDIONE)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☒ NO ☐ NA

15. DAILY DOSE(S)
#1) 200 mg, daily
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 01-OCT-2016 / Unknown
#2) Unknown

19. THERAPY DURATION
#1) Unknown
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History	Atrial fibrillation (Atrial fibrillation)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016491044

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

An 86-year-old female subject started to receive bosutinib (BOSULIF) via an unspecified route of administration, on 01Oct2016 at 200mg, daily for chronic myeloid leukemia. Ongoing medical history included hypertension, atrial fibrillation on myocardial infarction grade II, hypothyroidism and asthma. Concomitant medications included fluindione (PREVISVAN) dosage, indication and administration timeline unspecified. The subject experienced the event "multi-metastatic undifferentiated adenocarcinoma" (death, hospitalization) with onset 20Oct2016, outcome "fatal". The event "multi-metastatic undifferentiated adenocarcinoma" was rated grade 5. Probable progression of one her hemopathies noticed for one week with appearance of compressive tumoral syndrome and general status alteration. Anorexia, loss of autonomy and constipation. Acute renal insufficiency of functional type but possible compression of urinary tract by tumoral masses. The investigator first suggested the hypothesis of evolution of chronic lymphoid leukemia, but after results of histopathology of inguinal lymphadenopathy biopsy, it was revealed that it was a poorly differentiated adenocarcinoma, which was just one diagnostic for polymetastatic cancer. A possible gynecologic origin could be evoked due to high CA125. The diagnosis of "multi-metastatic undifferentiated adenocarcinoma" was determined as a result of a biopsy performed during an imaging assessment for possible transformation of her CLL (chronic lymphocytic leukemia) on 20Oct2016. Exam requested after the haematology consultation on 10Oct2016, when the patient initiated treatment with bosutinib after discontinuation of GLIVEC which caused an oedematous syndrome. The action taken for bosutinib and fluindione was dosage permanently withdrawn. The subject date of death was 02Nov2016. Reported cause of death: "Multi-metastatic undifferentiated adenocarcinoma". It was not reported if an autopsy was performed.

The investigator confirmed that the subject died on 02Nov2016 due to grade V polymetastatic adenocarcinoma. This fatal progression was due to a secondary primary malignancy and not to the disease under study. The worsening of general status, anorexia, loss of autonomy, constipation, acute renal insufficiency were the symptoms of the fatal polymetastatic cancer. The death was due to the polymetastatic cancer and not to the progression of the chronic myeloid leukemia. As of 04Apr2023, Polymetastatic adenocarcinoma responsible for alteration of general condition, compressive oedema leading to renal failure, itself responsible for VKA (vitamin K antagonists) overdose. Death of the subject on 02Nov2016 probably related to the polymetastatic adenocarcinoma.

According to the investigator, the event "multi-metastatic undifferentiated adenocarcinoma" was unrelated to the study drug BOSULIF and unrelated to concomitant drug.

Follow-up (03Nov2016): New information reported includes: reaction data (onset date updated from 18Oct2016 to 11Oct2016), clinical details, lab data, and death details.

Follow-up (22Nov2016): New information reported from the clinical team includes: indication, clarification of poorly differentiated adenocarcinoma and death information.

Follow-up (01Dec2016): New information received from the investigational site includes relevant lab data (high CA125).

Follow-up (14Dec2016). New information received from the study coordinator includes: suspect product data (start date 01Oct2016 and frequency for bosutinib).

Follow-up (01Mar2017): Follow-up attempts completed. No further information expected.

Follow-up (04Apr2023): This is a non-interventional study follow-up report from the investigator via CRO. Updated information included: suspect drug data (action taken), reaction data (event verbatim updated from "general status alteration" to "multi-metastatic undifferentiated adenocarcinoma", seriousness death added, outcome updated to fatal, cause of death updated to "multi-metastatic undifferentiated adenocarcinoma").

Follow-up (15May2023): This is a non-interventional study follow-up report received from clinical research technician for protocol B1871047 as query response. Updated information included: complete date of biopsy provided, clarification about clinical course.

Follow-up (03Oct2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information includes: The start date of the events was updated from 110ct2016 to 20Oct2016.

Case Comment: The company does not attribute the event "multi-metastatic undifferentiated adenocarcinoma" to suspect drug bosutinib. The onset of the SAE, a fatal second primary malignancy, was 10 days after the start of Bosutinib treatment. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	20-OCT-2016	Biopsy lymph gland	poorly differentiated adenocarcinoma	
2		Carbohydrate antigen 125	high	

Mfr. Control Number: 2016491044

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
3	20-OCT-2016	Imaging procedure	Unknown results	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Myocardial infarction (Myocardial infarction);
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism);
Unknown to Ongoing	Relevant Med History	Asthma (Asthma);
Unknown	Past Drug Event	GLIVEC (GLIVEC); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Oedema (Oedema)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		AUG	1937	79 Years	Male	70.00 kg		AUG	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
weight loss [Weight decreased]
nausea [Nausea]
Dysphonia [Dysphonia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from a contactable

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 22-OCT-2015 / 25-JUL-2016	#1) 278 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016535103

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

reporter(s) (Physician) for protocol B1871047.

A 79-year-old male patient received bosutinib (BOSULIF), first regimen from 22Oct2015 to 25Jul2016 at 300 mg 1x/day and second regimen since 27Jul2016 (ongoing) at 500 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: DIARRHOEA (non-serious) with onset Aug2016, outcome "recovered" (2018), described as "Diarrhea"; NAUSEA (non-serious) with onset Feb2018, outcome "recovered" (17Dec2018); WEIGHT DECREASED (non-serious) with onset Feb2018, outcome "not recovered", described as "weight loss"; DYSPHONIA (non-serious) with onset 2018, outcome "recovered" (2018). The action taken for bosutinib was dosage not changed.

The reporter considered "diarrhea", "weight loss" and "nausea" related to bosutinib. The reporter considered "dysphonia" not related to bosutinib.

Additional information: The events dysphonia and Diarrhea rated grade 1. The event dysphonia outcome was Recovered/Resolved. Action taken for dysphonia with bosutinib was dose not changed. Event dysphonia reported as non-serious. The patient no longer eating his food was resumed by food supplements explaining weight loss.

Follow-up (26Mar2018): New information received from the investigational site via the CRO includes: New events (weight loss, nausea).

Follow-up (27Jun2018): Follow-up attempts completed. No further information expected.

Follow-up (25Oct2022): This follow-up is received from the investigational site CRO. This is a follow-up to a non-interventional clinical study case.
Updated information includes: Reporter information, patient information, new adverse event (dyspnea), outcome of nausea updated to recovered on 17Dec2018 (previously not recovered), clinical course about weight loss.

Follow-up (06Jul2023): New information was received from a CRO reporting the recovery date of diarrhea.

Amendment: This follow-up report is being submitted to amend previous information: The verbatim of the event dyspnea updated to dysphonia.

Amendment: This follow-up report is being submitted to amend previously reported information: Event verbatim "diarrhea grade 1" updated to "diarrhea" in event tab, as reported on AE form. Diarrhea grade was 1 (information regarding grade should be reported only in narrative).

Case Comment: Considering the plausible drug-event temporal association and the consistency of these events with the known safety profile of the suspect product, a reasonable possibility that diarrhea and nausea is related are to bosutinib administration cannot be excluded. Weight decreased is possibly related to bosutinib as it occurred in a plausible drug-event temporal association. The patient's changing in diet provide alternative explanation. As per follow up, the reported dysphonia is deemed unrelated to bosutinib, which is more likely intercurrent medical condition or associated with underlying malignancy. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	500 mg, 1x/day; Unknown	Unknown	27-JUL-2016 / Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1952	64 Years	Male	62.00 kg	26	JUL	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
worsening of renal failure [Renal failure]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE.

This is a report from a Non-Interventional study source, for Protocol B1871047, study alias BOSEVAL.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 26-JUL-2016 / 12-MAY-2017

19. THERAPY DURATION
#1) 316 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing
#2) ASPEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#3) PLAVIX (CLOPIDOGREL BISULFATE) ; Ongoing
#4) ISOPTINE (VERAPAMIL HYDROCHLORIDE) ; Ongoing
#5) INIPOMP (PANTOPRAZOLE SODIUM SESQUIHYDRATE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Coronaropathy (Coronary artery disease)
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2016537036

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 64-year-old male subject was enrolled in the above mentioned study on an unspecified date and started to receive bosutinib (BOSULIF) orally, from 26Jul2016 to 12May2017 (pending clarification) at 500 mg once daily for chronic myeloid leukemia.
Relevant medical history included ongoing coronaropathy, ongoing dyslipidemia, myocardial infarction, hypercholesterolemia, ongoing renal failure since 22Dec2014 (disclosed on renal MRI angiography and ultrasound). Concomitant medications included atorvastatin calcium (TAHOR) for hypercholesterolemia, acetylsalicylate lysine (ASPEGIC), clopidogrel bisulfate (PLAVIX) for coronaropathy, verapamil hydrochloride (ISOPTINE) oral for myocardial infarction and pantoprazole (INIPOMP) oral for gastric protection; all ongoing.
On 26Jul2016, the subject experienced diarrhea, considered as non-serious (as reported). On 03Oct2016, the subject presented with worsening of renal failure rated grade 3 and assessed as medically significant. According to the investigator, this polyvascular subject had worsening of renal failure probably because of natural evolution of atherosclerosis. As a result of the event, the study drug bosutinib was permanently discontinued on 05Jun2017, the subject did not want to pursue the treatment. On 20Jul2017, renal MRI angiography was performed and disclosed thin and stenotic arteries. As of 19Sep2023, it was confirmed for event diarrhea action taken reported as No modification and for event renal failure aggravated action taken reported as permanently withdrawn on 12May2017. The outcome of the event diarrhea was recovered on an unknown date in Aug2016. The outcome of the worsening of renal failure was not recovered.

The investigator considered the event diarrhea as possibly related to bosutinib and unrelated to a concomitant drug. The investigator considered the event worsening of renal failure as unrelated to bosutinib and to concomitant drugs.

Follow-up (28Jul2017): New information reported includes: reaction data (added grade 4 renal failure (important medical event)), medical history data, concomitant medication data, and product data (start date of bosutinib updated from 25Jul2016 to 26Jul2016), and lab data.

Follow-up (25Aug2017): new information received from the investigational site includes: medical history; new event added (Renal failure worsened).

Follow-up (22Sep2017): follow-up attempts completed. No further information expected.

Follow-up (26Aug2020): New information received from the investigator via the CRO is as follows: Study drug data (bosutinib route of administration and indication provided; start date of bosutinib updated to 26Jul2016) and Reaction data (renal failure worsened to grade 4 with onset date 15May2017 was changed to worsening of renal failure with onset date 03Oct2016).

Follow-up (25Sep2020): New information received from the investigator includes relevant medical history (renal failure since 05Jun2014 disclosed on renal MRI angiography and ultrasound).

Follow-up (27Oct2021): New information from the investigational sit via CRO included: study drug start date; medical history details; Diarrhea onset date.

Follow-up (19Sep2023): New information from the investigational sit via CRO included:
Updated information included: Bosulif Stop Date updated, Initials updated to PRIVACY, and confirmed for event diarrhea action taken reported as No modification and for event renal failure aggravated action taken reported as permanently withdrawn on 12May2017.

Case Comment: By a plausible temporal relationship and absence of factors which may provide an alternative cause, the event diarrhea may be attributed to suspect drug bosutinib, the event is consistent with the known toxicity profile of the suspect product. Renal failure/condition aggravated is not related to bosutinib, considering which being consequences of natural evolution of atherosclerosis in a patient with ongoing history of renal failure.

The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	22-DEC-2014	Angiogram	renal failure	
2	20-JUL-2017	Angiogram	thin and stenotic arteries	
3	22-DEC-2014	Ultrasound kidney	renal failure	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description

Mfr. Control Number: 2016537036

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Myocardial infarction (Myocardial infarction);
Unknown	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
22-DEC-2014 to Ongoing	Relevant Med History	Renal failure (Renal failure); disclosed on renal MRI angiography and ultrasound

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1950	66 Years	Female	Unk	22	NOV	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

hepatic cytolysis [Hepatic cytolysis]
facial skin lesions as maculopapular erythema like-type of the three exposed areas (face and upper part of the trunk) [Rash maculo-papular]
Headache [Headache]
Arterial hypertension [Hypertension]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) VALSARTAN (VALSARTAN)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Unknown
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) arterial hypertension (Hypertension)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 10-OCT-2016 / 18-JAN-2017	#1) 102 days
#2) 05-JAN-2017 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LEXOMIL (BROMAZEPAM) Tablet ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017032855

24c. DATE RECEIVED BY MANUFACTURER
27-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 66-year-old female patient received bosutinib (BOSULIF), from 10Oct2016 to 18Jan2017 at 300 mg daily; valsartan (VALSARTAN), first regimen since 05Jan2017 (Batch/Lot number: unknown), oral and second regimen since 19Jan2017 (ongoing) (Batch/Lot number: unknown) at 80 mg daily for hypertension; dasatinib monohydrate (SPRYCEL), since 04Feb2017 (ongoing) (Batch/Lot number: unknown) at 100 mg alternate day, oral for chronic myeloid leukaemia. The patient's relevant medical history included: "arterial hypertension" (ongoing). Concomitant medication(s) included: LEXOMIL taken for irritability, anxiety (ongoing).
On 22Nov2016, the subject experienced arterial hypertension, which was assessed as non-serious and considered to be 'aggravation grade 2'. Clinical examination was unremarkable except blood pressure at 15/10 (unit not provided) whereas the treatment with valsartan (NISISCO) was withdrawn the beginning of Oct2016. The subject was asked to check his blood pressure and if increased to see the physician for reintroduction of treatment. The cardio-respiratory exam was normal. Action taken in the result of the event, arterial hypertension, was reported as dose not changed. On 05Dec2016, ASAT was 54 IU/l (normal range 5-34) and ALAT was 91 IU/l (normal range 0-55).
The subject experienced headache con 15Jan2017, which was assessed as non-serious and of grade 2. The subject was seen faster than planed due to skin rash occurred 15Jan2017 on face and trunk. In the result of the event, headache, bosutinib (BOSULIF) was withdrawn.
On 15Jan2017, the subject experienced facial skin lesions as maculopapular erythema like-type of the three exposed areas (face and upper part of the trunk) and hepatic cytolysis, both assessed as non-serious. The patient received desonide (LOCAPRED, ointment) for skin lesions since 19Jan2017 and ongoing. As a result of facial skin lesions and hepatic cytolysis, the study drug was permanently withdrawn on 19Jan2017 and no action was taken with valsartan and dasatinib monohydrate.
The clinical outcome of event hepatic cytolysis was resolved on 10Mar2017, of event maculopapular rash was resolved 26Jan2017, of event arterial hypertension was resolved in 2017, of event headache was resolved on 26Jan2017.

The investigator considered the events arterial hypertension and headache as possibly related to the study drugs bosutinib and not related to concomitant medications.
The investigator considered both events facial skin lesions and Hepatic cytolysis as possibly related to study drug bosutinib and also to the concomitant drug valsartan.
Follow-up (10Aug2018 and 14Aug2018): New information received from the investigational site included: stop date of bosutinib, reaction data (new event hematocele, lab data, causality assessment), new suspect product.

Follow-up (17Apr2019): New information received from the clinical team: new event (headache and arterial hypertension) added.

Follow-up (19Apr2019): New information received from the CRO: details of event (arterial hypertension and headache) updated.

Follow-up (30Apr2019): New information received included onset date and stop date of event maculo-papular rash and onset date and grade of hypertension updated.

Follow up (13May2019): follow up attempts completed. No further information expected.

Follow-up (16Aug2019): New information reported includes that the event hematocele is not reportable as per protocol (the event occurred more than 28 days after the last dose of bosutinib).

Follow-up (08Feb2023): New information received from the investigator via the CRO. Updated information: Patient's height.

Follow-up (25Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047.
Updated information: stop date of bosutinib updated, outcome of events "facial skin lesions as maculopapular erythema like-type of the three exposed areas (face and upper part of the trunk)" and "hepatic cytolysis" updated from not resolved to resolved and recovery date added.

Follow-up (27Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047.
Updated information included: delete event "myalgia".

Case Comment: Based upon FU the event myalgia was deleted from previous assessment.

A contributory role of bosutinib to the reported events Hepatic cytolysis, Maculopapular rash and Headache cannot be totally excluded, based on the temporal association and known product safety profile. The reported event Myalgia is possibly associated with the use of bosutinib based on the narrative information provided. The medications bromazepam, desonide, and valsartan may possibly be contributory to the reported event Myalgia based on a temporal relationship. The event arterial hypertension is assessed as unrelated to bosutinib; it is an ongoing medical history. The follow-up information received does not alter the previous company clinical evaluation.

Mfr. Control Number: 2017032855

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	05-DEC-2016	Alanine aminotransferase	91 IU/l	55 0
2	05-DEC-2016	Aspartate aminotransferase	54 IU/l	34 5
3	22-NOV-2016	Blood pressure measurement	15/10	
4		Blood thyroid stimulating hormone	normal	
5	16-JUL-2018	Histology	benign hematocele	
6	22-NOV-2016	Investigation	NORMAL	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#2) VALSARTAN (VALSARTAN) ; Regimen #2	80 mg, daily; Unknown	arterial hypertension (Hypertension)	19-JAN-2017 / Ongoing; Unknown
#3) SPRYCEL (DASATINIB MONOHYDRATE) ; Regimen #1	100 mg, alternate day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	04-FEB-2017 / Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		OCT	1949	66 Years	Male	62.00 kg	04	MAY	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Abdominal fullness [Abdominal distension]
Pallor [Pallor]
Right rotator cuff tendinitis [Rotator cuff syndrome]
Lumbar pain with hypoesthesia of the calf and left foot [Back pain]
Lumbar pain with hypoesthesia of the calf and left foot [Hypoaesthesia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 400 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 02-MAY-2016 / Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017044517

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-FEB-2021

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2017044517

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a Non-Interventional Study report for Protocol ID B1871047 with non-serious events only.

A 66-year-old male subject started to receive bosutinib (BOSULIF, film-coated tablets), orally, from 02May2016, at 400 mg once daily for an unspecified indication. The subject had medical history of ongoing arterial hypertension, and had no concomitant drugs. On 04May2016, the subject experienced grade 1 abdominal fullness and grade 1 pallor. Bosutinib was dose reduced and therapy was ongoing. On an unspecified date in May2017, the subject developed right rotator cuff tendinitis, rated as grade 2. It was reported that an infiltration of the right shoulder had been performed one month prior to the resolution date. Dose of bosutinib was not changed in response to this event. The subject had recovered from abdominal fullness and from pallor on 09Aug2016, from right rotator cuff tendinitis on 01Jun2017. In May2018, the subject experienced lumbar pain with hypoesthesia of the calf and left foot, which was assessed as non-serious. The event was assessed of grade 2. In result of the event, the dose of bosutinib (BOSULIF) was not changed. At the time of reporting, the subject had not recovered from the event, lumbar pain with hypoesthesia of the calf and left foot.

The investigator considered the events, abdominal fullness and pallor, as non-serious and possibly related to study drug bosutinib and unrelated to concomitant treatments; and considered right rotator cuff tendinitis as non-serious and unrelated to study drug bosutinib; and considered that there was not a reasonable possibility that the event, lumbar pain with hypoesthesia of the calf and left foot, was related to the study drug bosutinib and to concomitant medications.

Follow-up (11Jan2018): New information reported includes: medical history, event data (added inflammation of the right shoulder).

Follow-up (10Aug2018): New information received from the CRO includes: updated dose regimen of bosutinib, and added new event (lumbar pain with hypoesthesia of the calf and left foot).

Follow-up (12Aug2020): New information received from includes updated recovery date of pallor.

Follow-up (14Aug2020): New information reported includes event verbatim "sense of abdominal fullness and pallor" was updated to 2 separate events: abdominal fullness and pallor, grade of the events, updated recovery date of abdominal fullness, causality of these events vs concomitant medications.

Follow-up (23Feb2021): New information received from the study site included: event term updated from "Inflammation of the right shoulder" to "right rotator cuff tendinitis".

Case Comment: The limited information described about the cause of the reported events precludes a full clinical assessment of the case, and doubts remain on the final diagnosis. Until additional information becomes available, the company does not attribute abdominal fullness, pallor, right rotator cuff tendinitis, and Lumbar pain with hypoesthesia of the calf and left foot to suspect drug bosutinib.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	reduced dose; Oral	Unknown	Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		SEP	1937	79 Years	Male	116.00 kg	18	OCT	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Anal margin abscess [Anal abscess]
Bleeding in relation with hemorrhoidal pathology [Haemorrhoidal haemorrhage]
disabling cough with sputum [Sputum retention]
rash at the lumbar spine [Rash]
synovial effusion of the right knee [Joint effusion]
insomnia Grade 3 [Insomnia]
lower limbs oedema [Oedema peripheral]
Creatinine increased [Blood creatinine increased]
Knee pain [Arthralgia]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) SERETIDE (FLUTICASONE PROPIONATE, SALMETEROL XINAFOATE)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 17-OCT-2016 / Ongoing	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TRIATEC /00116401/ (CODEINE PHOSPHATE, PARACETAMOL) ; Ongoing
#2) ZYLORIC (ALLOPURINOL) ; 01-JAN-2005 / Ongoing
#3) XELEVIA (SITAGLIPTIN PHOSPHATE) ; Ongoing
#4) LASILIX /00032601/ (FUROSEMIDE) ; 16-JUL-2013 / Ongoing
#5) LANZOR (LANSOPRAZOLE) ; Ongoing
#6) SINTROM (ACENOCOUMAROL) ; Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Respiratory insufficiency (Respiratory failure)
SEP-2006 to Ongoing	Relevant Med History	Sleep apnea (Sleep apnoea syndrome)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017052881

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Fall [Fall]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 79-year-old male subject was enrolled in the above mentioned study on an unspecified date and started to receive bosutinib (BOSULIF) orally at 100 mg once a day from 17Oct2016 for an unspecified indication, and fluticasone propionate/salmeterol xinafoate (SERETIDE). The subject had a medical history of ongoing respiratory insufficiency, sleep apnea ongoing since Sep2006, bronchopulmonary congestion, arterial hypertension ongoing since 2002, ongoing cardiac failure, knee disorders (not detailed), obesity which both led to difficulty in walking and ongoing diabetes. Ongoing concomitant medications included codeine phosphate/paracetamol (TRIATEC) orally for hypertension arterial, allopurinol (ZYLORIC) from 01Jan2005 for hyperuricaemia and gout, sitagliptin phosphate (XELEVIA) orally for diabetes, furosemide (LASILIX) orally from 16Jul2013 for oedema prevention, lansoprazole (LANZOR) orally for gastrooesophageal reflux, acenocoumarol (SINTROM) orally for atrial flutter with ventricular rate, glimepiride (AMAREL) orally for diabetes, and bromazepam (LEXOMIL) orally for anxiety.
The subject experienced bleeding in relation with hemorrhoidal pathology on 18Oct2016, disabling cough with sputum (grade 2) in May2017, rash at the lumbar spine (grade 1) in Oct2017, synovial effusion of the right knee (grade 2) in Oct2017, insomnia (grade 3) on 23Oct2017, lower limbs oedema (grade 1) on 16Jan2017, creatinine increased (grade 1) on 23Apr2018. Laboratory analysis found blood creatinine at 202 umol/l (normal range: 59 - 104 umol/l), between 1/2 and 2 times normal range, on 23Apr2018. In Jan2018, the subject experienced knee pain following a fall (grade 1). It was reported that the subject fell into his bathtub (this event was considered as non-serious and rated as grade 2). No action was taken with bosutinib in response to this event. Per medical report dated 29Oct2018, the subject complained of pruritus of back well relieved with hydrocortisone butyrate (LOCOID). At the time of the physical examination, the subject presented with erythema grade 1 and some scratching lesions. To be noted that the subject received hydrocortisone butyrate since Oct2017 for sacrum. On an unspecified date in Feb2019, the subject experienced anal margin abscess rated grade 1 and assessed as non-serious. The event was disclosed during consultation on 06May2019, it was reported that the patient did not receive antibiotics for anal margin abscess in Feb2019. Despite the event, the suspect drug was pursued unchanged. All events except for anal margin abscess were assessed as non-serious. In response of the events, no action was taken regarding bosutinib. Symptomatic therapy was given in relation to event bleeding in relation with hemorrhoidal pathology. About event disabling cough with sputum, the subject presented already with bronchopulmonary congestion before inclusion in the study, which became invalidating. In response of the event synovial effusion of the right knee, the subject underwent evacuation of 50 ml and corticosteroids were introduced. The action taken for bosutinib was dosage not changed. The action taken for fluticasone propionate, salmeterol xinafoate was dosage permanently withdrawn. The event synovial effusion of the right knee was resolved in Oct2017 while anal margin abscess resolved on 06May2019. The outcome of disabling cough with sputum was resolved on 26Feb2018. The outcome of rash at the lumbar spine was resolved on 27May2019. The event bleeding in relation with hemorrhoidal pathology resolved on 16Jan2017. The event lower limbs oedema resolved on 29Oct2018. The event creatinine increased resolved on 25Jun2018. The event insomnia resolved on 27Feb2018. Event pain in knees resolved on 27May2019 and fall had resolved in Jul2018t. The subject remained disabled by pain in knees.

The investigator considered there was not a reasonable possibility that the events were related to bosutinib or to a concomitant medication.

Follow-up (12Apr2017): New information received from the investigational site includes event outcome, action taken for bosutinib, dosage regimen for bosutinib, no lab data performed, therapy for event received.

Follow-up (10Jan2018): New information received includes: medical history, concomitant medication details, new events 'disabling cough with sputum', 'rash at the lumbar spine', 'intolerance to fluticasone, salmeterol (SERETIDE)', 'synovial effusion of the right knee', insomnia', 'lower limbs oedema' added, cause relationship.

Follow-up (26Apr2018): New information received includes medical history (ongoing cardiac failure), frequency of bosutinib (from daily to once a day), new event creatinine increased with laboratory test and assessment (creatinine increased not related to bosutinib).

Follow-up (31Oct2018): New information includes: updated medical history, additional events 'pain in knees following a fall (grade 1)', 'erythema with scratching lesions (grade 1)'.

Follow-up (06Dec2018 and 10Dec2018): New information received includes details on fall.

Follow-up (22May2019) New information reported from CRO includes updated medical history, and new non serious event (anal margin abscess).

Follow-up (20Apr2022): This is report from a Non Interventional Study from the investigational site via the CRO.
Updated information includes: disabling cough with sputum recovered on 26Feb2018 and rash at the lumbar spine recovered on

Mfr. Control Number: 2017052881

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

27May2019.

Follow-up (08Feb2023): This is a follow-up report from the investigator via CRO. Updated information includes recovery date of the event "bleeding in relation with hemorrhoidal pathology", outcome of the events "lower limbs oedema" and "creatinine increased" updated from "Not recovered" to "Recovered", grade of event insomnia reported as Grade 3, verbatim of the event "pain in knees following a fall" updated to "Knee pain" and onset date of the event "Knee pain" updated from Jul2018 to Jan2018.

Follow-up (29Jun2023): This is a follow-up report from the investigator via CRO.
Updated information: reporter information updated, events Insomnia, Arthralgia details (stop date, outcome), event Fall details (start/stop date, outcome).

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from clinical team within the context of reconciliation for protocol B1871047.
Updated information: Events (intolerance to fluticasone, salmeterol (SERETIDE) (10Jul2017) and erythema with scratching lesions (Oct2018)) were deleted as site staff confirmed events are not clinically significants and does not have to be reported.

Case Comment: Based on current available information, the company concurs with the investigator that all reported events unrelated to the study medication bosutinib however more likely due to the ongoing medical history (respiratory insufficiency, sleep apnea and hypertension) and underlying diseases suggested by concomitant drugs (hyperuricaemia, diabetes, edema, gastrooesophageal reflux, atrial flutter, and anxiety). The event anal margin abscess was attributed to intercurrent medical condition and unrelated to bosutinib; the event outcome was recovered and no action was taken in response to the event for bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	23-APR-2018	Blood creatinine between 1/2 and 2 times normal value	202 umol/l	104 59

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) AMAREL (GLIMEPIRIDE) ; Ongoing

#8) LEXOMIL (BROMAZEPAM) ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Bronchial congestion (Lower respiratory tract congestion); bronchopulmonary congestion
2002 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
Unknown to Ongoing	Relevant Med History	Cardiac failure (Cardiac failure);
Unknown	Relevant Med History	Joint disorder NOS (Arthropathy); knee disorders (not detailed) leading to difficulty in walking
Unknown to Ongoing	Relevant Med History	Obesity (Obesity); leading to difficulty in walking
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus);

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		DEC	1952	63 Years	Male	113.00 kg	08	SEP	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Pleural effusion [Pleural effusion]
pleurisy [Pleurisy]
Chronic cholecystitis [Cholecystitis chronic]
Pneumothorax [Pneumothorax]
increase of pleural effusion [Pleural effusion]
Headache [Headache]
neck pain [Neck pain]
shoulder pain [Arthralgia]
Diarrhea [Diarrhoea]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) IKOREL (NICORANDIL)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, 1x/day	#1) Oral
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) coronary heart disease (Coronary artery disease)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 08-JAN-2016 / Unknown	#1) Unknown
#2) Unknown / 23-JUN-2017	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 13-FEB-2014 / Ongoing
#2) BISOCE (BISOPROLOL FUMARATE) ; JUN-2018 / Ongoing
#3) TAHOR (ATORVASTATIN CALCIUM) ; FEB-2014 / Ongoing
#4) TRIATEC (RAMIPRIL) ; Ongoing
#5) MOLSIDOMINE (MOLSIDOMINE) ; 26-JUN-2017 / Ongoing
#6) FUROSEMIDE (FUROSEMIDE) ; 30-JUN-2017 / Ongoing
(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Myelopathy (Myelopathy)
	Cervicarthrosic myelopathy	
13-FEB-2014 to Ongoing	Relevant Med History	Coronaropathy (Coronary artery disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017053135

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Diarrhea [Diarrhoea]
Lower limb oedema [Oedema peripheral]
persistence of discrete pleural effusion [Pleural effusion]
Pleural effusion in left base [Pleural effusion]
Troponin increase [Troponin increased]
Decrease of libido [Libido decreased]
Persistent slight pleural effusion [Pleural effusion]
Cutaneous pruritic lesions of lower limbs [Skin lesion]
Cutaneous pruritic lesions of lower limbs [Pruritus]
Fissural eczema hand, scalp and lips [Cheilitis]
Bad molecular results [Laboratory test abnormal]
Gastroduodenitis [Gastritis]
Migration of biliary lithiasis [Cholelithiasis]
Constipation [Constipation]
Pulmonary infection [Pneumonia]
Chest pain [Chest pain]
Carpal tunnel syndrome [Carpal tunnel syndrome]
Irregular cardiac rhythm [Arrhythmia]
cardiac insufficiency [Cardiac failure]
pruriginous abdominal cutaneous lesions [Prurigo]
phototoxic erythema of the lower and upper limbs [Photosensitivity reaction]
Elbow eczema [Eczema]
cutaneous xerosis [Dry skin]
right shoulder pain [Arthralgia]
tingling chest wall [Paraesthesia]
Broken teeth [Tooth fracture]
Right hand neurological impairment [Nervous system disorder]
ulnar compression [Nerve compression]
leiomyoma excised following colonoscopy [Leiomyoma]
eczema of popliteal fossa thigh and feet [Eczema]
Median nerve compression [Nerve compression]
Eczema of stasis of the lower limbs/Stasis dermatitis Grade 1 [Stasis dermatitis]
right anterior chest wall tingling [Paraesthesia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 63-year-old male patient received bosutinib (BOSULIF), first regimen since 08Jan2016 at 500 mg 1x/day, oral, second regimen since 08Sep2016 at 300 mg daily, third regimen from 08Sep2016 to 22Sep2016 at 100 mg daily, oral, fourth regimen from 23Sep2016 to 22Oct2016 at 200 mg daily, oral, fifth regimen from 23Oct2016 to 19Dec2016 at 300 mg daily, oral, sixth regimen from 20Dec2016 to 02Jan2017 at 400 mg daily, oral and seventh regimen from 03Jan2017 to 24Jun2019 at 500 mg 1x/day (500 mg, once daily), oral; nicorandil (IKOREL), (Batch/Lot number: unknown) till 23Jun2017, oral for coronary artery disease. The patient's relevant medical history included: "Cervicarthrosic myelopathy" (ongoing), notes: Cervicarthrosic myelopathy; "Coronaropathy", start date: 13Feb2014 (ongoing); "Myocardial infarction", start date: 13Feb2014, stop date: 13Feb2014, notes: Two stent insertion; "Two stent insertion" (unspecified if ongoing), notes: Two stent insertion, for the myocardial infarction; "Pulmonary embolism", start date: 2008, stop date: 2008; "acute coronary syndrome", start date: 13Feb2014 (ongoing); "type 2 diabetes", start date: 2008 (ongoing), notes: treated with benfluorex (MEDIATOR) before 2011; "sleep apnea syndrome", start date: May2013 (ongoing), notes: treated with continuous positive airway pressure; "pain related to carpal and cubital canal procedures" (ongoing), notes: pain related to carpal and cubital canal procedures; "surgery of right cubital canal", start date: 13Jan2014, stop date: 13Jan2014, notes: related pain; "surgery of right carpal canal", start date: 20Apr2015, stop date: 20Apr2015, notes: related pain; "arterial hypertension" (ongoing); "Chronic myeloid leukemia", start date: 05Oct2011 (ongoing); "Overweight" (unspecified if ongoing). Concomitant medication(s) included: KARDEGIC oral taken for prophylaxis, myocardial infarction, start date: 13Feb2014 (ongoing); BISOCE oral taken for hypertension, start date: Jun2018 (ongoing); TAHOR oral taken for prophylaxis, start date: Feb2014 (ongoing); TRIATEC oral taken for prophylaxis (ongoing); MOLSIDOMINE oral taken for coronary artery disease, start date: 26Jun2017 (ongoing); FUROSEMIDE oral taken for hypertension, start date: 30Jun2017 (ongoing); PANTOPRAZOLE oral taken for antacid therapy, start date: 30Jun2017 (ongoing). Past drug history included: Mediator for diabetes, notes: before 2011.
The following information was reported: HEADACHE (non-serious) with onset 08Sep2016, outcome "recovered" (09Sep2016); ARTHRALGIA (non-serious) with onset 08Sep2016, outcome "recovered" (09Sep2016), described as "shoulder pain"; DIARRHOEA (non-serious) with onset 09Sep2016, outcome "recovered" (13Mar2017), DIARRHOEA (non-serious) with onset 20Mar2018, outcome "recovered" (24Sep2018) and all described as "Diarrhea"; NECK PAIN (non-serious) with onset 09Sep2016, outcome "recovered" (09Sep2016); LABORATORY TEST ABNORMAL (non-serious) with onset 12Dec2016, outcome "not recovered", described as "Bad

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

molecular results"; SKIN LESION (non-serious), PRURITUS (non-serious) all with onset 12Dec2016, outcome "recovered" (13Mar2017) and all described as "Cutaneous pruritic lesions of lower limbs"; STASIS DERMATITIS (non-serious) with onset 12Dec2016, outcome "recovered" (13Mar2017), described as "Eczema of stasis of the lower limbs/Stasis dermatitis Grade 1"; CHEST PAIN (non-serious) with onset Jan2017, outcome "recovered" (Jan2017); LIBIDO DECREASED (non-serious) with onset Jan2017, outcome "recovered" (19Mar2018), described as "Decrease of libido"; TROPONIN INCREASED (non-serious) with onset 24Jan2017, outcome "recovered" (2017), described as "Troponin increase"; CHOLECYSTITIS CHRONIC (hospitalization, medically significant) with onset 31Jan2017, outcome "recovered" (24Mar2017), described as "Chronic cholecystitis"; CHEILITIS (non-serious) with onset 13Mar2017, outcome "recovered" (25Jan2018), described as "Fissural eczema hand, scalp and lips"; OEDEMA PERIPHERAL (non-serious) with onset 19Jun2017, outcome "recovered" (04Sep2017), described as "Lower limb oedema"; PHOTOSENSITIVITY REACTION (non-serious) with onset 20Jun2017, outcome "recovered" (Jun2017), described as "phototoxic erythema of the lower and upper limbs"; PLEURAL EFFUSION (hospitalization) with onset 24Jun2017, outcome "recovered" (26Sep2017); PLEURISY (prolonged hospitalization) with onset 24Jun2017, outcome "recovered" (26Sep2017); ECZEMA (non-serious) with onset 24Jul2017, outcome "recovered" (25Jan2018), described as "eczema of popliteal fossa thigh and feet"; PNEUMONIA (non-serious) with onset 13Sep2017, outcome "recovered" (20Oct2017), described as "Pulmonary infection"; CONSTIPATION (non-serious) with onset Sep2017, outcome "recovered" (Nov2017); GASTRITIS (non-serious) with onset Sep2017, outcome "recovered" (12Dec2017), described as "Gastroduodenitis"; CHOLELITHIASIS (non-serious) with onset 26Sep2017, outcome "recovered" (Oct2017), described as "Migration of biliary lithiasis"; LEIOMYOMA (non-serious) with onset 16Nov2017, outcome "recovered" (16Nov2017), described as "leiomyoma excised following colonoscopy"; PLEURAL EFFUSION (non-serious) with onset 11Dec2017, outcome "recovered" (19Mar2018), described as "Pleural effusion in left base"; NERVE COMPRESSION (non-serious) with onset Feb2018, outcome "recovered" (09Feb2018), described as "ulnar compression"; ARRHYTHMIA (non-serious) with onset 19Mar2018, outcome "recovered" (19Apr2019), described as "Irregular cardiac rhythm"; PLEURAL EFFUSION (non-serious) with onset 11Apr2018, outcome "recovered" (24Mar2019), described as "Persistent slight pleural effusion"; PLEURAL EFFUSION (non-serious) with onset 11Apr2018, outcome "recovered" (24Mar2019), described as "persistence of discrete pleural effusion"; CARPAL TUNNEL SYNDROME (non-serious) with onset 2018, outcome "recovered" (24Sep2018); NERVE COMPRESSION (non-serious) with onset 2018, outcome "recovered" (2018), described as "Median nerve compression"; ECZEMA (non-serious) with onset 24Sep2018, outcome "recovered" (17Dec2018), described as "Elbow eczema"; NERVOUS SYSTEM DISORDER (non-serious) with onset 08Oct2018, outcome "recovered" (25Mar2019), described as "Right hand neurological impairment";CARDIAC FAILURE (non-serious) with onset 05Mar2019, outcome "recovered" (04Jul2019), described as "cardiac insufficiency"; PRURIGO (non-serious) with onset Mar2019, outcome "recovered" (23Sep2019), described as "pruriginous abdominal cutaneous lesions"; PLEURAL EFFUSION (hospitalization) with onset 25Mar2019, outcome "recovered" (26Sep2019), described as "increase of pleural effusion"; DRY SKIN (non-serious) with onset 24Jun2019, outcome "recovering", described as "cutaneous xerosis"; PNEUMOTHORAX (medically significant) with onset 10Jul2019, outcome "recovered" (17Jul2019); ARTHRALGIA (non-serious) with onset 11Jul2019, outcome "not recovered", described as "right shoulder pain"; TOOTH FRACTURE (non-serious) with onset Sep2019, outcome "recovered" (Sep2019), described as "Broken teeth"; PARAESTHESIA (non-serious) with onset Sep2019, outcome "recovering", described as "right anterior chest wall tingling"; PARAESTHESIA (non-serious) with onset Sep2019, outcome "recovering", described as "tingling chest wall". The patient was hospitalized for pleural effusion (start date: 28Jun2017); for cholecystitis chronic (start date: 21Mar2017, discharge date: 24Mar2017, hospitalization duration: 3 day(s)). The patient underwent the following laboratory tests and procedures: Angiogram: (28Jun2017) No pulmonary embolism, moderate bilateral, notes: moderate bilateral pleural effusion; Anion gap (8-16): (28Jun2017) 12 mEq/l; Blood bicarbonate (20.0-31.0): (28Jun2017) 23.9 mmol/L; Blood calcium (2.08-2.65): (28Jun2017) 2.05 mmol/L; Blood chloride (99-109): (28Jun2017) 107 mmol/L; Blood creatinine (55-96): (28Jun2017) 91 umol/l; Blood electrolytes: (unspecified date) Normal; Blood glucose (4.1-5.9): (28Jun2017) 7.7 mmol/L; Blood osmolarity: (28Jun2017) 287 mOsm/l; Blood potassium (3.5-4.5): (28Jun2017) 4.5 mmol/L; Blood pressure measurement: (28Jun2019) increased at rest; Blood sodium (132-146): (28Jun2017) 138 mmol/L; Blood thyroid stimulating hormone (0.55-4.78): (28Jun2017) 0.57 MiU; Blood urea (3.3-8.3): (28Jun2017) 7.8 mmol/L; Brain natriuretic peptide (0.1-0.27): (28Jun2017) 0.19450 ng/ml, notes: to analyze with complementary information; Brain natriuretic peptide: (unspecified date) 1967; Cardiac stress test: (06May2019) performed; Chest X-ray: (22Jun2018) persistant slight bilateral pleural effusion; (20Jun2019) more abundant pleural effusion on the left...; (11Jul2019) Left hydropneumothorax; (12Jul2019) reattachment; (23Jul2019) left lung field attached on wall; (26Sep2019) disappearance of pneumothorax, notes: and absence of recurrence of pleural effusion; Cholangiogram: (21Mar2017) Free main bile duct and complete, notes: intrahepatic cholangiogram; Computerised tomogram thorax: (13Sep2017) bilateral pleural effusion pattern, notes: was reported, left apical parenchymal opacity located in upper segment of left upper lobe; (04Feb2019) bilateral pleural effusion; C-reactive protein: (04Sep2017) normal; C-reactive protein: (28Jun2017) Less than 4; Creatinine renal clearance: (unspecified date) 67 ml/min; Cytogenetic analysis (0-100): (27Nov2013) 0.026 %; (18Feb2014) 0.038 %; (03Jun2014) 0.017 %; (30Sep2014) 0.016 %; (06Jan2015) 0.013 %; (13Apr2015) 0.024 %; (20Jul2015) 0.018 %; (19Oct2015) 0.049 %; (14Dec2015) 0.05 %; (07Mar2016) 0.043 %; (13Jun2016) 0.14 %; (20Jul2016) 0.19 %; (12Dec2016) 1.7 %, notes: Increase in transcript rates, no demonstrated mutations; (13Mar2017) 0.01 %; Echocardiogram: (24Jun2019) No pulmonary arterial hypertension; (28Jun2019) normal; (30Jun2017) Ejection fraction maintained, notes: Left ventricular ejection fraction maintained, normal PR interval; Ejection fraction: (06May2019) 43 %; (28Jun2019) 50 %; Electrocardiogram: (09Sep2016) Unremarkable; (31Jan2018) results not provided; (19Mar2018) occasional premature supraventricular complexes, notes: but unmodified compared to the one performed on 31Jan2018; (28Jun2019) normal sinus rhythm with no repolarization disorde; (11Jul2019) Normal; Endoscopy gastrointestinal: (unspecified date) polyp treated with resection; Fibrin D dimer (0-500): (28Jun2017) 3800 ng/ml; Glomerular filtration rate (60-90): (28Jun2017) 77 ml/min, notes: mild renal failure; Glycosylated haemoglobin: (unspecified date) 5.9 %; Haemoglobin (134-167): (28Jun2017) 141 g/l; Histology: (21Mar2017) Chronic scleroatrophic cholecystitis, notes: chronic cholecystitis (vesicular lithiasis) Macroscopic examination: The sample(cholecystectomy) measured 6 cm of length and 2 cm of diameter; Mycobacterium test: (12Jul2019) Ongoing; N-terminal prohormone brain natriuretic peptide (0-0.3): (05Mar2019) 1.643 ng/ml; N-terminal prohormone brain natriuretic peptide (0-300): (25Jun2019) 1967 ng/l; Auscultation: (24Jun2019) vesicular murmur in the left base was reduced...; (28Jun2019) dyspnea - unrevealing examination; Platelet count (161-393): (28Jun2017) 223 x10 9/l; Pleural fluid analysis: (12Jul2019) cloudy liquid, white blood cells 12200 /mm3...; Protein total (57-82): (28Jun2017) 65 g/l; Red blood cell count (4.28-5.57):

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

(28Jun2017) 4.70 x10 12/l; Scan myocardial perfusion: (06May2019) No sign of ischemia was observed...; Troponin: (24Jan2017) increased; (28Jun2017) 0.000033 ug/ml, notes: normal range reported as: detection of myocardiac impairment more than 0.06 ug/l/detection of myocardial infarction more than 0.5 ug/l; Weight: (unspecified date) 113 kg; White blood cell count (4.05-9.92): (28Jun2017) 9.3 x10 9/l. The action taken for bosutinib was dosage permanently withdrawn on 24Jun2019; for nicorandil was dosage permanently withdrawn on 23Jun2017. Therapeutic measures were taken as a result of pleurisy, cholecystitis chronic, pleural effusion, skin lesion, pruritus, cheilitis, pneumonia, chest pain, carpal tunnel syndrome, nerve compression, leiomyoma.
Clinical course: Nicorandil was discontinued on 23Jun2017 and replaced by molsidomine started from 26Jun2017 and ongoing. On 08Sep2016, patient experienced headache (grade(G)3) and diarrhea (G1), shoulder pain (G3), non-serious. On 09Sep2016, underwent an ECG that was unremarkable, and experienced neck pain non-serious on 09Sep2016. For the events headache and pain to neck and shoulders went to the emergency room on 09Sep2016 for X-rays, BP and biology for cervical pain. It was not hospitalization, just consultation. On 12Dec2016 experienced cutaneous pruritic lesions of lower limbs, non-serious and resolved on 13Mar2017. In Jan2017 developed G1 chest pain. Subject(Sj) received treatment (TX) by nicorandil (IKOREL) and ramipril (TRIATEC). Event resolved in Jan2017. No action was taken with bosutinib in response to events. On 24Jan2017 developed G1 troponin increase and resolved in 2017. The INV was aware of the 2 events on 25Jan2017. As of 01Mar2017 there were 4 nummular lichenified plates still excoriated at the pretibial level of right lower limb and one plate nummular of left tibia with a small nodule of prurigo nearby. It was proposed to switch to dermocorticoids with betamethasone valerate (BETESIL) to treat the remaining lesions and to avoid the scraping and the lichenification of these lesions. TX with dermocorticoids was very effective. On Jan2017, sj developed G2 decrease of libido and resolved on 19Mar2018. On 31Jan2017, sj had chronic cholecystitis G3. On 07Feb2017 sj had a cholecystectomy scheduled for chronic cholecystitis G3. Seriousness criteria were hospitalization and medically important. Laparoscopic Cholecystectomy with cholangiography was scheduled. Consultation on 27Feb2017 with histopathology: presence of a symptomatic vesicular lithiasis that requires TX by laparoscopic route. Sj underwent cholecystectomy with laparoscopic cholangiography on 21Mar2017. Sampling was performed on 21Mar2017 for histopathologic studies. Macroscopic examination: The sample (cholecystectomy) measured 6 cm of length and 2 cm of diameter. The wall of normal thickness seemed to be fibrotic. No lymph node was observed. No biliary calculus was reported. Microscopic examination: Chronic scleroatrophic cholecystitis was diagnosed. Gallbladder wall was reduced to a thin fibrous strip, which allowed the persistence of few degenerative smooth muscle bundles. The wall was constituted of atrophied mucosa reduced to cuboidal or endothelial (AS REPORTED) form epithelium which was sj of mucinous metaplasia. Surgery report was as follows: The surgery was cholecystectomy with cholangiography by laparoscopy on 21Mar2017. The vesicular lithiasis was evidenced in Mar2017 and sj was treated by bosutinib therefore the chronic cholecystectomy was not a medical history. This surgery was performed on 21Mar2017 due to cholelithiasis. No physical or laboratory sign was suggestive of calculous migration of main bile duct. Sj suffered from chronic cholecystitis with atrophied gallbladder at the level of junction between segment IV and V of liver. Transcystic cholangiography revealed free main bile duct and complete intrahepatic cholangiogram. Dissection was particularly difficult on cystic pedicle near to main bile duct. Sj developed bad molecular results on 12Dec2016 and G2 fissural hand eczema hand, scalp and lips on 13Mar2017. The event 'bad molecular response' corresponded to molecular hematology test performed on 12Dec2016 finding a BCR/ABL level of 1.7%. BCR-ABL levels: 0.026% on 27Nov2013, 0.038% on 18Feb2014, 0.017% on 03Jun2014, 0.016% on 30Sep2014, 0.013% on 06Jan2015,0.024% on 13Apr2015, 0.018% on 20Jul2015, 0.049% on 19Oct2015,0.05% on 14Dec2015, 0.043% on 07Mar2016, 0.14% on 13Jun2016, 0.19% on 20Jul2016. Therapeutic measures were taken as a result of the event fissural hand eczema hand, scalp and lips included clobetasol (CARELUX GE) and betamethasone (DIPROSONE). On 19Jun2017, sj developed lower limb oedema rated G1 and resolved on 04Sep2017. On 24Jun2017, sj started to experience chest pains leading to hospitalization on 28Jun2017. Cardiac origin was excluded. Same day thoracic angiogram performed eliminated a pulmonary embolism; moderate bilateral pleural effusion was observed. Pleural effusion occurred on 24Jun2017; the sj experienced severe pleurisy G3 requiring prolonged hospitalization and resolved on 20Oct2017. No action was taken with bosutinib. On 24Jul2017 the sj experienced eczema of popliteal fossa thigh and feet (G2) and recovered on 25Jan2018. Laboratory analysis performed on 28Jun2017. On 30Jun2017 an EKG performed found LVEF maintained, normal PR interval, systolic pulmonary arterial pressure at 30 mmHg, dry pericardium, moderate bilateral pleural effusion. On 25Jul2017 pneumology visit was done and report was sent on 04Sept2017 mentioning moderate restrictive impairment related to overweight without obstructive syndrome. On 04Sep2017 haematologist visit was reported. Chest auscultation revealed a decrease of breath sounds in both lower lung fields with clear pleural rub on left side. CRP was normal. Repeat chest scan was planned and performed on 13Sep2017: sj developed pulmonary infection rated G2 and resolved on 20Oct2017. In response to this event bosutinib was withdrawn. It was also reported that bosutinib was ceased for concomitant event of bilateral pleurisy. Amoxicillin sodium clavulanic acid (AUGMENTIN) 3 times per day was prescribed for 7 days. The event did not reoccur after resumption of bosutinib. On 15Sep2017 pneumology consultation in emergency was reported following chest scan which showed bilateral pleurisy that was more important than in Jun2017, which looked symmetric but with clear increase of quantity of pleurisy. Thoracic scan report performed on 13Sep2017. In conclusion, bilateral pleural effusion pattern was reported and moreover left apical parenchymal opacity located in upper segment of left upper lobe which measured about 16 mm which required specialist advice. Facing a possible infectious origin amoxicillin potassium clavulanate (AUGMENTIN) 1 g 3 times a day for 7 days and prednisolone metasulfobenzoate sodium (SOLUPRED) at 40 mg by oral route once a day for 4 days were prescribed. On 30Jun2017 FUROSEMIDE 20 mg by oral route once a day was prescribed with renewal for a month. Sj would be examined on 26Sep2017 by pneumologist with X-ray imaging and repeat scan would be performed within a month for pleurisy evaluation. In case of sequelae showed by imaging, repeat examination would eventually be prescribed. On 14Sep2017 and 15Sep2017 bosutinib monohydrate (BOSULIF) was discontinued. The event diarrhea resolved on 13Mar2017. Sj was no more taking concomitant medications emollients and protective (XERACALM) and betamethasone sodium phosphate cream (DIPROSONE) because lesions healed on 13Mar2017. The outcome of event (cholecystectomy scheduled for chronic cholecystitis) was resolved on 21Mar2017, of headache, neck pain and shoulder pain was resolved on 09Sep2016, of event bad molecular results was not recovered, of event Fissural eczema hand, scalp and lips was recovered on 25Jan2018, and of pleural effusion and bilateral pleurisy was resolved on 26Sep2017. Sj was still receiving the study medication. In Sep2017, sj developed constipation rated G2 and resolved in Nov2017. In Sep2017, sj developed gastroduodenitis rated G2 and recovered on 12Dec2017. On 26Sep2017, sj developed migration of biliary lithiasis rated G2 and resolved in Oct2017. The investigator was advised of these 2 events in Sep2017. On 25Jan2018 fissural eczema hand, scalp and lips was resolved. On

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

09Feb2018 sj underwent surgery for the right carpal canal and the right ulnar compression. Sequelar pain and paresthesia were still present following these 2 surgeries. The event resolved on 09Feb2018. Sj was not receiving any concomitant medication at the onset of the event. The investigator was aware of this event during visit M18. On 09Feb2018, the patient underwent a double surgery for right carpal tunnel and ulnar compression. On 20Mar2018, sj developed diarrhea, rated G1 and recovered on 24Sep2018. At consultation visit on 28Jun2018, it was noted that sj had rare diarrheas, therefore the outcome of the event was resolving. Sj was not receiving any concomitant medication at the onset of the event. The investigator was aware of this event during visit M18. On 19Mar2018, sj developed irregular cardiac rhythm rated G1 recovered on 19Apr2019. He had irregular pulse during the medical visit therefore a repeat ECG was performed on the same day 19Mar2018: occasional premature supraventricular complexes but unmodified compared to the one performed on 31Jan2018 (results not provided). It was reported, the outcome of the irregular cardiac rhythm was not noted and a Holter ECG was planned. Regarding the event arrhythmia, the investigator was waiting for the Holter result to decide if the event was resolved or not. On 11Apr2018, sj developed persistent slight pleural effusion G1, assessed as non-serious and resolved on 24Mar2019. A chest X-ray was done on the same day and evaluated as persistent slight bilateral pleural effusion. On 08Oct2018, there was permanent paresthesia in the 4th and 5t finger of right hand with hypoesthesia of 5th finger of right hand. The patient complained of retraction and cold limbs at the level of this right hand. At that time, it was at 7 months from the 2nd ulnar nerve release on the right side. On 04Feb2019, Thoracic scan showed bilateral pleural effusion. On 05Mar2019 sj experienced cardiac insufficiency, which was assessed as non-serious and of G1. On 05Mar2019 N-terminal prohormone brain natriuretic peptide was 1643 ng/l (normal range 0 - 300 ng/l). On 25Mar2019, sj experienced increase of pleural effusion which was assessed as serious as hospitalization and of G2. Sj developed increase of bilateral pleural effusion. Sj refused to perform the pleural puncture. Sj presented with improvement of pleural effusion under diuretic. Cardiac insufficiency recovered on 04Jul2019. In Jun2017 there was an absence of pulmonary arterial hypertension. The first episode of the pleural effusion was in Jun2017. The possible several causes of pleural effusion were: heart failure, occurrence of pulmonary arterial hypertension, bosutinib. At the time of reporting, sj was recovering from the event increase of pleural effusion and was not recovered from the event cardiac insufficiency. Sj experienced pruriginous abdominal cutaneous lesions (G2) in Mar2019 and reported as non-serious and recovered on 23Sep2019. Sj presented for few weeks pruritus associated with cutaneous lesions. No action was taken with bosutinib in response to these events. On 25Mar2019, pleural effusion increased, became serious on 10Jul2019 when sj was hospitalized. Following the increase of pleural effusion, cardiac eval was requested. On 06May2019, myocardial scintigraphy showed anterior and inferior area of low levels of uptake similar to images performed after a stress test and at rest test, with no significant contraction disorder related to non-significant attenuation. No sign of ischemia was observed. Ejection fraction was at 43% with a diffuse dilation of left ventricular. Stress test performed at 60% of theoretical maximum heart rate due to sj's deconditioning. Despite the event, bosutinib was unchanged. On 03Jun2019, sj started lansoprazole (OGAST) antiulcer drug. Stomach pain was not resolved. On 20Jun2019, CXR showed a more pleural effusion on the left. Pleural effusion increased significantly. There was a decrease in ventilation of the lower left lobe. The pulmonologist decided to schedule an exploratory thoracentesis on 09Jul2019.On 24Jun2019, hematologist consult who had access to cardiac ultrasound did not show pulmonary arterial hypertension. On auscultation, vesicular murmur in the left base was significantly reduced with an effusion 1/3 of the way thru the fields. Pleural effusion rated as G2. On 28Jun2019, cardiology consultation, the sj did not complain of chest pain but presented with dyspnea (HYHA stage II), he regularly used the ventilator device. Examination was unrevealing except the overweight. Blood pressure tend to increase at rest. EKG disclosed normal sinus rhythm with no repolarization disorder. Cardiac US was normal: LVEF at 50%, no impairment of segmental motion, no valve disorder and no structural anomaly. Relaxation impairment during filling phase was detected during the examination but was variable. Blood work-up showed N-terminal pro-brain natriuretic peptide 1967, glycated hemoglobin 5.9%, creatinine clearance 67 mL/min. Blood electrolytes were normal. The cardiac origin of pleural effusion was evoked. A heart failure with preserved EF could (grade II dyspnea, preserved LVEF, high N-terminal pro-brain natriuretic peptide, variable relaxation impairment), no peripheral congestive sign, no signif valve dse and no sign of pulm HTN was detected but hardly involved in pleural effusion. On cardiac level, the initiation of valsartan sacubitril sodium salt complex (ENTRESTO) was scheduled after the next visit. A causal role of bosutinib (unspecified trade name) could not be excluded. On 02Jul2019, hematology consultation. Left pleural effusion clinically decreased. For the cardiologist, there are no clear signs of heart failure. On 09Jul2019, exploratory thoracentesis was planned but failure because pleural effusion was not very abundant. On 10Jul2019, sj with left basithoracic pain with dyspnea after one night under controlled positive pressure machine (sleep apnea). On 11Jul2019, chest X-ray found hydropneumothorax of the large left cavity. Advice for a quick specialized advice on possible drainage. On 11Jul2019, 17 p.m., sj went to the emergency room, the sj was stable, eupneic hypertensive and apyretic. ECG was normal with no indication of urgency to drain this day. At 9:00 p. m., transfer to pneumology unit. On 12Jul2019, drainage with reattachment on the repeat X-ray. Puncture analysis of pleural fluid showed cloudy liquid, white blood cells 12200 /mm3 of which neutrophils 32%, lymphocytes 26%, eosinophils 30%, monocytes 12%, proteins 44 g/L, no germ. After 3 days, the culture returned sterile. Mycobacteria test was pending. On 16Jul2019, sj was clinically stable. There was persistence of apical detachment. The drain was maintained. Repeat X-ray planned on 17Jul2019. On 23Jul2019, a chest X-ray was performed and found left lung field on wall another chest X-ray was done on 26Sep2019 and found that disappearance of pneumothorax and absence of recurrence of pleural effusion. The sj had no further TX for CML since 24Jun2019 because he had been in deep molecular response for 2.5 years. He was in TX free remission FU. On 16Sep2019, the sj experienced unspecified event. In response to the increase of pleural effusion, bosutinib was discontinued on 24Jun2019. On 17Jul2019, the sj was discharge from hospital. On 26Sep2019, the sj recovered from the event 'increase of pleural effusion'. The sj experienced cheilosis from Apr2017 to 27Apr2017, phototoxic erythema of the lower and upper limbs from 20Jun2017 to Jun2017, Eczema of the epicondyle from Feb2017 to Feb2017, Elbow eczema from 24Sep2018 to 17Dec2018, lower limbs pain from Oct2018 to 17Dec2018, cutaneous xerosis ongoing since 24Jun2019, Arterial hypertension from 11Jul2019 to 11Jul2019, right shoulder pain ongoing since 11Jul2019, tingling chest wall (a contralateral tingling sensation for about ten seconds several times a day on the right anterior chest wall) from Sep2019 (outcome recovering, action taken for bosutinib to the event was not applicable), broken teeth (The patient accidentally broke his teeth 21 and 22) from Sep2019 to Sep2019, right hand neurological impairment from 08Oct2018 to 25Mar2019, ulnar compression from Feb2018 to 09Feb2018, leiomyoma (rated as G2) excised following colonoscopy of 16Nov2017 recovered on the same day. The digestive endoscopy showed polyp treated with resection. After analysis, there was a complete exeresis of leiomyoma. The sj experienced serious AE Pneumothorax, 'already reported in increase of pleural effusion' from 10Jul2019 to 17Jul2019. On 20Apr2022, it was reported Median nerve compression from

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

2018 to 2018 with release of the median nerve. A pleural effusion was reported from 24Jun2017 to 26Sep2017, a discrete effusion from 11Apr2018 to 24Mar2019 and an increase of this effusion from 25Mar2019 to 26Sep2019. As of 23May2023, it was reported that following concomitant treatment with Xeracalm disprosone cream Ikorel the patient underwent a cholecystectomy with laparoscopic cholangiography on 21Mar2017, surgical procedure initiated because of a chronic cholecystitis (vesicular lithiasis) awareness of the event on 29Mar2017 (TEC).

The reporter considered "increase of pleural effusion", "headache", "neck pain", "shoulder pain", "diarrhea", "lower limb oedema", "troponin increase", "decrease of libido" and "persistent slight pleural effusion" related to bosutinib. The reporter considered "pleurisy", "chronic cholecystitis", "cutaneous pruritic lesions of lower limbs", "fissural eczema hand, scalp and lips", "bad molecular results", "gastroduodenitis", "migration of biliary lithiasis", "constipation", "pulmonary infection", "chest pain", "carpal tunnel syndrome", "irregular cardiac rhythm", "cardiac insufficiency", "pruriginous abdominal cutaneous lesions", "elbow eczema", "cutaneous xerosis", "tingling chest wall", "broken teeth", "right hand neurological impairment", "ulnar compression", "leiomyoma excised following colonoscopy", "eczema of popliteal fossa thigh and feet", "eczema of stasis of the lower limbs/stasis dermatitis grade 1" and "right anterior chest wall tingling" not related to bosutinib.
The reporter's assessment of the causal relationship of "pleural effusion", "pneumothorax", "persistence of discrete pleural effusion", "pleural effusion in left base", "phototoxic erythema of the lower and upper limbs", "right shoulder pain" and "median nerve compression" with the suspect product(s) bosutinib was not provided at the time of this report. Since no determination has been received, the case is managed based on the company causality assessment.

FU (29Oct2020): New information includes: new events.
FU (23Feb2021): Updated the verbatim term from fissural hand eczema to fissural eczema hand, scalp and lips, recovery date and causal relationship to conmeds and to Bosulif provided. New event: eczema of popliteal fossa thigh and feet was added.
FU (01Dec2021 and 02Dec2021): Updated information: patient's weight and height, new dosage of bosutinib, additional lab, ongoing coronaropathy; onset/ resolved date of some events; outcome of pleurisy and broken teeth; resolved date of leiomyoma, additional causality and clinical course.
FU (03Dec2021): Updated information: outcome of decrease of libido.
FU (01Mar2022): This is a Non-Interventional Study for Protocol B1871047. Updated information: decrease of libido onset updated.
FU (10Mar2022): Updated information included: The event Right hand neurological impairment recovery updated to 25Mar2019.
FU (19Apr2022),(20Apr2022),(22Apr2022): This is a non interventional study from the clinical team following a monitoring visit and a non-interventional study from the investigational site via the CRO. Updated information includes: Reaction data (Events pleural effusion Onset 11Dec2017, pleural effusion onset 11Apr2018, and Median nerve compression added, event increase of pleural effusion from 25MAR2019 serious as hospitalization, Gastroduodenitis recovered on 12Dec2017. Event stomach pain grade 2 on 28May2019 was deleted. Irregular cardiac rhythm recovered on 19Apr2019. pruriginous abdominal cutaneous lesions recovered on 23Sep2019, cardiac insufficiency recovered on 04Jul2019. Decrease of libido recovered on 19Mar2018. Event ' Carpal tunnel syndrome 'on 09Feb2018 changed to 'Carpal tunnel syndrome' from 2018 to 24Sep2018 unrelated to study drug. Diarrhea start date was changed from 19Mar2018 to 20Mar2018 and recovered on 24Sep2018. Event pleurisy recovered on 26Sep2017. For Event 'Carpal tunnel surgery' it was reported: a double surgery for right carpal tunnel and ulnar compression on 09Feb2018), Concomitant drug KARDEGIC was received for Myocardial infarction from 13Feb2014, FUROSEMIDE for hypertension, bisoprolol fumarate (BISOCE) for hypertension.
Follow-up (08Feb2023): This is a follow-up to a non-interventional study for protocol B1871047. Updated information: outcome of event tingling chest wall was updated to resolving, onset date of event shoulder pain corrected from 09Sep2016 to 08Sep2016; for event 'Persistent slight pleural effusion' onset updated to 11Apr2018, event recovered on 24Mar2019, event related to study drug. Event term 'Cholecystectomy scheduled for chronic cholecystitis' updated to 'Chronic cholecystitis' onset on 31-JAN-2017, recovered on 21-MAR-2017 ulnar compression unrelated to study drug.
Follow-ups (23May2023): This is a follow-up to a non-interventional study for protocol B1871047received from the CRO. Updated information included: Investigator Initial Aware Date, classification (Post Auth. Safety Study), reporter details (first name, postal code, city, address, email address), new reporter (other HCP), lab test Cytogenetic analysis details (low/high norm, new result- 13Mar2017, notes for 12Dec2016), Bosulif details (new dosage regimen), event Cholecystitis chronic details (stop date), new event (Stasis dermatitis Grade 1), clinical course.
Follow-up (28Jun2023 and 29Jun2023): This is a follow-up to a non-interventional study from CRO is as follows. Update information: The event term 'discrete effusion' was updated for 'persistence of discrete pleural effusion'. New event added 'right anterior chest wall tingling' in Sep2019, rated grade 1, resolving, unrelated to bosutinib and concomitant drugs.
Follow-up (26Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: seriousness of event "increase of pleural effusion" updated to serious (hospitalization).
Follow-up (26Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information includes: Investigator Initial Aware Date updated from 19Jun2017 to 08Sep2016 and stop date for bosutinib dosage regimen at 500 mg started on 03Jan2017 reported as 26Jun2019 (previously ongoing).
Follow-up (27Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: outcome of event Skin xerosis (24Jun2019) updated to resolving, reporter's causality for events skin xerosis and elbow eczema (24Sep2018) provided as not related to study drug bosutinib or concomitant medication.

Follow-up (14Nov2023): new information received from Clinical team following reconciliation.
Updated information: Query response (confirmed: the event Arterial hypertension (11Jul2019) has to be removed in Safety database as site staff confirmed AE is NCI and does not have to be reported when they answered to query. The event Eczema of the

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

epicondyle (Feb2017) has be removed in Safety database as site staff answered to query and replied that AE is already recorded under Eczema of stasis of the lower limbs. The event Cheilosis (Apr2017) has to be removed in Safety database as site staff answered to query and replied that AE is already recorded under another Cheilitis. The event Lower limbs pain (Oct2018) has to be removed in Safety database as site staff answered to query and replied that AE was not reported.

Case Comment: Considering the known drug safety profile, the company cannot exclude that pleural effusion (five episodes), shoulder and neck pain, headache, diarrhea (two episodes), and edema of lower limbs are related to the suspect drug bosutinib. Conversely, for all the remaining events, the reported information does not provide any evidence or argument suggesting a positive drug-event causal relationship, therefore the company considers all the other events unrelated to bosutinib. This case will be reassessed should additional information become available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	28-JUN-2017	Angiogram moderate bilateral pleural effusion	No pulmonary embolism, moderate bilateral	
2	28-JUN-2017	Anion gap	12 mEq/l	16 8
3	28-JUN-2017	Blood bicarbonate	23.9 mmol/L	31.0 20.0
4	28-JUN-2017	Blood calcium	2.05 mmol/L	2.65 2.08
5	28-JUN-2017	Blood chloride	107 mmol/L	109 99
6	28-JUN-2017	Blood creatinine	91 umol/l	96 55
7		Blood electrolytes	Normal	
8	28-JUN-2017	Blood glucose	7.7 mmol/L	5.9 4.1
9	28-JUN-2017	Blood osmolarity	287 mOsm/l	
10	28-JUN-2017	Blood potassium	4.5 mmol/L	4.5 3.5
11	28-JUN-2019	Blood pressure measurement	increased at rest	
12	28-JUN-2017	Blood sodium	138 mmol/L	146 132
13	28-JUN-2017	Blood thyroid stimulating hormone	0.57 MiU	4.78 0.55
14	28-JUN-2017	Blood urea	7.8 mmol/L	8.3 3.3
15		Brain natriuretic peptide	1967	
16	28-JUN-2017	Brain natriuretic peptide to analyze with complementary information	0.19450 ng/ml	0.27 0.1
17	28-JUN-2017	C-reactive protein	Less than 4 mg/l	
18	04-SEP-2017	C-reactive protein	normal	
19	06-MAY-2019	Cardiac stress test	performed	
20	22-JUN-2018	Chest X-ray	persistant slight bilateral	

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
			pleural effusion	
21	20-JUN-2019	Chest X-ray	more abundant pleural effusion on the left...	
22	11-JUL-2019	Chest X-ray	Left hydropneumothorax	
23	12-JUL-2019	Chest X-ray	reattachment	
24	23-JUL-2019	Chest X-ray	left lung field attached on wall	
25	26-SEP-2019	Chest X-ray and absence of recurrence of pleural effusion	disappearance of pneumothorax	
26	21-MAR-2017	Cholangiogram intrahepatic cholangiogram	Free main bile duct and complete	
27	13-SEP-2017	Computerised tomogram thorax was reported, left apical parenchymal opacity located in upper segment of left upper lobe	bilateral pleural effusion pattern	
28	04-FEB-2019	Computerised tomogram thorax	bilateral pleural effusion	
29		Creatinine renal clearance	67 ml/min	
30	27-NOV-2013	Cytogenetic analysis	0.026 %	1000
31	18-FEB-2014	Cytogenetic analysis	0.038 %	1000
32	03-JUN-2014	Cytogenetic analysis	0.017 %	1000
33	30-SEP-2014	Cytogenetic analysis	0.016 %	1000
34	06-JAN-2015	Cytogenetic analysis	0.013 %	1000
35	13-APR-2015	Cytogenetic analysis	0.024 %	1000
36	20-JUL-2015	Cytogenetic analysis	0.018 %	1000
37	19-OCT-2015	Cytogenetic analysis	0.049 %	1000
38	14-DEC-2015	Cytogenetic analysis	0.05 %	1000
39	07-MAR-2016	Cytogenetic analysis	0.043 %	1000
40	13-JUN-2016	Cytogenetic analysis	0.14 %	1000
41	20-JUL-2016	Cytogenetic analysis	0.19 %	1000
42	12-DEC-2016	Cytogenetic analysis Increase in transcript rates, no demonstrated mutations.	1.7 %	1000

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
43	13-MAR-2017	Cytogenetic analysis	0.01 %	100 0
44	30-JUN-2017	Echocardiogram Left ventricular ejection fraction maintained, normal PR interval	Ejection fraction maintained	
45	24-JUN-2019	Echocardiogram	No pulmonary arterial hypertension	
46	28-JUN-2019	Echocardiogram	normal	
47	06-MAY-2019	Ejection fraction	43 %	
48	28-JUN-2019	Ejection fraction	50 %	
49	09-SEP-2016	Electrocardiogram	Unremarkable	
50	31-JAN-2018	Electrocardiogram	results not provided	
51	19-MAR-2018	Electrocardiogram but unmodified compared to the one performed on 31Jan2018	occasional premature supraventricular complexes	
52	28-JUN-2019	Electrocardiogram	normal sinus rhythm with no repolarization disorde	
53	11-JUL-2019	Electrocardiogram	Normal	
54		Endoscopy gastrointestinal	polyp treated with resection	
55	28-JUN-2017	Fibrin D dimer	3800 ng/ml	500 0
56	28-JUN-2017	Glomerular filtration rate mild renal failure	77 ml/min	90 60
57		Glycosylated haemoglobin	5.9 %	
58	28-JUN-2017	Haemoglobin	141 g/l	167 134
59	21-MAR-2017	Histology chronic cholecystitis (vesicular lithiasis) Macroscopic examination: The sample(cholecystectomy) measured 6 cm of length and 2 cm of diameter	Chronic scleroatrophic cholecystitis	
60	12-JUL-2019	Mycobacterium test	Ongoing	
61	05-MAR-2019	N-terminal prohormone brain natriuretic peptide	1.643 ng/ml	0.3 0
62	25-JUN-2019	N-terminal prohormone brain natriuretic peptide	1967 ng/l	300 0
63	24-JUN-2019	Physical examination	vesicular murmur in the left base was reduced...	

Mfr. Control Number: 2017053135

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
64	28-JUN-2019	Physical examination	dyspnea - unrevealing examination	
65	28-JUN-2017	Platelet count	223 x10 9/l	393 161
66	12-JUL-2019	Pleural fluid analysis	cloudy liquid, white blood cells 12200 /mm3...	
67	28-JUN-2017	Protein total	65 g/l	82 57
68	28-JUN-2017	Red blood cell count	4.70 x10 12/l	5.57 4.28
69	06-MAY-2019	Scan myocardial perfusion	No sign of ischemia was observed...	
70	24-JAN-2017	Troponin	increased ug/ml	
71	28-JUN-2017	Troponin normal range reported as: detection of myocardiac impairment more than 0.06 ug/l/detection of myocardial infarction more than 0.5 ug/l	0.000033 ug/ml	
72		Weight	113 kg	
73	28-JUN-2017	White blood cell count	9.3 x10 9/l	9.92 4.05

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Unknown	08-SEP-2016 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	100 mg, daily; Oral	Unknown	08-SEP-2016 / 22-SEP-2016; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Oral	Unknown	23-SEP-2016 / 22-OCT-2016; 30 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Oral	Unknown	23-OCT-2016 / 19-DEC-2016; 58 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	400 mg, daily; Oral	Unknown	20-DEC-2016 / 02-JAN-2017; 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	500 mg, once daily; Oral	Unknown	03-JAN-2017 / 24-JUN-2019; 2 years 5 months 22 days

Mfr. Control Number: 2017053135

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) PANTOPRAZOLE (PANTOPRAZOLE) ; 30-JUN-2017 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
13-FEB-2014 to 13-FEB-2014	Relevant Med History Two stent insertion	Myocardial infarction (Myocardial infarction);
Unknown	Relevant Med History Two stent insertion, for the myocardial infarction	Stent placement (Stent placement);
2008 to 2008	Relevant Med History	Pulmonary embolism (Pulmonary embolism);
13-FEB-2014 to Ongoing	Relevant Med History	Acute coronary syndrome (Acute coronary syndrome);
2008 to Ongoing	Relevant Med History treated with benfluorex (MEDIATOR) before 2011	Type 2 diabetes mellitus (Type 2 diabetes mellitus);
MAY-2013 to Ongoing	Relevant Med History treated with continuous positive airway pressure	Sleep apnea syndrome (Sleep apnoea syndrome);
Unknown to Ongoing	Relevant Med History pain related to carpal and cubital canal procedures	Procedural pain (Procedural pain);
13-JAN-2014 to 13-JAN-2014	Relevant Med History related pain	Peripheral nerve decompression (Peripheral nerve decompression);
20-APR-2015 to 20-APR-2015	Relevant Med History related pain	Carpal tunnel decompression (Carpal tunnel decompression);
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
Unknown	Past Drug Event before 2011	MEDIATOR (MEDIATOR); Drug Indication: Diabetes (Diabetes mellitus)
05-OCT-2011 to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);
Unknown	Relevant Med History	Overweight (Overweight);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1973	43 Years	Male	73.00 kg	04	OCT	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Lower limb pain [Pain in extremity]
Coccyx fracture while skiing [Fractured coccyx]
Constipation [Constipation]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) ICLUSIG (PONATINIB HYDROCHLORIDE)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, daily	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloblastic leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 01-SEP-2016 / 24-MAY-2018	#1) 569 days
#2) 25-MAY-2018 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017066942

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
06-MAR-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047. This is a Non-Interventional study reporting non-serious events only.

A 43-year-old male subject received oral bosutinib (BOSULIF, film coated-tablet) at 500 mg daily from 01Sep2016 to 24May2018 for chronic myeloblastic leukemia. The subject received ponatinib hydrochloride (ICLUSIG) from 25May2018, at unspecified dose, for unspecified indication.
Medical history was none. On 04Oct2016, the subject experienced diarrhea, CTCAE grade 1, which was reported as non-serious. The subject recovered from diarrhea in Jun2017. On an unspecified date in Oct2016, the subject experienced lower limb pain, CTCAE grade 2, which was reported as non-serious. The subject recovered from lower limb pain on 02Nov2016. Bosutinib was pursued at unchanged dosage in response to these events. Therapeutic measure taken as result of the event diarrhea included racecadotril (TIORFAN) and result of the event lower limb pain included paracetamol (unspecified trade name). The subject presented with coccyx fracture in 2018 while skiing, assessed as non-serious and grade 1 by the investigator. On 26Feb2018, the subject fully recovered from coccyx fracture. On 24May2018, the subject developed lack of efficacy with bosutinib, rated grade 1. The subject was treated with bosutinib for a chronic myeloblastic leukemia in chronic phase which stayed relatively resistant. Bosutinib was permanently withdrawn on 24May2018 since blood count and liver function test were strictly normal but the study of the residual disease still showed a very slight decrease of molecular signal. The subject experienced constipation in May2018. The event was reported as non-serious and rated grade 1. The event resolved on 21Aug2018. Action taken with bosutinib for this event was reported as not applicable, no action was taken with ponatinib hydrochloride (ICLUSIG).
The investigator considered the event diarrhea as possibly related to study drug.
The investigator considered event lack of efficacy as related to study drug bosutinib and unrelated to concomitant medications.
The investigator considered the event coccyx fracture while skiing and lower limb pain as not related to bosutinib.
According to the reporter, the event constipation was unrelated to bosutinib and related to concomitant drug ponatinib hydrochloride.

Follow-up (03Apr2017): New information received includes dose, frequency and route of administration of suspect drug. The investigator considered the events lower limb pain and diarrhea as possibly related to study drug (Initially the reporter's assessment of the causal relationship of the event limb pain with bosutinib was not provided. It was now informed that the investigator considered the event lower limb pain as possibly related to study drug).

Follow-up (10Jul2017): New information received from investigational site includes product start date.

Follow-up (11Aug2017): Follow-up attempts completed. No further information expected.

Follow-up (17Aug2018): New information received from the CRO includes: product information added, new non-serious event lack of efficacy of bosutinib added.

Follow-up (25Apr2019): New information received includes new event coccyx fracture.

Follow-up (03May2019): New information received from the investigator, includes: Relevant medical history and concomitant medications information updated. Event 'coccyx fracture' outcome, grading, seriousness and causality assessment (previously missing, now unrelated), provided. Action with bosutinib in response to 'coccyx fracture', provided.

Follow-up (22May2019): New information received from the investigational site included updated action taken with bosutinib with updated stop date and reason of the withdrawal.

Follow-up (30Aug2019): New information received from the investigational site included: Event lower limb pain onset date updated. Recovery date for previously reported event 'diarrhea' provided. Investigator's causality for previously reported event 'lower limb pain' updated from 'related' to 'unrelated'.

Follow-up (01Jul2020): new information received includes updated therapy dates and doses of bosutinib, additional event (constipation) and additional suspect drug ponatinib hydrochloride (suspect only for the event constipation).

Follow-up (06Jul2020) : New information received from investigational includes start date for co-suspect ponatinib hydrochloride.

Follow-up (06Mar2023): This is a Non-interventional study report for Protocol B1871047.
Updated information includes Investigator Aware Date reported as 26Feb2018 for event 'Fractured coccyx'.

Case Comment: Based on the information provided and temporal association, the Company considers there is a reasonable possibility that the reported events lower limb pain and diarrhea are related to BOSUTINIB. Coccyx fracture is more likely secondary to an accident rather than an adverse reaction of bosutinib. Constipation is not related to bosutinib but is more likely related to concomitant drug ponatinib hydrochloride.
The follow-up information received does not alter the previous company clinical evaluation.

Mfr. Control Number: 2017066942

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Full blood count	strictly normal	
2		Liver function test	strictly normal	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		JAN	1945	71 Years	Female	80.00 kg		NOV	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea grade 1 [Diarrhoea]
Diarrhea grade 1 [Diarrhoea]
Diarrhea grade 3 [Diarrhoea]
Nausea [Nausea]
vomiting [Vomiting]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukaemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 09-NOV-2016 / Unknown	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2016 to Unknown	Relevant Med History	Carotid artery stenosis (Carotid artery stenosis) tight stenosis of the right carotid for which an endarterectomy was performed on 13Jul2016
13-JUL-2016 to 13-JUL-2016	Relevant Med History	Endarterectomy (Endarterectomy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017067222

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 71-year-old female patient received bosutinib (BOSULIF), first regimen since 09Nov2016 at 500 mg daily and second regimen since 06Dec2017 (ongoing) at 400 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: "carotid stenosis", start date: 2016 (unknown if ongoing), notes: tight stenosis of the right carotid for which an endarterectomy was performed on 13Jul2016; "endarterectomy", start date: 13Jul2016, stop date: 13Jul2016; "Chronic myeloid leukemia", start date: 12Apr2009 (ongoing). The patient's concomitant medications were not reported. Past drug history included: Tasigna, stop date: 22Jun2016, notes: withdrawn due to tight stenosis of the right carotid.
The following information was reported: DIARRHOEA (non-serious) with onset Nov2016, outcome "recovered" (May2017), DIARRHOEA (non-serious) with onset 06Nov2017, outcome "recovered" (10Jan2018) and all described as "Diarrhea grade 1"; NAUSEA (non-serious) with onset 06Nov2017, outcome "recovered" (10Jan2018); VOMITING (non-serious) with onset 06Nov2017, outcome "recovered" (10Jan2018); DIARRHOEA (non-serious) with onset 06Dec2017, outcome "recovered" (10Jan2018), described as "Diarrhea grade 3". The action taken for bosutinib was dosage reduced. Therapeutic measures were taken as a result of diarrhoea, diarrhoea.

The reporter considered "diarrhea grade 1", "diarrhea grade 3", "nausea" and "vomiting" related to bosutinib.

Additional information: It was reported onset date of Diarrhea grade 1 was 01Nov2016. Action taken was dose not changed for diarrhea (onset date 01Nov2016). Patient presented with profuse diarrhea related to bosutinib at the dose of 400 mg once daily. Corrective treatments taken orally for diarrhea included loperamide hydrochloride (IMODIUM) and diosmectite (SMECTA) from 10Dec2016 to 01Feb2017.

Follow-up (22Feb2017): New information received from the investigational site includes: Action taken (reported as slow escalation of the dose for bosutinib) and confirmation that the loperamide hydrochloride (IMODIUM) and diosmectite (SMECTA) were corrective treatments of the event.

No follow-up attempts are needed. No further information is expected.

Follow-up (14Apr2017): New information received from the investigational site includes: medical history (carotid stenosis, endarterectomy) and past drug history.

Follow-up (18May2017): Follow-up attempts completed. No further information expected.

Follow-up (07Dec2017): This is a follow-up to a non-interventional clinical study case reporting non-serious events only.
Medical history included ongoing chronic myeloid leukemia since 12Apr2009. The subject was treated with bosutinib since 09Nov2016 at 500 mg daily (onset date updated from 10Dec2016 to 09Nov2016 and dose from 400 mg once daily to 500 mg daily). On 06Nov2017, the subject experienced diarrhea grade 1, assessed as non-serious. As a result of this event, bosutinib daily dose was reduced to 400 mg 1x/day from 06Dec2017. The subject received an unspecified symptomatic treatment but did not recover from the event. According to the Investigator, this event was related to bosutinib.

Follow-up (23Mar2018): New information received from the investigator via the CRO includes: clinical course details, reaction data (added diarrhea onset 10Jan2018), and causality assessment (considered related).

Follow-up (03Aug2018): New information received from the CRO is as follows: On 06Nov2017, the subject experienced nausea and vomiting which were assessed of grade 2 and non-serious. In result of the events, the dose of bosutinib (BOSULIF) was reduced. On 06Dec2017, the subject had recovered from the events, nausea and vomiting. The investigator considered the events nausea and vomiting as related to the study drug bosutinib but not related to concomitant medications.

Follow-up (27Feb2023): This is a follow-up report received from CRO.
Information updated: Onset date of event diarrhea (grade 3) updated from 10Jan2018 to 06Dec2017; Recovery date updated from 07Mar2018 to 10Jan2018. Onset date of event diarrhea (grade 1) updated from 10Dec2016 to 01Nov2016; Recovery date updated from 01Feb2017 to 01May2017.

Follow-up (03Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter (Physician) for protocol B1871047.
Updated information: Onset and recovery dates of events updated: Diarrhea grade 1 from Nov2016 to May2017 then diarrhea grade 1 from 06Nov2017 to 10Jan2018 (resolved), nausea and vomiting resolved on 10Jan2018.

Follow-up attempts are completed. No further information is expected.

Case Comment: The company cannot exclude a causal relationship between the event 'diarrhea' (all episodes), nausea, vomiting and suspect drug bosutinib (BOSULIF) according to drug safety profile as expected toxicity.

Mfr. Control Number: 2017067222

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, 1x/day; Unknown	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	06-DEC-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to 22-JUN-2016	Past Drug Event	TASIGNA (TASIGNA); withdrawn due to tight stenosis of the right carotid
12-APR-2009 to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		OCT	1938	78 Years	Female	91.00 kg	01	DEC	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Lithiasic cholecystitis [Cholecystitis]
Pyelonephritis [Pyelonephritis]
Unexplained prolonged fever and inflammatory syndrome [Pyrexia]
Unexplained prolonged fever and inflammatory syndrome [Inflammation]
Right parietal meningioma [Meningioma]
Episode of coma without known etiology [Coma]
Aspiration pneumopathy [Pneumonia aspiration]
Arterial hypertension [Hypertension]
Arthrosis flare-up [Osteoarthritis]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) IXPRIM (PARACETAMOL, TRAMADOL HYDROCHLORIDE)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 3x/day	#1) Unknown
#2) 2 DF, 3x/day	#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) arthrosis flare-up (Osteoarthritis)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 06-JUL-2016 / Ongoing	#1) Unknown
#2) SEP-2018 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) METFORMIN EMBONATE (METFORMIN EMBONATE) ; 11-JUL-2016 / Ongoing
#2) ACETYLSALICYLIC ACID (ACETYLSALICYLIC ACID) ; 11-JUL-2016 / Ongoing
#3) ATORVASTATIN (ATORVASTATIN) ; 11-JUL-2016 / Ongoing
#4) PARACETAMOL (PARACETAMOL) ; 11-JUL-2016 / Ongoing
#5) LEVODOPA / BENSERAZIDE (BENSERAZIDE, LEVODOPA) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017073687

24c. DATE RECEIVED BY MANUFACTURER
24-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Right lumbosciatica [Sciatica]
Arthrosis flare-up [Osteoarthritis]
Drug intolerance to IXPRIM [Drug intolerance]
Bulbar ulcer [Ulcer]
Scalp wound [Wound]
Dizziness [Dizziness]
Slight rhabdomyolysis [Rhabdomyolysis]
Alteration of general status [General physical health deterioration]
Constipation [Constipation]
Malnutrition [Malnutrition]
Sacred eschar [Decubitus ulcer]
Flare up of chondrocalcinosis of the joints of both wrists [Chondrocalcinosis]
Corticosteroid-induced diabetes [Steroid diabetes]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 78-year-old female subject started to receive bosutinib (BOSULIF) on 06Jul2016 at 100 mg 3 times a day, for an unspecified indication. Concomitant suspect drugs included paracetamol/ tramadol hydrochloride (IXPRIM) via an unspecified route of administration from Sep2018 at 2 DF three times a day for arthrosis flare-up and prednisone (CORTANCYL), current treatment included 30 mg of prednisone and that the posology had been reduced to 10 mg every 15 days. Medical history included diabetes, dyslipidemia, and impaired liver function, chronic cholestasis all ongoing from an unspecified date. Concomitant medications included metformin embonate for diabetes, acetylsalicylic acid for anti-thrombosis prophylaxis, atorvastatin for dyslipidemia, and paracetamol for arthrosis, all by oral route, ongoing since 11Jul2016; benserazide/ levodopa (LEVODOPA / BENSERAZIDE) 125 mg per day for tremor from an unspecified date.
On 01Dec2016, the subject developed arthrosis flare-up, rated grade 2 and non-serious. The subject was seen in consultation by the physician for her ninth month and the arthrosis flare-up was not resolved. The subject experienced arterial hypertension in Oct2017 considered as non-serious event and assessed as grade 2. The subject informed the doctor at the M18 visit that she has started a treatment with amlodipine (unspecified trade name) after her M15 visit in Oct2017, she started at 5 mg per day then switched to 10 mg / day in Nov2017 and dose always ongoing. The event arterial hypertension had not resolved. On 10Jan2017, the subject experienced right lumbosciatica considered as non-serious event and assessed grade 2.
The investigator reported that during consultation M18, the subject informed the doctor of the appearance of a right lumbosciatica from 10Jan2018 for which she took paracetamol (unspecified trade name) via oral route since unknown date and diclofenac sodium (VOLTARENE gel) since Jan2018. The event lumbosciatica was resolved on 18Oct2017.
Paracetamol / tramadol hydrochloride (IXPRIM) was initiated in Sep2018 for arthrosis flare-up at the dose of 2 DF thrice daily (in the morning, at noon and in the evening). Action taken of Paracetamol / tramadol hydrochloride was unknown in response to drug intolerance. In Sep2018, the subject experienced arthrosis flare-up and drug intolerance to IXPRIM, both assessed as non-serious and rated grade 2.
The investigator added as comment "The subject said she had presented with an arthrosis flare-up for which she had taken paracetamol / tramadol hydrochloride. She did not well tolerated paracetamol / tramadol hydrochloride (drug intolerance). These two adverse events had resolved at the time of consultation dated 09Oct2018."
The subject presented with lithiasic cholecystitis on 08Nov2018 which required hospitalization. This event was rated as grade 3. Since 08Nov2018, the subject presented with nausea, vomiting and abdominal pain leading to a fall. She was hospitalized in infectious disease department on 11Nov2018 via the medical emergencies unit. On examination, there was abdominal pain in the right hyponchondrium, laboratory signs of inflammation, anicteric cholestasis and hepatic cytolysis. Abdomen ultrasound found vesicular lithiasis of 3 cm in diameter. A treatment with amoxiciline 1000 mg 3/day for 10 days was introduced. The event lithiasic cholecystitis resolved on 26Nov2018. Action taken with study drug in response to the event lithiasic cholecystitis was permanently withdrawn. The subject experienced bulbar ulcer (grade 2), non serious, on 19Nov2018, superficial small bulbar ulcer difficult to examin, viewed by gastroscopy and treated with eupantol. The outcome of bulbar ulcer was recovered on 26Nov2018. The patient also experienced dizziness in Sep2018. The event was non-serious (grade 1). The event resolved in Sep2018. In response to this event bosutinib was not changed.
On 11Jul2019, the subject experienced pyelonephritis, which led to hospitalization and assessed of grade 3. In the result of the event, no action was taken regarding bosutinib.
On 12Jul2019, the subject developed slight rhabdomyolysis, rated grade 1 and considered as not serious. CPK was 395 IU/l on 12Jul2019 (normal values less than 169), and 271 IU/l on 13Jul2019. Laboratory test included C-reactive protein on 12Jul2019 at 115.9 mg/l (normal range 0 - 4.9 mg/), on 06Aug2019 at 168.7 mg/l; urine analysis on 12Jul2019 showed presence of E. Coli. The subject was hospitalized from 12Jul2019 to 22Jul2019, initially for a fall with extended ground station (she could not get up once on the ground). The subject reported that sliding on 12Jul2019 on her blankets, and was unable to get up. In the emergency, the subject was febrile at 38.6 degrees C. Urine analysis made on 12Jul2019 found WBC at 270 x10^3/ml, red blood cells at 13 x10^3/ml and numerous epithelial cells. Polymorph flora with presence of numerous Gram+ and Gram- bacillus, evocating vaginal flora. Presence of E.Coli at 10^6 /ml and lactobacillus at 10 at 10^6 /ml. The subject left the hospital to the Aftercare and Rehabilitation Care on

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

22Jul2019 with antibiotic treatment. The event pyelonephritis resolved on 22Jul2019. On 27Jul2019, the subject experienced unexplained prolonged fever and inflammatory syndrome, which led to hospitalization and assessed of grade 3. In the result of the event, no action was taken regarding bosutinib. The subject had hyperthermia on 27Jul2019 with a temperature of 38.6 degrees C, 48 h after the withdrawal of amoxicillin. The only point of clinical call was lumbar pain. A cytobacteriological urine exam was done again and found an enterobacter cloacae with multiple resistances, requiring isolation. It was then decided to put the subject under amikacin. The event rhabdomyolysis resolved on 02Sep2019: CPK was 22 IU/l on 02Sep2019. On 12Sep2019, CRP was 3.6 mg/l. The event Unexplained prolonged fever and inflammatory syndrome resolved on 13Sep2019.
C-reactive protein on 06Aug2019 was 168.7 mg/l for a normal value of 4.9. Biological test found a biological inflammatory syndrome with a C-reactive protein at 120 mg/l, leukocytosis at 11 G/l. The urine strip test found one cross of leucocytes and 3 blood crosses. On day 6 of treatment, the subject presented with a new peak at 39 motivating a new hospitalization on 07Aug2019 (date of which the event became serious). No action was taken with bosutinib in response to those events.
On 07Aug2019, the subject developed alteration of general status, considered as not serious and constipation, rated grade 2 and considered as not serious. The events resolved on 13Sep2019. No action was taken with bosutinib in response to these events.
On 13Aug2019, the subject developed malnutrition, rated grade 2 and considered as not serious. On 13Aug2019, albumin was 27.6 g/l (normal range 35-52). The event has not resolved. The subject was started on hyperprotein diet. No action was taken with bosutinib in response to this event.
On 19Aug2019, the subject was found with grade 1 right parietal meningioma, considered as not serious. The event did not resolve. No action was taken with bosutinib in response to this event. Lumbar puncture was normal. On 19Aug2019, a brain CT was performed disclosing an occipital calcified nodular lesion of 17 mm on the right side. Sacred eschar was rated grade 2. The encephalic magnetic resonance imaging (MRI) performed from distance has confirmed the presence of meningioma but without any other anomaly. The electroencephalogram performed 72 hours later found slow waves-type anomalies with left posterior predominance associated with rare sharp waves. After discussion with neurologists, in the context, a treatment with lacosamide (VIMPAT) has been introduced. There was no recurrence of the event.
On 19Aug2019, the subject developed an episode of coma without known etiology, rated grade 2, serious as per hospitalization or prolongation of hospitalization. The event resolved on 19Aug2019. No action was taken with bosutinib in response to this event. On 19Aug2019, onset of an episode of coma, possibly secondary to an epilepsy seizure, but with no witness. The subject was found with Glasgow score at 3, having vomited and inhaled. She was treated by piperacillin sodium, tazobactam sodium (TAZOCILLINE) for 7 days, with a good evolution on the respiratory level. Regarding the etiology of this coma, there was no ionic disorder or hypoglycemia at the time of coma, the brain CT performed in emergency found only a 16 mm parietal meningioma, on the right side, without mass effect. The lumbar puncture was normal. The encephalic MRI performed from distance on 05Sep2019 confirmed the presence of meningioma measured 16 mm but no other anomalies. There was no recurrence of the event.
On 19Aug2019, the subject developed aspiration pneumopathy, rated grade 3 and considered as not serious. The event resolved on 26Aug2019. No action was taken with bosutinib in response to this event.
On 27Aug2019, the subject developed sacred escha grade 3 r, considered as not serious. Due to prolonged bed rest, and alteration of the general state, the skin condition has deteriorated, with the appearance of a sacred bedsore, taken in charge with air mattress, mobilization, local care, and hyperprotein diet. The evolution was finally favourable with the achievement of the cicatrisation. The event resolved on 13Sep2019. No action was taken with bosutinib in response to this event.
In Aug2019, the patient developed a flare up of chondrocalcinosis of the joints of both wrists, rated grade 2 and considered as not serious. The event resolved on 13Sep2019. No action was taken with bosutinib in response to this event.
On 04Sep2019, the patient developed grade 2 corticosteroid-induced diabetes, considered as not serious. Following the introduction of corticosteroid therapy, there has been an increase of blood glucose, between 2 g and 2.5 g. Hba1c was 5.7% before the start of treatment. After consulting endocrinologists, a basal bolus-treatment was started on 14Sep2019 with insulin detemir (LEVEMIR) 24 IU in the morning (duration of action shorter than the insulin glargine (LANTUS)), and fast bolus 8 IU at each meal, to adapt according to blood sugar levels. The event had not resolved. No action was taken with bosutinib in response to this event.
It was also reported scalp wound of 1 cm, clean, no signs of neurological localisation or meningeal syndrome, with onset date on 11Nov2018. Scalp wound following a fall from her hight (fall in the context of cholecystitis with lithiasis), non-serious. Event scalp wound was rated as grade 1. Scalp wound resolved on 05Mar2019. The action taken in response to the events (arthrosis flare-up and drug intolerance) for paracetamol/ tramadol hydrochloride was temporarily withdrawn on unknown date. No action was taken with bosutinib in response to the events.
On 11Feb2020, the subject experienced acute pancreatitis and Inhalation pneumonia, both were rated grade 5 and required hospitalization and led to the patient's death. The site described that Patient was referred by the doctor for deterioration of general condition on hyperthermia (40 degrees C in the emergency room), diarrhea, vomiting and desaturation. Saturation was corrected under 5l of O2. Diagnosis was made in the emergency room, before hospitalization: acute pancreatitis probably lithiasic (disturbed hepatic check-up and vesicular lithiasis known from 2019), complicated by inhalation pneumonia. On 12Feb2020, C-reactive protein was 171.1 mg/l (normal range: 0- 4.9), blood culture revealed dimicrobial culture of Klebsiella pneumoniae and Escherichia coli, GGT was 478 IU/ L (normal ranges: 0- 39), AST was 165 IU/ L (normal ranges: 0- 34.5). The patient died on 15Feb2020. Hospitalization report was not available at the report. It was unknown if autopsy was performed. No action was taken for bosutinib in response to acute pancreatitis and Inhalation pneumonia.

The investigator considered that acute pancreatitis and Inhalation pneumonia were unrelated to bosutinib or to a concomitant drug. According to the investigator, all the events were unrelated to study drug bosutinib.
The event drug intolerance to IXPRIM as unrelated to bosutinib but related to concomitant paracetamol / tramadol hydrochloride.
The investigator considered the event corticosteroid-induced diabetes as unrelated to study drug and related to concomitant medication prednisone (CORTANCYL).

Follow-up (02May2017): New information received includes: clinical course details.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (22May2017): Follow-up attempts completed. No further information expected.

Follow-up (23Jan2018): New information from the investigator included: concomitant drugs, new events (right lumbosciatica and arterial hypertension), treatment for events, seriousness assessment (considered right lumbosciatica and arterial hypertension as non-serious), causality assessment (right lumbosciatica and arterial hypertension unrelated to study drug bosutinib and to concomitant drugs) and event outcome.

Follow-up (13Apr2018): New information received from the investigational site was as follows: clarification on action taken.

Follow-up (11Oct2018): New information received includes: concomitant suspect drug added, new events osteoarthritis flare-up and drug intolerance added.

Follow-up (08Jan2019): New information received included added new event lithiasic cholecystitis.

Follow-up (11Mar2019): New information received from the site through CRO included subject's ethnicity and new event "bulbar ulcer", non serious (grade 2), onset date 19Nov2018, outcome and causality per investigator, last action taken (no action was taken with bosutinib).

Follow-up (19Apr2019): New information received from the site through CRO includes: new event (scalp wound) added.

Follow-up (26Apr2019): New information received through CRO included new event dizziness (non-serious).

Follow-up (08Aug2019). This follow-up is received from the investigator site via CRO. New information includes: Dizziness recovered in Sep2018, new adverse events (pyelonephritis and recurrence of pyelonephritis), lab data, clinical course.

Follow-up (29Aug2019). New information from the study coordinator includes lab data.

Follow-up (22Oct2019): New information received from the CRO includes: additional medical history (chronic cholestasis), updated bosutinib start date, updated CRP upper normal limit, updated clinical course, additional events (slight rhabdomyolysis, alteration of general status, constipation, malnutrition, meningioma, coma, aspiration pneumopathy, sacred eschar, chondrocalcinosis of the joints, corticosteroid-induced diabetes); previously reported event term "recurrence of pyelonephritis" with onset on 27Jul2019 was corrected to "unexplained prolonged fever and inflammatory syndrome" with causality assessment unchanged.

Follow-ups (14Nov2019 and 14Nov2019): New information received includes: lab data, details on concomitant drug prednisone administration, seriousness criteria of event episode of coma without known etiology was changed from non serious to hospitalization or prolongation of hospitalization.

Follow-ups (25Nov2019): New information received from the investigational site via CRO includes severity for events right parietal meningioma, corticosteroid-induced diabetes and sacred eschar.

Follow-up(17Feb2020): New information received included: new events "acute pancreatitis" and "inhalation pneumonia" added, death details, lab data and clinical course.

Follow-up(28Feb2020): New information received included: death date updated.

Follow-up (02Sep2020): New information received from the investigator via the CRO included: event term updated from chondrocalcinosis of the joints of both wrists to flare up of chondrocalcinosis of the joints of both wrists, and Coma without known etiology was rated grade 2.

Follow-up (04Apr2023): new information received from the investigator via the CRO.
Updated information: Patient data (patient initials, height) updated, rating for the event scalp wound added, stop date for the event bulbar ulcer added, action taken of Ixprim updated, onset date and outcome for the event right lumbosciatica updated, stop date for the event right lumbosciatica added.

Follow-up (03Oct2023): This is a non-interventional study follow up report received from the investigator via CRO.
Updated information included: outcome of event arthrosis flare-up of 01Dec2016 updated to resolved on 18Oct2017, BOSULIF start date updated to 06Jul2016 (previously reported as 07Jul2016).

Follow-up (04Oct2023): This is a non-interventional study follow up report received from the investigational site via CRO.
Updated information included: outcome of event arthrosis flare-up of 01Dec2016 updated to not recovered.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047 following study reconciliation.
Updated information included: Fatal events "Acute pancreatitis" and "inhalation pneumonia" of 11Feb2020 should be removed from this case as the patient had already completed the study follow-up period when occurred. Events previously reported by mistake.

Follow-up (24Nov2023). This follow-up is received from the investigational site via CRO. Updated information: Action taken to the

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

event lithiasic cholecystitis.
Follow-up attempts are completed. No further information is expected.

Case Comment: The Company cannot completely exclude the possible causality between the reported hypertension and the administration of the study drug of bosutinib, based on the known safety profile of bosutinib. Conversely, arthrosis flare-up, right lumbosciatica, lithiasic cholecystitis, dizziness, pyelonephritis, unexplained prolonged fever with inflammatory syndrome, slight rhabdomyolysis, alteration of general status, constipation, malnutrition, meningioma, coma, aspiration pneumopathy, sacred eschar, chondrocalcinosis of the joints, and corticosteroid-induced diabetes are considered unrelated to suspect drug bosutinib. They are more likely intercurrent and self-supporting diseases, or medical conditions associated with the underlying malignancy and its possible immunosuppressive status, and the diabetes is due to corticosteroid regimen in the setting of medical history of diabetes. Similarly, the reported bulbar ulcer and scalp wound are unrelated to bosutinib administration, scalp wound likely due to the mentioned fall. In addition, the event drug intolerance was related to paracetamol / tramadol hydrochloride and unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12-FEB-2020	Aspartate aminotransferase	165 IU/l	34.5 0
2	13-AUG-2019	Blood albumin	27.6 g/l	52 35
3	12-JUL-2019	Blood creatine phosphokinase	395 IU/l	169
4	13-JUL-2019	Blood creatine phosphokinase	271 IU/l	169
5	02-SEP-2019	Blood creatine phosphokinase	22 IU/l	169
6	12-FEB-2020	Blood culture	Dimicrobial culture of Klebsiella pneumoniae and E dimicrobial culture of Klebsiella pneumoniae and Escherichia coli	
7	19-AUG-2019	Blood electrolytes	no ionic disorder	
8	2019	Blood glucose	2-2.5 g	
9	19-AUG-2019	Blood glucose	no hypoglycemia g	
10		Body temperature	39 Centigrade	
11		Body temperature	40 Centigrade	
12	12-JUL-2019	Body temperature	38.6 Centigrade	
13	27-JUL-2019	Body temperature	38.6 Centigrade	
14	FEB-2020	Body temperature	40 (hyperthermia) Centigrade	
15	12-JUL-2019	C-reactive protein	115.9 mg/l	4.9 0
16	12-JUL-2019	C-reactive protein	120 mg/l	4.9 0
17	06-AUG-2019	C-reactive protein	168.7 mg/l	4.9 0
18	12-SEP-2019	C-reactive protein	3.6 mg/l	4.9 0
19	12-FEB-2020	C-reactive protein	171.1 mg/l	4.9 0

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
20	19-AUG-2019	Coma scale	3	
21	19-AUG-2019	Computerised tomogram head	occipital calcified nodular lesion of 17 mm	
		on the right side (parietal meningioma), without mass effect		
22	05-SEP-2019	Computerised tomogram head	16 mm parietal meningioma	
23	AUG-2019	Electroencephalogram	slow waves-type anomalies	
		with left posterior predominance associated with rare sharp waves		
24	19-NOV-2018	Endoscopy upper gastrointestinal tract	bulbar ulcer	
25	12-FEB-2020	Gamma-glutamyltransferase	478 IU/l	39 0
26		Glycosylated haemoglobin	5.7 %	
27		Laboratory test	laboratory signs of inflammation	
		anicteric cholestasis and hepatic cytolysis.		
28	2019	Lumbar puncture	normal	
29	2019	Magnetic resonance imaging head	presence of meningioma	
		without any other anomaly		
30	05-SEP-2019	Magnetic resonance imaging head	meningioma measured 16 mm	
31		Physical examination	abdominal pain in the right hyponchondrium	
32		Ultrasound abdomen	vesicular lithiasis of 3 cm in diameter	
33	12-JUL-2019	Urine analysis	WBC at 270 x10^3/ml, red blood cells at 13 x10^3/m	
		and numerous epithelial cells. Polymorph flora with presence of numerous Gram+ and Gram- bacillus, evocating vaginal flora. Presence of E.Coli at 10^6 /ml and lactobacillus at 10 at 10^6 /ml.		
34	12-JUL-2019	Urine analysis	one cross of leucocytes and 3 blood crosses	
35	12-JUL-2019	Urine analysis	presence of E. Coli	
36	27-JUL-2019	Urine analysis	enterobacter cloacae with multiple resistances	
37	12-JUL-2019	White blood cell count	11 x10 9/l	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION

Mfr. Control Number: 2017073687

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#3) CORTANCYL (PREDNISONE) ; Regimen #1	30 mg, UNK; Unknown	Unknown	Unknown; Unknown
#3) CORTANCYL (PREDNISONE) ; Regimen #2	10 mg, cyclic every 15 days; Unknown	Unknown	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Impaired liver function (Hepatic function abnormal);
Unknown to Ongoing	Relevant Med History	Cholestasis (Cholestasis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1959	57 Years	Male	107.00 kg		SEP	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Epigastric pain [Abdominal pain upper]
Muscular pain [Myalgia]
Diabetes [Diabetes mellitus]
Rhinosinusitis [Sinusitis]
Diarrhea [Diarrhoea]
Dental disorder(grade 2) [Tooth disorder]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) METFORMIN (METFORMIN)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 02-SEP-2016 / 17-SEP-2016	#1) 16 days
#2) Unknown / 30-AUG-2017	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) APROVEL (IRBESARTAN) ; 2013 / Ongoing
#2) ADRENALINE (EPINEPHRINE) ; SEP-2017 / SEP-2017
#3) CLAMOXYL (AMOXICILLIN) ; SEP-2017 / SEP-2017

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
2013 to Ongoing	Relevant Med History	Ruptured Achilles tendon (Tendon rupture)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017077787

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
02-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
A 57-year-old male patient received bosutinib (BOSULIF), first regimen from 02Sep2016 to 17Sep2016 at 100 mg 1x/day, second regimen from 18Sep2016 to 03Oct2016 at 200 mg 1x/day, third regimen from 04Oct2016 to 04Oct2016 at 300 mg 1x/day and fourth regimen since 05Oct2016 (ongoing) at 400 mg 1x/day; metformin (METFORMIN), (Batch/Lot number: unknown) till 30Aug2017. The patient's relevant medical history included: "Hypertension arterial", start date: 2013 (ongoing); "Rupture Achilles tendon", start date: 2013 (ongoing). Concomitant medication(s) included: APROVEL oral taken for hypertension, start date: 2013 (ongoing); ADRENALINE taken for local anaesthesia, start date: Sep2017, stop date: Sep2017; CLAMOXYL oral taken for antibiotic therapy, start date: Sep2017, stop date: Sep2017.

In Oct2016, the subject experienced epigastric pain, the event was rated grade 1; in Sep2016, the subject experienced muscular pain, the event was rated grade 2, both events considered as non-serious. On 15Dec2016, the subject experienced rhinosinusitis considered as non-serious event. On 07Mar2017, the subject experienced diabetes grade 2 considered as non-serious. Starting from 03Feb2017, the previously reported muscular pain changed from grade 2 to grade 1 and was still considered non-serious. On 01Aug2017, the subject developed diarrhea rated grade 2 and disappeared upon withdrawal of metformin on 30Aug2017 and was considered non-serious. In Sep2017, the subject experienced dental disorder, which was assessed as non-serious and rated grade 2. As a result of the event, the last action taken with bosutinib was no change. The events epigastric pain resolved on 26Jan2017, dental disorder resolved in Sep2017, rhinosinusitis resolved on 04Jan2017, diarrhea resolved on 30Aug2017, muscular pain was resolved on 31Aug2017 and diabetes grade 2 was still ongoing at the time of the last reporting.

The investigator considered there was a reasonable possibility that the events epigastric pain and muscular pain were related to the study medication bosutinib and not related to concomitant medication.
The investigator considered there was not a reasonable possibility that the event rhinosinusitis, diabetes, diarrhea and dental disorder (grade 2) were related to the study medication bosutinib and concomitant medication. As of 17Jul2023, it was reported according to the investigator, the event Diarrhea was related to Metformin, which was discontinued as action taken.

Follow-up (29May2017): New information received as follows: investigator awareness date and outcome data (epigastric pain updated to resolved, and muscular pain updated to recovering).

Follow-up (27Jun2017): New information received from investigator includes: reaction data (added diabetes grade 2 and muscular pain grade 1), and causality (diabetes considered unrelated and muscular pain considered related).

According to Pfizer procedures, diabetes mellitus is included in MedDRA List Critical Term, as always serious event. Seriousness criterion: Medically Significant.

Follow-up (27Sep2017): New information reported includes: product information (bosutinib at the dosage regimen 300 mg once a day was administered on 04Oct2016 only, and 400 mg once a day (not 200 mg once a day as previously reported) since 05Oct2016 and ongoing), and reaction data (added event 'diarrhea').

Follow-up (03Jul2018 and 04Jul2018): New information reported includes new event "dental disorder", and concomitant medications.

Follow-up (10Aug2018): New information reported includes: product information (bosutinib was administered at 200 mg once a day from 05Oct2016 (not 400 mg once a day as previously reported)) and event data (onset date and outcome of event muscular pain (grade 2) updated, outcome of event muscular pain grade 1 updated).

Follow-up (28Feb2019).Amendment: This follow-up report is being submitted to amend previously reported information: to amend CTCAE grade for event epigastric pain from 2 to 1.

Follow-up (20Dec2019): New information provided includes: Previously reported event 'diabetes' has been upgraded by the reported from non-serious to serious (seriousness criteria not provided/specified) and outcome updated. The previously reported 2 separate events of 'muscular pain' have been coded as one single episode since the 2 events correspond to different grades of the same event but changing in time. Event outcome for 'muscular pain' updated and recovery date provided.

Follow-up (27Mar2020): New information received from the investigational site via CRO included: diabetes was updated as non-serious.

Follow-up (04Jul2022): This is a non-interventional follow-up study report (Post Authorization Safety Study) received from contactable reporters (Physician and Other HCP) for protocol B1871047.
Updated information includes: outcome for event myalgia changed from recovered/resolved to recovering/resolving.

Follow-up (10May2023): This is a follow-up report from the investigator via CRO.
Updated information: bosutinib dosage details added, event details updated (grade 2 added for dental disorder).

Mfr. Control Number: 2017077787

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (17Jul2023): new information received from the investigator via the CRO.
Investigator Initial Aware Date (Diabetes and Muscular pain): 03May2017. Investigator Initial Aware Date (Diarrhea): 31Aug2017.
Event Muscular pain updated: onset date updated (03Feb2017, previously Sep2016), end date added (31Aug2017), outcome updated to recovered.
According to the investigator, the event Diarrhea was related to Metformin, which was discontinued as action taken.

Follow-up attempts are completed. No further information is expected.

Amendment: This follow-up report is being submitted to amend previous information: update the start date of the event myalgia to Sep2016.

Case Comment: The company cannot exclude a causal relationship between the events abdominal pain and myalgia and suspect drug bosutinib according to drug safety profile as expected toxicity. There was not a reasonable possibility that the reported diabetes, rhinosinusitis, dental disorder and diarrhea were related to the study medication bosutinib and concomitant medication.
The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	Unknown	18-SEP-2016 / 03-OCT-2016; 16 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	Unknown	04-OCT-2016 / 04-OCT-2016; 1 day
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, 1x/day; Unknown	Unknown	05-OCT-2016 / Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		AUG	1971	45 Years	Male	110.00 kg	13	DEC	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

episode of refractory cardiac insufficiency [Cardiac failure]
episode of acute renal insufficiency [Acute kidney injury]
Nausea [Nausea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 200 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 12-DEC-2016 / 02-MAR-2017

19. THERAPY DURATION
#1) 81 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#2) XARELTO (RIVAROXABAN) ; Unknown / 24-JAN-2017
#3) DIFFU K (POTASSIUM CHLORIDE) ; Ongoing
#4) CORDARONE (AMIODARONE HYDROCHLORIDE) ; Ongoing
#5) EUPANTOL (PANTOPRAZOLE SODIUM SESQUIHYDRATE) ; Ongoing
#6) ESIDREX (HYDROCHLOROTHIAZIDE) ; Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event	recovered, related to past therapy, no corrective treatment
Unknown to Ongoing	Relevant Med History	Arrhythmia (Arrhythmia) not related to past tyrosin kinase inhibitor, currently treated

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017089554

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 45-year-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 12Dec2016 at 200 mg, 1x/day. The subject had pursued bosutinib at the posology of 200 mg per day in one intake, treatment which had been introduced on 12Dec2016 due to significative re-increase in his BCRABL transcrit, at 15%, compatible with the loss of a complete cytogenetic response. Medical history included decompensation related to previous treatment with dasatinib (unspecified trade name) for which no treatment was introduced, ongoing rhythm disorder not related to past tyrosin kinase inhibitor, currently treated, ongoing myocardiopathy not related to past tyrosin kinase inhibitor, currently treated, coarctation from which he recovered, not related to past tyrosin kinase inhibitor, not treated, ongoing hypothyroidism not related to past tyrosin kinase inhibitor, currently treated, ongoing non-insulin-dependent diabetes not related to past tyrosin kinase inhibitor, currently treated, ongoing overweight not related to past tyrosin kinase inhibitor, heterogenous goitre from which he recovered, not related to past tyrosin kinase inhibitor, not treated, ongoing renal failure not related to past tyrosin kinase inhibitor, currently treated, and ongoing anxiety not related to past tyrosin kinase inhibitor, currently treated. Concomitant medications included levothyroxine sodium (LEVOTHYROX) 100 (unspecified unit) per day ongoing for hypothyroidism, rivaroxaban (XARELTO) 20 (unspecified unit) per day for rhythm disorder stopped on 24Jan2017, potassium chloride (DIFFU K) 1200 (unspecified unit) per day ongoing for dilated myocardiopathy, amiodarone hydrochloride (CORDARONE) 200 (unspecified unit) per day ongoing for rhythm disorder, pantoprazole sodium sesquihydrate (EUPANTOL) 20 (unspecified unit) per day ongoing for gastroesophageal reflux prophylaxis, hydrochlorothiazide (ESIDREX) 12.5 (unspecified unit) per day ongoing for dilated myocardiopathy, furosemide (LASILIX) 500 (unspecified unit) per day ongoing for dilated myocardiopathy, bisoprolol fumarate (BISOCE) 5 (unspecified unit) per day ongoing for dilated myocardiopathy, allopurinol (unspecified trade name) 200 (unspecified unit) per day ongoing for renal failure, bromazepam (unspecified trade name) 3 (unspecified unit) per day ongoing for anxiety, domperidone (MOTILIUM) unspecified dose daily started on 09Jan2017 and ongoing for nausea, and warfarin sodium (COUMADINE) 3 mg per day started on 25Jan2017 and ongoing for rhythm disorder. The subject experienced an episode of refractory cardiac insufficiency on 24Jan2017, an episode of acute renal insufficiency on 23Feb2017 (rated as non-serious), and nausea (rated as grade 2) on 13Dec2016. The subject was hospitalized for cardiac insufficiency from 24Jan2017 to 15Feb2017. The subject's hospitalization was prolonged as a result of cardiac insufficiency. Since 02Mar2017, the subject has been re-hospitalized in cardiology unit for a further external electric shock and modification of his anticoagulant treatment with switch from rivaroxaban (XARELTO) to warfarin (COUMADINE). He saw the nephrologist in consultation, in the context of renal failure, with recent degradation of creatinine posterior to introduction of bosutinib, which suggest the responsibility of bosutinib in the current degradation of renal function. The patient underwent lab tests and procedures which included blood creatinine: recent degradation in 2017. The action taken in response to the event for bosutinib was permanently withdrawn on 02Mar2017. The subject received bisoprolol (CARDENSIEL) 25 (unspecified unit) per day from 23Feb2017 to 21Mar2017 for the treatment of the event cardiac failure. The subject did not receive treatment for the episode of acute renal insufficiency. The outcome of cardiac insufficiency was recovered on 22Mar2017, the episode of acute renal insufficiency was recovered on 17Mar2017, nausea on 13Dec2016 was recovered on 02Mar2017.

The investigator considered there was not a reasonable possibility that the event "episode of refractory cardiac insufficiency" was related to bosutinib. The investigator considered there was a reasonable possibility that the events "episode of acute renal insufficiency" and "nausea" were related to bosutinib. There was not a reasonable possibility that the events were related to concomitant treatment.

Follow-up (05Sep2017). This follow-up is received from the investigator includes: study drug data (start date, dosing and action taken), (event data: added cardiac insufficiency and renal failure), event criteria, event causality, and event outcomes (subject recovered from event cardiac failure)

Follow-up (27Sep2017): New information reported includes event details, medical history, concomitant medications and treatment of the event cardiac failure.

Follow-up (19Oct2017): New information received from investigational site includes: hospital stop date, seriousness criteria (confirmed renal insufficiency did not require hospitalization), and bosutinib stop date.

Follow-up (04Feb2022): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047 from the investigator via CRO. Updated information includes: reaction data (event "renal insufficiency" updated to "episode of acute renal insufficiency", its seriousness criteria updated from serious to non-serious, recovery date; verbatim of event "cardiac insufficiency" updated to "episode of refractory cardiac insufficiency").

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047 following study reconciliation. Nausea details (grade and outcome).

Case Comment: Given the known suspect drug profile and a plausible temporal association, based on the information currently provided, the company concurs with the causality assessment provided by the investigator, considering acute renal insufficiency and nausea related to bosutinib, whereas cardiac insufficiency is assessed as unrelated. The follow-up information received does not alter the previous company clinical evaluation.

Mfr. Control Number: 2017089554

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	2017	Blood creatinine	recent degradation	

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) LASILIX (FUROSEMIDE) ; Ongoing

#8) BISOCE (BISOPROLOL FUMARATE) ; Ongoing

#9) ALLOPURINOL (ALLOPURINOL) ; Ongoing

#10) BROMAZEPAM (BROMAZEPAM) ; Ongoing

#11) MOTILIUM (DOMPERIDONE) ; 09-JAN-2017 / Ongoing

#12) COUMADINE (WARFARIN SODIUM) ; 25-JAN-2017 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event	dasatinib (DASATINIB); Drug Reaction: Decompensation cardiac (Cardiac failure) recovered, related to past therapy, no corrective treatment
Unknown to Ongoing	Relevant Med History	Cardiomyopathy (Cardiomyopathy); not related to past tyrosin kinase inhibitor, currently treated
Unknown	Relevant Med History	Coarctation of aorta (Coarctation of the aorta); recovered, not related to past tyrosin kinase inhibitor, not treated
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism); not related to past tyrosin kinase inhibitor, currently treated
Unknown to Ongoing	Relevant Med History	Non-insulin-dependent diabetes mellitus (Type 2 diabetes mellitus); not related to past tyrosin kinase inhibitor, currently treated
Unknown to Ongoing	Relevant Med History	Overweight (Overweight); not related to past tyrosin kinase inhibitor
Unknown	Relevant Med History	Goiter (Goitre); recovered, not related to past tyrosin kinase inhibitor, not treated
Unknown to Ongoing	Relevant Med History	Renal failure (Renal failure); not related to past tyrosin kinase inhibitor, currently treated
Unknown to Ongoing	Relevant Med History	Anxiety (Anxiety); not related to past tyrosin kinase inhibitor, currently treated

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1952	64 Years	Female	74.00 kg	10	MAR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Anemia [Anaemia]
Left ulnar nerve canal syndrome [Ulnar tunnel syndrome]
vertigo [Vertigo]
Anemia [Anaemia]
Nausea [Nausea]
Low back pain [Back pain]
Hepatic cytolysis [Hepatic cytolysis]
Anemia [Anaemia]
Iron deficiency [Iron deficiency]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosutinib (BOSUTINIB) Unknown
#2) LIPANTHYL (FENOFIBRATE)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Oral
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukaemia (Chronic myeloid leukaemia)
#2) Hypertriglyceridemia (Hypertriglyceridaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 16-DEC-2016 / Unknown	#1) Unknown
#2) Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) DIAMICRON (GLICLAZIDE) ; DEC-2014 / Ongoing
#2) METFORMINE (METFORMIN HYDROCHLORIDE) ; DEC-2014 / Ongoing
#3) SEROPLEX (ESCITALOPRAM OXALATE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
04-OCT-2016 to 18-NOV-2016	Relevant Med History	Pancreatitis (Pancreatitis)
04-OCT-2016 to Unknown	Relevant Med History	Chronic renal failure (Chronic kidney disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017171681

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
18-OCT-2022

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Anemia [Anaemia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL- LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
A 64 year-old female subject received bosutinib (BOSULIF) by oral route for chronic myeloid leukaemia as follows: from 16Dec2016 at 100 mg once daily, from 30Dec2016 at 200 mg once daily, from 15Jan2017 at 300 mg once daily, from Jan2017 at 400 mg once daily, from Mar2017 to Mar2017 at 500 mg once daily (gradual increase up to 500 mg) then since 13Mar2017, reduction to 300 mg once daily due to hepatic cytolysis. Medical history included pancreatitis from 04Oct2016 to 18Nov2016, chronic renal failure since 04Oct2016, ongoing medical history of diabetes since Dec2014, ongoing hypertriglyceridemia, ongoing depression and ongoing dyslipidemia. Concomitant suspect drug included ongoing fenofibrate (LIPANTHYL) for hypertriglyceridemia. Other concomitant medications included gliclazide (DIAMICRON) and metformin hydrochloride (METFORMINE) for diabetes ongoing since Dec2014, LEMOXYL (as reported), and escitalopram oxalate (SEROPLEX).
In Mar2017, the subject experienced iron deficiency, rated grade 3 and considered as not serious. On 10Mar2017, the subject developed anemia, rated CTCAE grade 3 and non-serious. On 10Mar2017, the subject experienced a hepatic cytolysis (2x normal value) rated CTCAE grade 1 and non-serious. On 15May2017, the subject developed anemia, rated CTCAE grade 3 and which required hospitalization or prolongation of hospitalization. The patient remains in grade 1-2 from 01Jun2017 until 27Jun2017 (grade 3). It was reported that asthenia was related to anemia. The asthenia was not a new event it was related to the anemia. On 27Jun2017, the subject developed anemia assessed as non-serious and rated grade 3. On an unspecified date in Jun2017, the subject experienced nausea rated CTCAE grade 1 and non-serious. On 21Aug2017, the subject experienced anemia, rated grade 3 and considered as not serious. In Jan2018, the subject experienced left ulnar nerve canal syndrome, rated grade 3 and considered serious due to hospitalization. In 2018, the subject experienced low back pain, rated grade 1 and considered as not serious. On 17Oct2018, the subject experienced vertigo rated grade 2 and considered as medically significant since leading the subject to present to the emergency unit on 19Oct2018. It was reported that between each episode of grade 3 anemia, the subject fluctuated with a grade 1-2 anemia which was considered as not clinically significative.
The subject underwent lab tests and procedures which included: on 24Nov2016 aspartate aminotransferase (AST) 24, alanine aminotransferase (ALT) 21, and bilirubin 7 umol/l; on 10Mar2017 hemoglobin 7.7 g/dl (normal range 12.7-15.9), AST 64, ALT 95, and bilirubin 5 umol/l; on 15May2017 hemoglobin 6.9 g/dl (normal range 12-15); on 16May2017 AST 28, ALT 32, gamma glutamyl transferase (GGT) 18, alkaline phosphatase 179, and other pancreatic enzymes were 64.
As a result of the event hepatic cytolysis, bosutinib daily dose was reduced. The subject was transfused with 2 concentrates of red blood cells on 13Mar2017. In response to anemia (onset 15May2017), the subject received transfusion on 18May2017. Iron deficiency that had needed some transfusions (grade 3). The subject recovered from the event anemia (onset 10Mar2017) on 30Mar2017 and recovered from the event hepatic cytolysis on 16May2017. The event anemia (onset 15May2017) resolved on 27Jun2017. The event nausea (Jun2017) resolved on 07Sep2017. Anemia (onset date 27Jun2017) resolved on 12Jul2017. Anemia (onset 21Aug2017) resolved on 07Sep2017, iron deficiency resolved on 28May2018, left ulnar nerve canal syndrome resolved on 21Jun2018, the event low back pain did not resolve. Vertigo fully resolved in Oct2018.

According to the investigator, the event anemia (onset 10Mar2017) and anemia (15May2017) was related to study drug bosutinib. According to the investigator, the event nausea was related to bosutinib and not related to concomitant drugs and the event hepatic cytolysis was not related to bosutinib and was related concomitant drug fenofibrate (LIPANTHYL). The investigator considered the events anemia (onset 21Aug2017), anemia (onset 27Jun2017), iron deficiency, left ulnar nerve canal syndrome, low back pain and vertigo as unrelated to study drug bosutinib and concomitant medications. The investigator considered that the event "anemia" was unrelated to any concomitant drugs.

Follow-up (18May2017 and 19May2017): New information received includes: relevant medical history (acute renal failure not ongoing), additional lab data, reaction data (additional serious event anemia), therapeutic measures, and clinical course details.

Follow-up (29May2017): New information received from the clinical team includes: the investigator initial aware date for the second episode of anemia.

Follow-up (21Jun2017): New information received includes: subject data (weight and height), medical history (added diabetes and hypertriglyceridemia), concomitant medications, action taken (updated from dose not changed to unknown), reaction data (added hepatic cytolysis and nausea), and causality assessment.

Follow-up (31Aug2017): follow-up attempts completed. No further information expected.

Follow-up (03Aug2018): New information received from CRO included: Additional medical history, dosage of bosutinib, indication of concomitant medication fenofibrate, additional events (anemia with onset date 01Sep2017, iron deficiency, left ulnar nerve canal syndrome, low back pain), action taken (dose not changed), outcome of events, causality assessment for events.

Follow-up (25Oct2018): Follow-up attempts completed. No further information expected.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (30Jul2019 and 31Jul2019): New information received from the investigator includes: route of administration of bosutinib, additional events anemia (onset date 27Jun2017) and vertigo, additional concomitant medications (LEMOXYL and SEROPLEX), additional lab data.

Follow-up (09Sep2019): New information received includes updated dose of bosutinib, updated concomitant drugs, outcome of anemia (onset 15May2017) and nausea.

Follow-up (20Sep2019): New information received from the clinical team includes dates and dosages of administration of bosutinib, updated action taken, updated dates for anemia episodes stop date 01Jun2017 (instead of stop date 16Jun2017) and then from 21Aug2017 (instead of 01Sep2017).

Follow-up (01Oct2019): New information received from the clinical team includes: the medical history of renal failure was chronic (instead of acute as previously reported).

Follow-ups (03Oct2022): This is a non-interventional study report (Post Authorization Safety Study) received from the CRO for protocol B1871047. Updated information included: patient's details, stop date of the event anemia with onset date 15May2017 changed from 01Jun2017 to 27Jun2017, bosutinib dosage starting on 16Dec2016 reported at 500mg, new event (asthenia), serious criteria for the event 'left ulnar nerve canal syndrome' updated to serious (H).

Amendment (13Oct2022): This follow-up report is being submitted to amend previously reported information: changing dose information: first dose (start date 16Dec2016) from 500mg to 100 mg.

Follow-up (18Oct2022): This is a non-interventional study report (Post Authorization Safety Study) received from the CRO for protocol B1871047. Updated information included: reaction data (asthenia has been deleted).

Case Comment: Based on the clinical information currently provided, the company concurs with the causality assessment expressed by the investigator, considering there is a reasonable possibility that anemia (onset 10Mar2017 and 15May2017) and nausea are related to the suspect, study drug bosutinib. In agreement with the causality assessment provided by the investigator, considering the events hepatic cytolysis, anemia (onset 01Sep2017 and 27Jun2017), iron deficiency, left ulnar nerve canal syndrome, low back pain, vertigo are unrelated to study drug bosutinib and concomitant medications.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	24-NOV-2016	Alanine aminotransferase	21	
2	10-MAR-2017	Alanine aminotransferase	95	
3	16-MAY-2017	Alanine aminotransferase	32	
4	24-NOV-2016	Aspartate aminotransferase	24	
5	10-MAR-2017	Aspartate aminotransferase	64	
6	16-MAY-2017	Aspartate aminotransferase	28	
7	16-MAY-2017	Blood alkaline phosphatase	179	
8	24-NOV-2016	Blood bilirubin	7 umol/l	
9	10-MAR-2017	Blood bilirubin	5 umol/l	
10	MAR-2017	Blood iron	deficiency	
11	16-MAY-2017	Gamma-glutamyltransferase	18	
12	10-MAR-2017	Haemoglobin	7.7 g/dl	15.9 12.7
13	15-MAY-2017	Haemoglobin	6.9 g/dl	15 12

Mfr. Control Number: 2017171681

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
14	16-MAY-2017	Pancreatic enzymes	64	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #2	200 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	30-DEC-2016 / Unknown; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	300 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	15-JAN-2017 / Unknown; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	400 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	JAN-2017 / Unknown; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #5	500 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	MAR-2017 / MAR-2017; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #6	300 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	13-MAR-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
DEC-2014 to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus);
Unknown to Ongoing	Relevant Med History	Hypertriglyceridemia (Hypertriglyceridaemia);
Unknown to Ongoing	Relevant Med History	Depression (Depression);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		DEC	1949	67 Years	Male	84.00 kg	10	MAY	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
subclavicular artery stenosis [Subclavian artery stenosis]
worsening of renal failure [Renal failure]
Arthralgia on ankles,wrists and neck [Arthralgia]
huge fatigue [Fatigue]
dyspnea [Dyspnoea]
Diarrhea [Diarrhoea]
Chills [Chills]
DIFFUSE ODEMAS CUTANEOUS, ENT AND THORACIC [Skin oedema]
DIFFUSE ODEMAS CUTANEOUS, ENT AND THORACIC [Pharyngeal **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) GLIVEC (IMATINIB MESILATE) **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Oral
#2) 200 mg, daily	#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 02-MAY-2017 / 19-MAY-2017	#1) 18 days
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CANDESARTAN (CANDESARTAN) ; Ongoing
#2) PREVISCAN [FLUINDIONE] (FLUINDIONE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Arteriopathy (Arterial disorder)
Unknown	Relevant Med History	Angioplasty (Angioplasty)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017231076

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

oedema]
itching [Pruritus]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 67-year-old male subject received bosutinib (BOSULIF), from 02May2017 to 19May2017 at 300 mg daily, oral for chronic myeloid leukemia; imatinib mesilate (GLIVEC), first regimen (Batch/Lot number: unknown) at 200 mg daily, second regimen (Batch/Lot number: unknown) at 100 mg daily and third regimen since 26Jun2017 (ongoing) (Batch/Lot number: unknown), oral for chronic myeloid leukemia; dasatinib monohydrate (SPRYCEL), first regimen (Batch/Lot number: unknown) at 70 mg daily and second regimen from 20May2017 (Batch/Lot number: unknown) to 25Jun2017, oral for chronic myeloid leukemia. The patient's relevant medical history included: "Lower limb arteriopathy" (unspecified if ongoing); "Multiple angioplasty" (unspecified if ongoing); "Arterial hypertension" (ongoing); "Subrenal abdominal aortic aneurysm" (unspecified if ongoing); "renal disease" (unspecified if ongoing), notes: before starting bosutinib; "Chronic obstructive pulmonary disease" (ongoing); "Chronic renal insufficiency" (ongoing); "Type 2 diabetes" (ongoing). Concomitant medication(s) included: CANDESARTAN oral taken for hypertension (ongoing); PREVISCAN [FLUINDIONE] oral taken for aneurysm (ongoing). The subject presented with chills in May2017 which were reported as non-serious and rated grade 1. The subject was very cold and needed heating system. On 10May2017, the subject experienced renal failure increased, CTCAE grade 1, which was reported as non-serious. On 12May2017, the subject experienced diarrhea, CTCAE grade 2, which was reported as non-serious; dyspnea CTCAE grade 2, was reported as non-serious; arthralgia on wrists, ankles and neck, CTCAE grade 2, which was reported as non-serious, and huge fatigue assessed as non-serious and rated grade 2. The subject experienced "subclavicular artery stenosis" , grade 2, serious (hospitalization) from May2017. Action taken for bosutinib in response to this event was not applicable. On 31May2017: the subject presented with signs of tinnitus and vertigo. Doppler ultrasound on 31May2017 revealed 65-70% stenosis of left intern carotid. This stenosis was associated to an intermittent inversed flow of left vertebra related to a left subclavicular stenosis. The physician explained to the subject that tinnitus and vertigo symptoms might be relieved by a better vascularization. Hence, the subject was hospitalized from 21Aug2017 in order to perform left prevertebral subclavicular angioplasty. The patient had itching from May2017, rated grade 1, non-serious, recovered in May2017. No action was taken with bosutinib in response to this event. On 19May2017, the subject presented with an early and significant clinical and biological intolerance to bosutinib. In this context, it was decided to permanently withdraw bosutinib on 19May2017. It was also reported that bosutinib was permanently stopped in response to renal failure increased, arthralgia on ankles, wrists and neck, and huge fatigue. A switch to dasatinib (SPRYCEL) was planned at the dose of 70 mg daily initially to start in a week to 10 days in order to recover a correct clinical condition. The subject was advised that toxicity will need to be monitored with this new drug due to risk of shortness of breath, dasatinib being a provider of pleural effusions and pulmonary arterial hypertension. On 27Jun2017, the subject developed bilateral and symmetric edema of eyelids which was rated grade 2 and considered as non-serious event. On 27Jun2017, the subject developed throat oedema assessed as non-serious and rated grade 1. On 04Jul2017, the subject was monitored for chronic myeloid leukemia and presented intolerance to imatinib mesilate (GLIVEC) at 200 mg daily, with bosutinib at 300 mg daily and dasatinib at 70 mg daily. He had presented eyelid edema and laryngeal oedema, objectified by the ENT, and a feeling of generalized pruritus while on imatinib mesilate. Bosutinib and dasatinib led to flare-up of acute renal failure, arthralgia and diarrhea. Nevertheless, in terms of efficiency, the BCR transcript had decreased from 250% to 1% under imatinib mesilate 200 mg. Further medical discussion, it was decided to resume imatinib mesilate at the dose of 100 mg and increase it gradually. The subject therefore resumed imatinib mesilate one week before the consultation and there was recurrence of eyelid edema, and laryngeal and nasal discomfort but less than the previously described symptoms. Good efficiency of ITK but very poor tolerance was noted. Gradual increase of the dose of imatinib mesilate to 100 mg for a further 2 months was performed. The subject was hospitalized from 21Aug2017 to 23Aug2017 in order to perform left prevertebral subclavian angioplasty. In Oct2017 the subject experienced diffuse odemas cutaneous, ENT and thoracic. The event diffuse odemas cutaneous, ENT and thoracic was rated grade 2. On 27Dec2017, the subject experienced ankle itching assessed as non-serious and rated grade 1. In response to chills bosutinib was withdrawn. The final action taken with bosutinib in response to the events was permanently discontinued on 19May2017 while no action was taken with imatinib mesilate. Action taken of dasatinib monohydrate was not reported. Action taken of candesartan was withdrawn due to left subclavian artery tight stenosis. The subject had recovered from renal failure increased on 21Jun2017, subclavicular artery stenosis on 23Aug2017, arthralgia on ankles, wrists and neck in May2017, dyspnea in May2017, diarrhea in May2017, chills on 04Jul2017, itching in May2017, throat oedema on 30Aug2017; huge fatigue in May2017; the outcome of Diffuse odemas cutaneous, ENT and thoracic was unknown.

The investigator considered the events 'arthralgia on wrists, ankles and neck', 'renal failure increased', 'diarrhea', 'huge fatigue', 'dyspnea', 'chills" as related to bosutinib and unrelated to a concomitant medication.
The investigator considered the events 'subclavian stenosis', 'Diffuse odemas cutaneous, ENT and thoracic', 'throat oedema' and 'ankle itching' as unrelated to bosutinib and as related to imatinib mesilate, and informed that 'throat oedema' and 'ankle itching' were not to be reported as adverse events for bosutinib, event itching unrelated to bosutinib or to any concomitant drug.
According to the investigator, the event left subclavian artery tight stenosis was related to candesartan.
The investigator considered the event subclavicular artery stenosis as unrelated to bosutinib or to any concomitant drug.

Follow-up (10Aug2017): Follow-up attempts completed. No further information expected.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (13Dec2017): New information received included updated event from 'heavy fatigue + dyspnea' to dyspnea alone, and updated outcome of dyspnea.

Follow-up (07Feb2018): New information received includes: concomitant drug, event data (added bilateral and symmetric edema of eyelids).

Follow-up (21Feb2018): New information received includes an update about dose, frequency and therapy dates for bosutinib, relevant medical history and concomitant medications, new event "Subclavian stenosis" along with its seriousness and causality assessment.

Follow-up (03May2018): follow-up attempts completed. No further information expected.

Follow-up (25Apr2019): New information received includes two additional events chills and itching

Follow-up (20Aug2019): New information received from the Site includes updated onset date and outcome for chills and itching (onset date: from '23Jun2017' to 'May2017'; outcome: from 'unknown' to 'recovered'), and causality assessment for chills and itching (previously missing).

Follow-ups (30Aug2019): New information received from the Site included bosutinib therapy details (route and indication for use), updated SAE (from 'subclavian stenosis' to 'subclavian artery stenosis'), additional AEs ('throat edema' and 'huge fatigue'), updated clinical outcome for renal failure increased (from 'recovering' to 'recovered' on 21Jun2017), updated recovery date for 'subclavian artery stenosis' (from '22Aug2017' to '21Aug2017'), updated clinical outcome for 'arthralgia on ankles, wrists and neck' (from 'recovering' to recovered' in May2017), and treatments received.

Follow-up (10Sep2019): New information received included: medical history (renal disease); new suspect drug dasatinib monohydrate; clinical course.

Follow-up (01Oct2019): New information received from the investigational site includes deletion of events throat oedema and ankle itching (assessed as unrelated to bosutinib and as related to imatinib mesilate; deleted as they occurred more than 28 days after bosutinib withdrawal).

Follow-up (25Oct2019): New information received from investigational site includes removed event 'bilateral and symetric edema of eyelids' as out of reporting period.

Follow-up (02Jul2020): This follow-up is received from the investigational site reporting renal failure onset date was updated to 10May2017.

Amendment: Case is being re-submitted to amend the received date indicated in the last follow-up of to 02Jul2020.

Follow-up (30Jul2020): New information received includes updated causality assessment for the event 'chills and itching'.

Follow-up (04Nov2021 and 05Nov2021): New information received from the investigator via CRO includes: medical history data (arterial hypertension ongoing, new: ongoing chronic obstructive pulmonary disease, ongoing chronic renal insufficiency and ongoing type 2 diabetes mellitus), SPRYCEL data (additional dosage with start/stop date, route of administration), GLIVEC data (additional dosage with start/stop date, route of administration), event data (verbatim updated to left subclavian artery tight stenosis, stop date updated), new event (edema), and concomitant medication data (candesartan withdrawn).

Amendment: This follow-up report is being submitted to amend previously reported information: investigator causality assessment for candesartan added, candesartan was changed from concomitant medication to suspect product, hospitalization stop date added.

No follow-up attempts are needed. No further information is expected.

Follow-up (03Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047

Updated information: updated Candesartan to ongoing, updated awareness date, reporter details added.

Follow-up (07Mar2023): New information received from the CRO is as follows:
Updated information: The event verbatim chills and itching was changed to chills.

Follow-up (18Sep2023): This is a non-interventional study follow up report received from the investigational site via the CRO.
Updated information: events details (new event itching, Event "Left subclavian artery tight stenosis" deleted, Event term "oedemas" was changed to "Diffuse odemas cutaneous, ENT and thoracic").

Follow-up (03Oct2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Updated information includes: no action was taken for bosutinib in response to event itching in May2017.

Follow-up (19Oct2023 and 23Oct2023): This is a non-interventional study follow up report received from the clinical team in response to the query.
Updated information includes: new event "subclavicular artery stenosis" added, onset date, stop date, outcome, seriousness, causality assessment added and clinical event course.

Case Comment: By close temporal relationship and absence of factors which may provide an alternative cause, the reported events "renal failure increased, Arthralgia on ankles, wrists and neck, dyspnea,, fatigue, Diarrhea" may be attributed to suspect drug bosutinib; the events are consistent with the known toxicity profile of the suspect product. A contributory role of co suspect and dasatinib to these events cannot be excluded. The reported 'chills and itching' and "Diffuse odemas cutaneous, ENT and thoracic" are unlikely related to bosutinib administration. "subclavicular artery stenosis" is more likely an intercurrent medical condition and unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Cytogenetic analysis	from 250% to 1% under GLIVEC %	
2	31-MAY-2017	Ultrasound Doppler	65-70% stenosis of left intern carotid	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#2) GLIVEC (IMATINIB MESILATE) ; Regimen #2	100 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	Unknown; Unknown
#2) GLIVEC (IMATINIB MESILATE) ; Regimen #3	UNK; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	26-JUN-2017 / Ongoing; Unknown
#3) SPRYCEL (DASATINIB MONOHYDRATE) ; Regimen #1	70 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	Unknown; Unknown
#3) SPRYCEL (DASATINIB MONOHYDRATE) ; Regimen #2	UNK; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	20-MAY-2017 / 25-JUN-2017; 1 month 6 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
Unknown	Relevant Med History	Abdominal aortic aneurysm (Aortic aneurysm);
Unknown	Relevant Med History before starting bosutinib	Renal disease (Nephropathy);
Unknown to Ongoing	Relevant Med History	Chronic obstructive pulmonary disease (Chronic obstructive pulmonary disease);
Unknown to Ongoing	Relevant Med History	Chronic renal insufficiency (Chronic kidney disease);
Unknown to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1949	67 Years	Female	52.00 kg	15	JAN	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
fall [Fall]
ENT infectious episode [Upper respiratory tract infection]
Malaise [Malaise]
vomiting [Vomiting]
nausea [Nausea]
epigastric pain [Abdominal pain upper]
fatigue [Fatigue]
loss of appetite [Decreased appetite]
joint pain [Arthralgia]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) CLAMOXYL /00249601/ (AMOXICILLIN)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 250 mg, daily	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE

#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) ENT infectious episode (Upper respiratory tract infection)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 01-JAN-2017 / Unknown	#1) Unknown
#2) 17-JAN-2017 / 19-JAN-2017	#2) 3 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

#1) FORADIL (FORMOTEROL FUMARATE) ; 21-JUL-2012 / Ongoing
#2) BECOTIDE (BECLOMETASONE DIPROPIONATE) ; 21-JUL-2012 / Ongoing
#3) RHINOCORT /00212602/ (BECLOMETASONE DIPROPIONATE) ; 21-JUL-2012 / Ongoing
#4) KESTIN (EBASTINE) ; 21-JUL-2012 / Ongoing
#5) INEXIUM /01479302/ (ESOMEPRAZOLE MAGNESIUM) ; 21-JUL-2012 / Ongoing
#6) LASILIX /00032601/ (FUROSEMIDE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Sinusitis recurrent (Sinusitis)
Unknown	Relevant Med History	Asthma (Asthma)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.

2017238696

25b. NAME AND ADDRESS OF REPORTER

NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER

14-NOV-2023

24d. REPORT SOURCE

☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT

27-FEB-2024

25a. REPORT TYPE

☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

cephalgia [Headache]
palpitation [Palpitations]
tinnitus [Tinnitus]
malaise [Malaise]
RECTAL BLEEDING [Rectal haemorrhage]
unbalance sensation [Balance disorder]
majoration of asthmatic symptoms with cough [Asthma]
phlegm [Productive cough]
Spontaneous ecchymosis [Ecchymosis]
OVARIAN CYST [Ovarian cyst]
PTH INCREASED [Blood parathyroid hormone increased]
CUTANEOUS XEROSIS [Dry skin]
NAUSEA [Nausea]
VOMITING [Vomiting]
DIARRHEA [Diarrhoea]
oral erosive lichen [Rash papular]
dog bite wound [Animal bite]
Urinary infection [Urinary tract infection]

Case Description: OBSERVATIONAL STUDY-EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.

A 67-year-old female patient received bosutinib (BOSULIF), first regimen since 01Jan2017 at 250 mg daily, oral, second regimen from 08Feb2017 to 26Apr2017 at 300 mg daily, oral, third regimen from 26Apr2017 to 04May2017 at 400 mg daily, oral, fourth regimen from 05May2017 to 04Jul2017 at 400 mg daily, oral, fifth regimen since 04Jul2017 (ongoing) at 300 mg daily, oral and sixth regimen since 26Feb2018 (ongoing) at daily (alternation 200 mg / 300 mg, daily) for chronic myeloid leukaemia; amoxicillin (CLAMOXYL /00249601/), from 17Jan2017 (Batch/Lot number: unknown) to 19Jan2017 for upper respiratory tract infection. The patient's relevant medical history included: "repetitions sinusitis" (ongoing); "asthma" (unspecified if ongoing); "Chronic dehydration" (ongoing during study duration); "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: FORADIL oral taken for asthma, start date: 21Jul2012 (ongoing); BECOTIDE oral taken for asthma, start date: 21Jul2012 (ongoing); RHINOCORT /00212602/ oral taken for sinusitis, start date: 21Jul2012 (ongoing); KESTIN oral taken for sinusitis, start date: 21Jul2012 (ongoing); INEXIUM /01479302/ oral taken for prophylaxis, start date: 21Jul2012 (ongoing); LASILIX /00032601/. The patient also received unspecified concomitant therapy.
The following information was reported: UPPER RESPIRATORY TRACT INFECTION (non-serious) with onset 15Jan2017, outcome "recovered" (Jan2017), described as "ENT infectious episode"; DIARRHOEA (non-serious) with onset 17Jan2017, outcome "recovered" (18Jan2018), described as "DIARRHEA"; NAUSEA (non-serious) with onset 18Jan2017, outcome "recovered" (18Jan2017); VOMITING (non-serious) with onset 18Jan2017, outcome "recovered" (18Jan2017); MALAISE (non-serious) with onset 15Mar2017, outcome "recovered" (15Mar2017); RECTAL HAEMORRHAGE (non-serious) with onset 22Mar2017, outcome "recovered" (22Mar2017), described as "RECTAL BLEEDING"; DRY SKIN (non-serious) with onset 03Apr2017, outcome "not recovered", described as "CUTANEOUS XEROSIS"; HEADACHE (non-serious) with onset 26Apr2017, outcome "not recovered", described as "cephalgia"; ABDOMINAL PAIN UPPER (non-serious) with onset 26Apr2017, outcome "not recovered", described as "epigastric pain"; FATIGUE (non-serious) with onset 26Apr2017, outcome "not recovered"; ARTHRALGIA (non-serious) with onset 26Apr2017, outcome "not recovered", described as "joint pain"; DECREASED APPETITE (non-serious) with onset 26Apr2017, outcome "not recovered", described as "loss of appetite"; ASTHMA (non-serious) with onset 26Apr2017, outcome "not recovered", described as "majoration of asthmatic symptoms with cough"; NAUSEA (non-serious) with onset 26Apr2017, outcome "not recovered"; PALPITATIONS (non-serious) with onset 26Apr2017, outcome "not recovered", described as "palpitation"; PRODUCTIVE COUGH (non-serious) with onset 26Apr2017, outcome "not recovered", described as "phlegm"; TINNITUS (non-serious) with onset 26Apr2017, outcome "not recovered"; BALANCE DISORDER (non-serious) with onset 26Apr2017, outcome "not recovered", described as "unbalance sensation"; VOMITING (non-serious) with onset 26Apr2017, outcome "not recovered"; MALAISE (non-serious) with onset 03May2017, outcome "recovered" (04May2017); OVARIAN CYST (non-serious) with onset 22Jan2018, outcome "not recovered"; ECCHYMOSIS (non-serious) with onset 26Feb2018, outcome "recovered" (29Apr2019), described as "Spontaneous ecchymosis"; FALL (medically significant) with onset 13Mar2018, outcome "recovered" (25Nov2019); BLOOD PARATHYROID HORMONE INCREASED (non-serious) with onset 2018, outcome "recovered" (2018), described as "PTH INCREASED"; RASH PAPULAR (non-serious) with onset Sep2018, outcome "recovered" (Feb2019), described as "oral erosive lichen"; URINARY TRACT INFECTION (non-serious) with onset 24Dec2018, outcome "recovered" (03Jan2019), described as "Urinary infection"; ANIMAL BITE (non-serious) with onset 19Sep2019, outcome "recovered" (25Sep2019), described as "dog bite wound". The patient underwent the following laboratory tests and procedures: Blood creatinine (45-84): (16Oct2017) 97 mmol/L; Blood parathyroid hormone: (2018) increased; Colonoscopy: (unspecified date) unknown result; Culture stool: (unspecified date) positive (blood); Magnetic resonance imaging: (unspecified date) unknown result; Ultrasound pelvis: (02May2018) stable cyst; Ultrasound scan: (unspecified date) unknown result. The action taken for bosutinib was dosage not changed. The action taken for amoxicillin was dosage permanently withdrawn on 19Jan2017. Therapeutic measures were taken as a result of fall, upper respiratory

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

tract infection, malaise, diarrhoea, rash papular, urinary tract infection.
On 15Jan2017, the subject experienced non-serious ENT infectious episode, rated grade 3. No action was taken with bosutinib in response to the event. Therapeutic measures were taken as a result of the event ENT infectious episode and included amoxicillin (CLAMOXYL) and carbocisteine (BRONCHOKOD). The subject had recovered from the event ENT infectious episode in Jan2017.
On 17Jan2017 the subject developed diarrhea which was considered as non-serious event and rated grade 2. No action was taken with bosutinib in response to the event but amoxicillin (CLAMOXYL), was permanently withdrawn. The event resolved on 18Jan2018.
On 18Jan2017 the subject experienced nausea and vomiting which were considered as non-serious events and rated grade 1. No action was taken with bosutinib in response to the events. The events nausea and vomiting resolved on 18Jan2017.
On 15Mar2017, the subject presented malaise grade 2 with visual problems which has been resolved from 2 to 3 months accompanied with the palpitation and sweating. No action was taken with bosutinib in response to the event. The subject had recovered from the event malaise grade 2 on 15Mar2017. It was confirmed that visual problems, palpitations and sweating were not considered as additional events, these were subsumed under the diagnosis of malaise by the investigator.
On 22Mar2017 the subject experienced rectal bleeding which was considered as non-serious event and rated grade 1. Stool culture was positive (blood); colonoscopy was prescribed. No action was taken with bosutinib in response to the event. At reporting time, the event rectal bleeding was not resolved.
On 03Apr2017 the subject developed cutaneous xerosis which was considered as non-serious event and rated grade 1. No action was taken with bosutinib in response to the event. At reporting time, the event cutaneous xerosis was not resolved.
On 26Apr2017, the subject developed intolerance which was rated grade 1. The posology of bosutinib was reduced since 04Jul2017 by the subject with approval of her prescribing physician from 400 to 300 mg per day due to several grade 1 adverse events.
On 03May2017 the subject experienced malaise non-serious and rated grade 2. The subject decided not to take bosutinib on 04May2017 and bosutinib was resumed at same dose on 05May2017 according to physician decision. Symptoms improved after administration of paracetamol (unspecified trade name). The event malaise resolved on 04May2017.
On 13Mar2018 the subject experienced a fall, rated grade 3 and assessed as medically significant. The subject reported by phone that she fell on 12Mar2018 or 13Mar2018 (reported on 13Mar2018 on SAE form) and went to the emergency room for sutures on her right arm and on two legs. She also reported a hematoma on her forehead. The bandages were managed by a home nurse. Change of end date due to leg wounds. In consultation report of dermatologist of 08Jul2019 wound was in the process of epidermization and the in consultation report of dermatologist of 25Nov2019 there was no anymore comments on the wounds. No action was taken with bosutinib in response to the event. The event fall was resolved on 25Nov2019.
On 16Oct2017 the subject presented with signs of dehydration associated to high serum creatinine and to grade 1 cutaneous xerosis. Creatinine was at 97 mmol/l (normal range 45 -84) on 16Oct2017. This event cutaneous xerosis appeared following the events of diarrhea and loss of appetite reported previously. No action was taken with bosutinib. In response to the event, Furosemide (LASILIX) was withdrawn.
On 22Jan2018 the subject developed ovarian cyst and in 2018 the subject developed PTH increased, which were considered as non-serious events and rated grade 1. MRI for ovarian cyst and ultrasound for PTH increased were requested. No action was taken with bosutinib in response to the events. At reporting time, ovarian cyst was not resolved and PTH increased was resolved in 2018.
On 26Feb2018 the subject presented with Spontaneous ecchymosis non-serious and rated grade 1. No action was taken with bosutinib in response to the event. The subject recovered from the event Spontaneous ecchymosis on 29Apr2019.
In Sep2018 the subject experienced oral erosive lichen, for which she received treatment, and recovered in Feb2019. Bosutinib was withdrawn in response to the event oral erosive lichen. It was unknown if the event recurred after reintroduction of study drug. Physician's notes during the medical consultation: lingual or oral mycosis with several treatments (Triflucan and Fungizone). Picture taken of the tongue and showed to the dermatologist who put into question the diagnosis of mycosis and who discontinued the antifungal treatments. Treatment with mouthwashes only with bicarbonate + mycological samples in 2 weeks if the lesions were persisting. The patient decided by herself to discontinue bosutinib following this lichen. In the report of 28Nov2019, the patient was informed that as the residual disease remained inferior or equal to 0.1 %, the monitoring will be continued without the necessity of treatment resumption.
On 24Dec2018 the subject experienced Urinary infection, non-serious and rated grade 2. No action was taken with bosutinib in response to the event. The subject was treated with antibiotic therapy (cefizim 10 days) starting 24Dec2018 and recovered on 03Jan2019.
The event "Fall" was assessed as an important medical event; all the other events were considered non serious by Investigator.
Reporter comment: 02May2018: pelvis ultrasound: stable cyst.

The reporter considered "fall", "ent infectious episode", "malaise", "vomiting", "nausea", "epigastric pain", "fatigue", "loss of appetite", "joint pain", "cephalgia", "palpitation", "tinnitus", "malaise", "rectal bleeding", "unbalance sensation", "majoration of asthmatic symptoms with cough", "phlegm", "spontaneous ecchymosis", "ovarian cyst", "pth increased", "cutaneous xerosis", "nausea", "vomiting", "diarrhea", "oral erosive lichen", "dog bite wound" and "urinary infection" not related to bosutinib.

According to the investigator, the event diarrhea was unrelated to bosutinib and related to concomitant drug amoxicillin (CLAMOXYL), events nausea and vomiting on 18Jan2017 were related to concomitant drug amoxicillin (CLAMOXYL) which was withdrawn in response to the events.
According to the investigator, the events ENT infectious, malaise, Spontaneous ecchymosis, fall, ovarian cyst, PTH increased, rectal bleeding, cutaneous xerosis, oral erosive lichen and urinary infection were considered not related to the study drug bosutinib (BOSULIF) nor concomitant drugs. The events Nausea and Vomiting were considered unrelated to the study drug bosutinib but related to a unspecified concomitant drug.
The investigator believed that all of the symptoms could be considered as not related to bosutinib. Indeed, the prescribing physician and the subject both reported that these symptoms were the same that with the previous tyrosin-kinase2 inhibitor which had been introduced for symptoms for which imatinib had already been suspected for, and the switch did not change anything. As a conclusion, all the adverse events listed in SmPC were be present (little or much) in the subject who admitted that maybe they did not have

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

anything to do with a tyrosin-kinase inhibitor. The reduction of dose did not change anything. The adverse event described both by the physician and the subject as exacerbation of asthma was in fact: no asthma attack, no modification of background treatment, just glair. The investigator proposed to keep the notification with generic term "various multiple manifestations without underlying diagnosis" not related to bosutinib according to last information. Upon follow-up it was reported that the cutaneous xerosis and loss of appetite were considered by site to be reported as "various multiple manifestations without underlying diagnosis".

Follow-up (04May2018): New information reported includes that amoxicillin (CLAMOXYL) was prescribed on 17Jan2017 for ENT infection episode and was discontinued on 19Jan2017. Dehydration was not an event. Chronic dehydration was a medical history. Furosemide (LASILIX) was withdrawn due to the event malaise.

Follow-up (10Jul2018): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. New information received from investigational site is as follows:The reporter confirmed furosemide was a concomitant drug.

Follow-up (09Oct2018): New information received included: the subject experienced Lingual "mycosis" ?? (as reported) in Sep2018 which was reported as non-serious. The event was rated grade 1. The physician reported during visit: lingual or oral with several treatments fluconazole (TRIFLUCAN) and amphotericin B (FUNGIZONE). For the dermatologist the diagnosis was doubtful and decided to stop anti-fungal treatment. Treatment with mouth bath only with bicarbonate was initiated and mycological sampling was scheduled in 2 weeks if lesions were persistent. In response to the event, no action was taken with bosutinib. At reporting time, the event was not resolved. According to the investigator, the event (Lingual "mycosis" ??) was unrelated to study drug and to concomitant drugs.

Follow-up (25Feb2020) : New information from CRO is as follows:The subject experienced dog bite wound on 19Sep2019 reported as non-serious and rated grade 3. In response to this event, no action taken with study drug. The outcome of the event was resolved on 25Sep2019.
According to the reporter, the event was unrelated to study drug and to concomitant drugs.

Follow-up (07Jun2022). This follow-up is received from the investigational site via CRO. Updated information: Patient height was updated. PTH INCREASED onset date was updated to 2018 from 22Jan2018. Event was recovered on unspecified date in 2018. Event verbatim ecchymosis was updated to spontaneous ecchymosis. Event fall onset date updated to 13Mar2018 and recovered on 25Nov2019.

Follow-up (08Feb2023): This is a follow-up report from the investigator via CRO. Updated information includes: seriousness of the event fall (medically significant); case upgraded to serious; causality assessment and action taken for events nausea and vomiting (reported as related to an unspecified concomitant drug); verbatim of the event "Lingual "mycosis??" updated to "Oral erosive lichen"; outcome of the event "Spontaneous ecchymosis" updated from "Not recovered" to "Recovered"; recovery date of the event diarrhea updated from 18Jan2017 to 18Jan2018; grade of the event "ENT infectious episode", recovery date of "ENT infectious episode" updated from 31Jan2017 to Jan2017 and additional non-serious event "Urinary tract infection".

Follow-up (22May2023): This is a non-interventional study follow-up report. Updated information included: lab test added, outcome and stop date for event oral erosive lichen, and reporter comment.

Follow-up (11Jul2023): This is a non-interventional study follow-up report. Updated information included: study drug detail (The dosage of Bosulif was updated from 100 mg daily to 250 mg daily from 01Jan2017), event details (stop date of event rectal bleeding updated), investigator's assessment for nausea and vomiting on 18Jan2017 with concomitant drug amoxicillin.

Follow-up (25Jul2023): This is a non-interventional study follow-up report received from the investigator via the CRO. Updated information includes: medical history (ongoing CML), suspect drug data (bosutinib dosing regimen), clinical course of treatment (patient withdrew bosutinib after event oral erosive lichen and was informed no need to resume treatment as residual disease remained inferior or equal to 0.1 %).

Follow-up (25Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.
Updated information includes: dosage regimen of Bosulif.

Follow-up (27Sep2023). This follow-up is received from the clinical team in response to a query confirming
chronic dehydration is part of the patient medical history and ongoing during the study duration.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: reaction data (event muscular weakness deleted) and clinical comment on events Cutaneous xerosis and Loss of appetite.

Case Comment: Based on a compatible temporal association and known product safety profile, there was a reasonable possibility that the reported event of upper respiratory infection, malaise, vomiting, nausea, epigastric pain, fatigue, loss of appetite, joint pain, cephalgia, palpitation, tinnitus and malaise were related to suspected product bosutinib. Events muscular weakness, unbalance sensation and majoration of asthmatic symptoms with cough and more important phlegm, fall, Oral fungal infection and ecchymosis are unrelated to bosutinib but more like attributed to intercurrent medical condition. It is noted that asthma is in the medical history.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The reported dog bite wound, rectal bleeding, ovarian cyst, PTH increased, dry skin, Urinary tract infection, nausea, vomiting and diarrhea are unrelated to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-OCT-2017	Blood creatinine	97 mmol/L	84 45
2	2018	Blood parathyroid hormone	increased	
3		Colonoscopy	unknown result	
4		Culture stool Positive	positive (blood)	
5		Magnetic resonance imaging	unknown result	
6	02-MAY-2018	Ultrasound pelvis	stable cyst	
7		Ultrasound scan	unknown result	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	08-FEB-2017 / 26-APR-2017; 78 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	26-APR-2017 / 04-MAY-2017; 9 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	05-MAY-2017 / 04-JUL-2017; 61 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	04-JUL-2017 / Ongoing; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	alternation 200 mg / 300 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	26-FEB-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Dehydration (Dehydration);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
PRIVACY	FRANCE	19	DEC	1970	46 Years	Female	81.00 kg	13	APR	2017	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Metrorrhagia intermittent [Intermenstrual bleeding]
Nausea [Nausea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.

(Continued on Additional Information Page)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 12-APR-2017 / 15-MAY-2017

19. THERAPY DURATION
#1) 34 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Fibroma (Fibroma)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017257861

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
13-APR-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 46 year-old female patient received bosutinib (BOSULIF), from 12Apr2017 (Batch/Lot number: unknown) to 15May2017 at 400 mg 1x/day. Relevant medical history included: "fibroma" (ongoing). The patient's concomitant medications were not reported.
The following information was reported: INTERMENSTRUAL BLEEDING (non-serious) with onset 26Apr2017, outcome "not recovered", described as "Metrorrhagia intermittent"; NAUSEA (non-serious) with onset 13Apr2017, outcome "recovered" (15May2017), described as "Nausea". The Events Metrorrhagia and Nausea were reported as non-serious, grade 2.Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage permanently withdrawn on 15May2017.

According to the investigator, the events were related to study drug bosutinib.

Follow-up (19Jun2017): New information received from investigational site includes: The Center ID/Subject ID was updated.

Fllow-up (15Nov2021): This follow-up is received from the investigational site via CRO.
Information updated: Event verbatim for metrorrhagia updated to metrorrhagia intermittent. Outcome of metrorrhagia updated to not recovered.

Follow-up (13Apr2023): This follow-up is received from the investigational site via CRO. Updated Information included: patient's weight changed. Additional information: Event Metrorrhagia and Nausea are reported as non-serious, grade 2.

Case Comment: Drug causality for suspect drug in the onset of the reported events cannot be excluded.
The follow up information does not alter the previous company clinical evaluation.
The impact of this report on the benefit/risk profile of the Pfizer drug is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	15-MAY-2017	Ultrasound uterus	normal	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1938	78 Years	Female	64.00 kg	23	MAR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

enclaved vesicular lithiasis [Calculus bladder]
Cytolytic hepatitis [Hepatic cytolysis]
TSH increased [Blood thyroid stimulating hormone increased]
Face oedema [Face oedema]
Bronchitis [Bronchitis]
Lumbago [Back pain]
osteoarthritis flare-up of the right shoulder [Osteoarthritis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 17-MAR-2017 / 30-MAR-2017

19. THERAPY DURATION
#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

#1) CARDENSIEL (BISOPROLOL FUMARATE) ; 2002 / Ongoing
#2) PREVISCAN (FLUINDIONE) ; 2002 / Ongoing
#3) EZETROL (EZETIMIBE) ; 2013 / Ongoing
#4) HEMIGOXINE (DIGOXIN) ; Ongoing
#5) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Unknown
#6) TRAMADOL (TRAMADOL) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2002 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
2002 to Ongoing	Relevant Med History	Arrhythmia (Arrhythmia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017280754

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
06-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 78-year-old female subject received bosutinib (BOSULIF), first regimen from 17Mar2017 to 30Mar2017 at 100 mg once daily, second regimen from 31Mar2017 to 13Apr2017 at 200 mg once daily, third regimen from 14Apr2017 to 04Jun2017 at 300 mg once daily, fourth regimen from 04Aug2017 to 06Sep2018 at 100 mg daily, fifth regimen from 07Sep2018 to 18Apr2019 at 300 mg once daily and sixth regimen since 19Apr2019 (ongoing) at 400 mg daily for an unspecified indication. Medical history included arterial hypertension ongoing since 2002, arrhythmia ongoing since 2002, hypercholesterolemia ongoing since 2013 and ongoing Chronic myeloid leukemia. Concomitant medications included oral bisoprolol fumarate (CARDENSIEL) ongoing since 2002 for arterial hypertension, oral fluindione (PREVISCAN) ongoing since 2002 for arrhythmia, oral ezetimibe (EZETROL) ongoing since 2013 for hypercholesterolemia, oral digoxin (HEMIGOXINE) ongoing for cardiac disorder, and tramadol and levothyroxine sodium (LEVOTHYROX) at the time of the hepatic event or during the 2 weeks prior to the onset date of the hepatic event (no detail provided). The subject developed cytolytic hepatitis on 17May2017, rated grade 3 and non-serious. It was confirmed that the event cytolytic hepatitis was a new event not a recurrence or worsening of preexisting disease. The subject experienced TSH increased on 23Mar2017 (seriousness unknown) and face oedema from 13Apr2017 to 15Jun2017 (seriousness unknown). On 03Jan2018, the subject experienced a lumbago grade 2 (non-serious). On 28Apr2018, the subject experienced a bronchitis grade 2 (non-serious). On Nov2018, the subject presented with enclaved vesicular lithiasis which was rated as grade 3 and required hospitalization. There was acute enclaved vesicular lithiasis which required coelioscopic cholecystectomy on 10Dec2018. Post-operative follow-up was simple. In response to enclaved vesicular lithiasis, bosutinib was discontinued for 5 days and then reintroduced at the same dose. Laboratory analysis was done and found alanine aminotransferase (normal range: less than 35) at 225 on 19May2017, 102 on 26May2017, 73 on 01Jun2017, 156 on 09Jun2017, 46 on 22Jun2017, 32 on 20Jul2017 and 19 on 31Jul2017; Aspartate aminotransferase (normal range: less than 35) at 145 on 19May2017, 58 on 26May2017, 50 on 01Jun2017, 123 on 09Jun2017, 42 on 22Jun2017, 39 on 20Jul2017 and 32 on 31Jul2017; Gamma-glutamyltransferase (GGT) (normal range: less than 38) at 118 on 19May2017, total bilirubin (normal range: 5 - 21) was at 19 on 19May2017, TSH at 4.6 MiU on 23Mar2017. The subject underwent cholecystectomy on 18Dec2018 which required hospitalization. The subject experienced osteoarthritis flare-up of the right shoulder on 02Apr2019 reported as non-serious and rated grade 2. The subject was treated by bosutinib prior to experience oestoearthritis flare-up of the right shoulder. No action for bosutinib in response to this event (Post-therapy). Treatment received for blood thyroid stimulating hormone increased was readministration of levothyroxine (LEVOTHYROX) via oral route on 13Apr2017. The subject did not present any additional signs or symptoms. As of 14May2023, it was reported that the Investigator Initial Aware Date for event Lumbago was 01Feb2018 while the Investigator Initial Aware Date for event Osteoarthritis flare up was 19Apr2019. The event cytolytic hepatitis was rated grade 3 on 17May2017, then grade 1 on 26May2017, resolution on 31Jul2017. In response to cytolytic hepatitis, bosutinib was temporaraily discontinued and the event did not reappear at the product reintroduction. BOSULIF treatment still ongoing at the end of the study. The last action taken with bosutinib was dose not changed. The outcome of the event cytolytic hepatitis was resolved on 31Jul2017, of the event lumbago was resolved on 01Feb2018, of event bronchitis was resolved in May2018, of the event face oedema was resolved on 15Jun2017, and of the event TSH increased was resolved in 2017, of event enclaved vesicular lithiasis was resolved on 10Dec2018. The subject recovered from osteoarthritis flare-up of the right shoulder in Nov2019. No adverse event recurred following reintroduction of study drug.

According to the investigator, the event cytolytic hepatitis was related to study drug bosutinib and unrelated to concomitant drugs. The causal relationship between lumbago and bronchitis and study drug was assessed as not related. The investigator considered the events face oedema, TSH increased and enclaved vesicular lithiasis as not related to the study drug or concomitant medication. According to the investigator, the event osteoarthritis flare-up of the right shoulder was unrelated to study drug and to concomitant drug.

Follow-up (04Aug2017): New information received from the investigator included: event outcome.

Amendment: This follow-up report is being submitted to amend previously reported information: (event cytolytic hepatitis was downgraded to non-serious as this was how the PI reported the seriousness initially).

Follow-up (15May2018): New information received included: new events (blood thyroid stimulating hormone increased, face oedema, lumbago grade 2, and bronchitis grade 2), treatment received, laboratory data (TSH 4.6IU/l), action taken with study drug (dose not changed), and clinical course.

Follow-up (16May2018): This case is being submitted to notify that the follow-up information previously considered to have been initially received by the company on 15May2018 was instead received on 16May2018.

Follow-up (26Jun2018): New information reported includes bosutinib dose, reaction data (treatment), investigator causality assessment for face oedema and TSH increased.

Follow-up (03Jul2018): New information received from clinical team included that the event cytolytic hepatitis was a new event not a recurrence or worsening of preexisting disease, concomitant medications, and lab data.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (24Dec2018): New information received from the study site includes: surgical procedure (cholecystectomy).

Follow-up (16Jan2019): New information received from the study site upon the query includes: new event (cholecystitis), and last action taken for bosutinib updated. This case was upgraded as serious in this follow-up, due to serious event "cholecystitis".

Follow-up (01Oct2019): new information received from CRO is as follows: Event term updated to enclaved vesicular lithiasis (previously cholecystitis), Outcome of events bronchitis, TSH increased updated to recovered, new adverse event osteoarthritis flare-up of the right leg (reported as non-serious), onset date of enclaved vesicular lithiasis updated to Nov2018, onset date of cytolytic hepatitis updated to 17May2017.

Follow-up (07Jan2021): New information received from the study site includes: updated action taken (from dose not changed to permanently withdrawn in response to event acute enclaved vesicular lithiasis).

Follow-up (07Jan2021): New information received includes: Reaction data (event term updated from "osteoarthritis flare-up of the right leg" to "osteoarthritis flare-up of the right shoulder") and Clinical outcome (updated to recovered for the event osteoarthritis flare-up of the right shoulder).

Follow-up (19Mar2021): New information received includes: action taken of bosutinib.

Follow-up (14May2023): This is a report from a Non-Interventional study source from the investigational site via the CRO. Updated information includes: reporter information (F/UP activities possible was updated), patient details (patient initials changed from UNK to PRIVACY), product details (dosage regimen was updated), event details (outcome and stop date for event Lumbago was updated), Investigator Initial Aware Date was changed from 04Jun2017 to 13Apr2017 and clinical course details (Investigator Initial Aware Date for event Lumbago: 01Feb2018, Investigator Initial Aware Date for event Osteoarthritis flare up: 19Apr2019).

Follow-up (06Sep2023 and 06Sep2023): This is a non-interventional study follow up report from clinical team and the investigational site via the CRO.
Updated information included: patient age updated, medical history added, dosage regimen of bosutinib added, clinical event cytolytic hepatitis course.

Case Comment: In agreement with the investigator, that there was not a reasonable possibility that the event enclaved vesicular lithiasis was related to the study drug bosutinib. There was a reasonable possibility that the event cytolytic hepatitis was related to the study drug bosutinib. The other events were unrelated to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	19-MAY-2017	Alanine aminotransferase	225	35
2	26-MAY-2017	Alanine aminotransferase	102	35
3	01-JUN-2017	Alanine aminotransferase	73	35
4	09-JUN-2017	Alanine aminotransferase	156	35
5	22-JUN-2017	Alanine aminotransferase	46	35
6	20-JUL-2017	Alanine aminotransferase	32	35
7	31-JUL-2017	Alanine aminotransferase	19	35
8	19-MAY-2017	Aspartate aminotransferase	145	35
9	26-MAY-2017	Aspartate aminotransferase	58	35
10	01-JUN-2017	Aspartate aminotransferase	50	35
11	09-JUN-2017	Aspartate aminotransferase	123	35
12	22-JUN-2017	Aspartate aminotransferase	42	35

Mfr. Control Number: 2017280754

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
13	20-JUL-2017	Aspartate aminotransferase	39	35
14	31-JUL-2017	Aspartate aminotransferase	32	35
15	19-MAY-2017	Blood bilirubin	19	21 5
16	23-MAR-2017	Blood thyroid stimulating hormone	4.6 MiU	
17	19-MAY-2017	Gamma-glutamyltransferase	118	38

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	Unknown	31-MAR-2017 / 13-APR-2017; 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	Unknown	14-APR-2017 / 04-JUN-2017; 1 month 22 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	100 mg, daily; Unknown	Unknown	04-AUG-2017 / 06-SEP-2018; 1 year 1 month 3 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, 1x/day; Unknown	Unknown	07-SEP-2018 / 18-APR-2019; 7 months 12 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	400 mg, daily; Unknown	Unknown	19-APR-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		NOV	1936	80 Years	Male	62.00 kg		MAR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

inguinal hernia [Inguinal hernia]
Diarrhea [Diarrhoea]
chronic renal insufficiency [Chronic kidney disease]
Itch [Pruritus]
Musculoskeletal pain [Musculoskeletal pain]
erythema located in neck and under the armpit [Erythema]
Accidental fall [Fall]
Swallowing difficult [Dysphagia]
actinic keratosis [Actinic keratosis]
left sided neck cramp [Muscle spasms]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 29-MAR-2017 / 12-APR-2017

19. THERAPY DURATION
#1) 15 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2012 to Ongoing	Relevant Med History	Coronaropathy (Coronary artery disease)
2011 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017282432

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

joint pain in left and right feet [Arthralgia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE.

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

An 80-year-old male subject started to receive bosutinib (BOSULIF, film-coated tablets) via an unspecified route of administration, from 29Mar2017 to 12Apr2017 at 100 mg once daily, from 13Apr2017 to 27Apr2017 at 200 mg once daily, from 27Apr2017 to 14Jun2017 at 300 mg once daily, and from 15Jun2017 and ongoing at 200 mg daily, for chronic myeloid leukemia. Relevant medical history included ongoing arterial hypertension since 2011, ongoing coronaropathy since 2012, joint pain since 09Apr2012 and exacerbation of joint pain (grade 2, non-serious, not recovered) in 2016. Concomitant medications were not reported. On 13Apr2017, the subject experienced diarrhea Grade 2. The event was considered as non-serious. The action taken with bosutinib was modified to dose reduced. The subject received tramadol (unspecified trade name) orally from 28Apr2017 and ongoing and prednisone (CORTANCYL) orally from 18May2017 to 28May2017 as treatment for pain. The event diarrhea resolved on 16Jun2017. The subject had an accidental fall on 14Dec2017, rated Grade 2, reported as non-serious event. No action was taken with bosutinib in response to the event. In Mar2017, the subject experienced itch and swallowing difficult. Both events were rated Grade 1 and non-serious. The subject experienced musculoskeletal pain from 19Apr2017. The event musculoskeletal pain was rated Grade 2 and was confirmed to be non-serious. Action taken for study drug, as a result of these events, was reported as dose not changed. In May2017, the subject recovered from the events itch and swallowing difficult in May2017. The event accidental fall resolved on 14Dec2017, and musculoskeletal pain recovered on 15Jun2017. On 15Sep2017, the subject experienced erythema located in neck and under the armpit considered non-serious and rated Grade 1. No action was taken for bosutinib. On 01Aug2018, the subject experienced actinic keratosis considered non-serious and rated Grade 1. No action was taken for bosutinib. On 01Sep2018, the subject experienced inguinal hernia rated Grade 2. Event inguinal hernia was considered as serious adverse event as it required the hospitalization. The subject underwent ambulatory surgery of the inguinal hernia on 08Oct2018. No action was taken for bosutinib. The subject experienced chronic renal insufficiency on 20Sep2018, non-serious, with outcome of not recovered. Chronic renal insufficiency was rated Grade 2. No action was taken with study drug in response to the event. Inguinal hernia resolved on 08Oct2018. Events actinic keratosis and erythema located in neck resolved on 04Apr2019. On 26Sep2019, the subject experienced creatinine increased, Grade 2, non-serious, with outcome of not recovered. Event "Creatinine increased" was subsumed under event "chronic renal insufficiency", considered symptom of this event. No action taken with study drug in response to the event. On 08Jan2020, the subject experienced left sided neck cramp rated grade 2, non-serious, with outcome of recovered on 12Jan2020. No action was taken with bosutinib in response to this event. Patient had joint pain in feet, left and right on 01Sep2019. The event joint pain was rated grade 1. The event outcome was not recovered. Action taken was dose not changed. Event reported as non-serious. Musculoskeletal pain resolved on 21Sep2017. It was confirmed that joint pain in left and right feet (01Sep2019) should be considered as event.

The reporter considered "diarrhea", "musculoskeletal pain" and "erythema located in neck and under the armpit" related to bosutinib and not related to concomitant medication. The reporter considered "inguinal hernia", "chronic renal insufficiency", "itch", "accidental fall", "swallowing difficult", "actinic keratosis", "left sided neck cramp" and "joint pain in left and right feet" not related to bosutinib or to concomitant medication.

Follow-up (13Sep2019): New information received from the CRO includes: event verbatim "erythema located in neck" updated to "erythema located in neck and under the armpit ", seriousness criteria of event inguinal hernia added hospitalization, treatment for inguinal hernia. This case has been upgraded to serious.

Follow-up (03Dec2019): New information received from the investigational site via CRO included: new events (Joint pain in feet, left and right, Creatinine increased) reported, updated recovery date of event diarrhea (from 18Apr2017 to 16Jun2017).

Follow-up (06Jan2020): New information received from the CRO and investigation site via CRO included: reaction data (upon the consultation of 19Apr2012 it was mentioned in the medical file that the subject had joint pain since 09Apr2012, i.e. before the start of bosutinib).

Follow-up (04Aug2020): New information received from investigator via the CRO included: suspect drug data (indication was provided as "chronic myeloid leukemia"), reaction data (added new event "left sided neck cramp").

Follow-up (14May2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from the investigational site via the CRO for protocol B1871047.
Updated information includes: Patient's information, new adverse event (joint pain in left and right feet).

Follow-up (13Jul2023): This is a follow-up to amend previously reported information: removed event bone pain.

Follow-up (07Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: reaction data (outcome of joint pain in left and right feet updated to recovered on 21Sep2017 and confirmed that

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

joint pain in left and right feet (01Sep2019) should be considered as event).

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: Event "Creatinine increased" removed as event from this case as it was subsumed under event "chronic renal insufficiency".

Case Comment: As per FU event creatinine increased was removed and subsumed under chronic renal insufficiency.

Based on temporal association and known drug profile, the reported events chronic renal insufficiency, diarrhea, itch are possibly related to bosutinib. The events accidental fall, difficulty swallowing, musculoskeletal pain, erythema, inguinal hernia, actinic keratosis, neck cramp are more likely attributed to intercurrent medical condition and unrelated to bosutinib. "joint pain in left and right feet" occurred more than 2 years after starting bosutinib, is considered unrelated to bosutinib, to be noted, patient had joint pain since 09Apr2012 and exacerbation of joint pain in 2016, before starting suspect product.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	26-SEP-2019	Blood creatinine	increased	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	13-APR-2017 / 27-APR-2017; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	27-APR-2017 / 14-JUN-2017; 49 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	15-JUN-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2016 to Unknown	Relevant Med History	Joint pain (Arthralgia); exacerbation; grade 2, non-serious, not recovered
09-APR-2012 to Unknown	Relevant Med History	Joint pain (Arthralgia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		MAY	1965	52 Years	Male	115.00 kg	04	JUL	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Bilateral testicular pain [Testicular pain]
diabetes [Diabetes mellitus]
Heavy legs [Limb discomfort]
paresthesia [Paraesthesia]
Diabetes [Diabetes mellitus]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 06-MAR-2017 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) EPROSARTAN (EPROSARTAN) ; Ongoing
#2) FENOFIBRATE (FENOFIBRATE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
Unknown to Ongoing	Relevant Med History	Hypertriglyceridemia (Hypertriglyceridaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017297939

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol B1871047.

A 52-year-old male subject started to receive bosutinib (BOSULIF), film-coated tablet, via an unspecified route of administration at 400 mg daily from 06Mar2017 and ongoing for an unspecified indication. Medical history included ongoing arterial hypertension, ongoing hypertriglyceridemia, diabetes. Concomitant medication included: eprosartan (unspecified trade name) orally, ongoing for arterial hypertension, fenofibrate (unspecified trade name) orally, ongoing for hypertriglyceridemia.
The subject developed bilateral testicular pain grade 1 on 04Jul2017. According to the investigator, the event was considered as a non-serious event. The action taken in response to the event for bosutinib was dose not changed. The subject had recovered from the event bilateral testicular pain on 10Nov2017 .
The subject experienced heavy legs on 11Oct2017, rated grade 1. This event was considered as non-serious. Action taken was not reported. At reporting time, the event was resolved on 17Nov2017.
The subject experienced diabetes rated grade 1 on 27Oct2017. The event was considered as non-serious. Action taken was not reported. At reporting time, outcome of the event was unknown.
The subject experienced paresthesia on 10Nov2017 which was considered as non-serious. No action was taken with bosutinib in response to the event. At reporting time, the event was resolved on 06Feb2018.
On 19Oct2018, the subject experienced diabetes rated grade 2 assessed as non-serious. As a result of the event the subject received metformin (STAGID) but it was ineffective. No action was taken with bosutinib in response to the event. At reporting time, the outcome of the event was unknown.

According to the investigator, the events bilateral testicular pain, heavy legs and two episodes of diabetes were considered unrelated to study drug bosutinib or to concomitant medication. Diabetes was also reported as medical history (clarification pending).
The reporter's assessment of the causal relationship of the event paresthesia with the suspect product bosutinib was not provided at the time of this report. Since no determination has been received, the case is managed based on the company causality assessment.

Follow-up (19Dec2017 and 22Dec2017): New information received from investigational site includes new events (diabetes, heavy legs, paresthesia), medical history, start date of bosutinib updated.

Follow-up (26Mar2018): follow-up attempts completed. No further information expected.

Follow-up (21Nov2018): New information received from CRO: patient experienced new episode of diabetes.

Follow-up (09Mar2023). This is a non-interventional study follow-up report received from the investigational site via CRO. Updated information includes: outcome for the event Paresthesia updated.

Follow-up attempts are not needed. No further information is expected

Follow-up (02Nov2023): Amendment: This follow-up report is being submitted to amend previous information:Event Heavy legs: outcome updated (Recovered), stop date added (17Nov2017).

Follow-up (14Nov2023): This follow-up is received in the context of reconcliliation from the clinical team.
Information updated: outcome and stop date of event Bilateral testicular pain.

Case Comment: Based on the information currently provided, the events bilateral testicular pain, diabetes (both episodes), heavy legs and paresthesia were considered unrelated to study drug bosutinib or to concomitant medication.
The follow-up information received does not alter the previous company clinical evaluation.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Diabetes (Diabetes mellitus);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		AUG	1970	45 Years	Male	92.00 kg		JUL	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

hyperkalemia [Hyperkalaemia]
Diarrhea [Diarrhoea]
Fatigue [Fatigue]
Hypotension [Hypotension]
Inflammatory syndrome [Inflammation]
weight loss [Weight decreased]
Hepatomegaly [Hepatomegaly]
Tachycardia [Tachycardia]
Dyspnea on effort [Dyspnoea exertional]
Hepatic Fibrosis [Hepatic fibrosis]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosutinib (BOSUTINIB) Unknown
#2) SPRYCEL (DASATINIB MONOHYDRATE)

(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, daily	#1) Unknown
#2) 70 mg, daily	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 30-JUN-2016 / 06-JUL-2016	#1) 7 days
#2) 10-JUL-2017 / 09-NOV-2018	#2) 492 days

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) COVERAM (AMLODIPINE BESILATE, PERINDOPRIL ARGININE)
#2) METFORMIN (METFORMIN) ; 2013 / 21-JUN-2017

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus)
2014 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017372690

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
15-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

gynecomastia [Gynaecomastia]
asthenia [Asthenia]
lower limbs oedema [Oedema peripheral]
folate deficit [Folate deficiency]
HYPERCALCEMIA [Hypercalcaemia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 45-year-old male subject started to receive bosutinib via an unspecified route of administration, for an unspecified indication, at 200 mg daily from 30Jun2016 to 06Jul2016, at 300 mg daily from 07Jul2016 to 13Jul2016, at 400 mg daily from 14Jul2016 to 23Aug2016, and at 300 mg once daily from 24Aug2016 to 21Jun2017, and dasatinib monohydrate (SPRYCEL) at 70 mg daily orally from 10Jul2017 to 09Nov2018 for chronic myeloid leukemia. The subject's medical history included: type 2 diabetes mellitus from 2013, arterial hypertension from 2014, dyslipidemia from 2013, and left benign thoracic paravertebral mass from 15Mar2016, all ongoing, cirrhosis and active alcoholic intoxication from an unknown date. Concomitant medications administered orally included: amlodipine besilate/perindopril arginine (COVERAM) from 2014 to 23Aug2016 for arterial hypertension and metformin from 2013 to 21Jun2017 for type 2 diabetes mellitus.
The subject experienced diarrhea and fatigue in Jul2016, both stated as non-serious events. He started to receive loperamide hydrochloride (IMODIUM) from Jul2016 as needed for diarrhea. Diarrhea was rated grade 2 and resolved on 06Jul2017. Fatigue was rated grade 2 and resolved on 30Aug2017. In response to event diarrhea, bosutinib was permanently withdrawn. In response to the event fatigue bosutinib dose was reduced.
The subject experienced hypotension in Aug2016. Hypotension was rated grade 1 and resolved on 22Feb2017. On 24Aug2016, he experienced inflammatory syndrome which was rated grade 2, with hyper leukocytosis. Both events were stated as non-serious. Inflammatory syndrome resolved on 30Aug2017. In response to hypotension and inflammatory syndrome, bosutinib dose was reduced. Amlodipine besilate/perindopril arginine was withdrawn on 23Aug2016 for hypotension. White blood cell count on 24Aug2016 was 19.21 x10^9/l, and 14.54 x10^9/l on 22Feb2017. Hyperleukocytosis was a symptom of inflammatory syndrome (with neutrophil polynucleosis), thrombocytosis was also present, and fibrinogen was high. Only the inflammatory syndrome was considered adverse event. The subject experienced hepatomegaly which was rated grade 2 on 26Oct2016 and did not resolve, tachycardia which was rated grade 1 on 22Feb2017 and resolved on 21Jun2017, and dyspnea on effort in 2017 (also reported as 'between Nov2016 and Feb2017'), resolved on 21Jun2017, all stated as non-serious events and dose not changed in response to the three events. The subject experienced weight loss on 22Feb2017, stated as non-serious event and rated grade 2. Weight loss resolved on 16Jun2018. Bosutinib dose was not changed in response to the event. On 29May2017, the subject experienced hepatic fibrosis, stated as non-serious event and rated grade 2. The event "hepatic fibrosis" which was not resolved at the time of the report. Bosutinib dose was not changed in response to hepatic fibrosis. On 31Aug2017, the subject developed gynecomastia. On 06Dec2017, he presented with asthenia. Gynecomastia and asthenia were assessed as non-serious and rated grade 1. No action was taken with dasatinib in response to asthenia. The action taken with bosutinib in response to gynecomastia and asthenia was not provided. It was reported that metformin was ongoing at report time. On 22Oct2018, asthenia was resolved. At the time of the report, gynecomastia was not resolved. On 29May2017, the subject experienced lower limbs oedema considered non-serious and rated grade 1. Bosutinib dose was not changed in response to lower limbs oedema. The event resolved on 21Jun2017. On 06Jul2017, the subject experienced hypercalcemia considered non-serious and rated grade 1. The event recovered on 30Aug2017. Action taken with bosutinib regarding the event hypercalcemia was reported as not changed. On 06Jul2017, the subject experienced hyperkalemia considered non-serious and rated grade 1. The event recovered on 07Jul2017. Action taken with bosutinib regarding the event hyperkalemia was reported as not changed. On 21Jul2017, the subject experienced folate deficit considered non-serious and rated grade 1. Bosutinib dose was not changed in response to folate deficit. The event outcome was unknown. On 23Oct2018, the subject developed bilateral pleural effusion mainly on the right side rated grade 3 and on 09Nov2018 a cardiac decompensation rated grade 2. Cardiac decompensation was assessed as non-serious by the investigator, while bilateral pleural effusion mainly on the right side led to the subject's hospitalization. The subject was seen on consultation on 23Oct2018. At this time, anomaly was detected during the lung auscultation. X-ray was prescribed and disclosed right pleurisy. The subject also presented with a cough, a febrile peak at 38°C and white expectorations. As a result, dasatinib was withdrawn on 09Nov2018 and the subject was hospitalized in pneumology unit for management. Conclusion: bilateral pleural effusion mainly on the right side and cardiac decompensation with discovery of pulmonary hypertension suspected to be secondary to dasatinib. Complementary investigations for pulmonary arterial hypertension were ongoing at report time. Right catheterism performed on 23Nov2018 found elevation of pulmonary arterial pressure while on high flow probably in the context of liver disease. Treatment at discharge included metformin 500 mg (unspecified trade name), furosemide 140 mg (unspecified trade name), telmisartan (MICARDIS 80 mg), and nicotine (NICOPATCH 21mg). Therapy for chronic myeloid leukemia was proposed to the subject: imatinib at 200 mg once daily. On 21Nov2018, bilateral pleural effusion mainly on the right side fully resolved. At the time of the report, the subject had not recovered yet from cardiac decompensation.
Bosutinib dose was increased according to the protocol from 200mg to 300mg then to 400mg before the investigator decision to reduce the dose from 400mg to 300mg due to diarrhea and fatigue, which were present from bosutinib initiation in Jul2016. Bosutinib was permanently withdrawn due to diarrhea and inflammatory syndrome. Bosutinib was withdrawn on 21Jun2017. Dasatinib was withdrawn on 09Nov2018 and the last action taken was reported as not applicable.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The reporter's assessment of the causal relationship of the event hyperkalaemia with the suspect product was not provided at the time of this report. Since no determination has been received, the case is managed based on the company causality assessment.

The investigator considered the events diarrhea, fatigue, hypotension, inflammatory syndrome, and weight loss as related to the study drug, while the events hepatomegaly, tachycardia, dyspnea on effort, hepatic fibrosis, gynecomastia, asthenia, lower limbs oedema, folate deficit, and hypercalcemia were considered as unrelated to bosutinib. The investigator considered that there was not a reasonable possibility that the events tachycardia, hepatomegaly, lower limbs oedema, folate deficit, hypercalcemia was related to a concomitant drug. The investigator considered the events asthenia and bilateral pleural effusion mainly on the right side as related to the concomitant dasatinib. Hepatomegaly related to the medical history of the patients: diabetes and alcoholism. The investigator considered the event hyperkalemia as non-serious, not related to the study drug bosutinib and concomitant medications.

Follow-up (08Sep2017). New information received from the investigational site includes: action taken with bosutinib and metformin, additional non-serious events (weight loss, hepatic fibrosis), outcome and relatedness of the new events.

Follow-up (12Oct2017). New information received from the investigational site includes: severity of the events previously reported, outcome of the events, action taken with bosutinib.

Follow-up (03Nov2017): Follow-up attempts completed. No further information expected.

Follow-up (09Nov2018). New information received from the investigational site includes: additional suspect product (dasatinib), additional non-serious events (gynecomastia and asthenia), action taken with bosutinib and outcome and relatedness of the new events.

Follow-up (15Nov2018). New information received from the investigational site includes: start date, dose, route of administration and indication of dasatinib, action taken with bosutinib updated.

Follow-ups (09Jan2019): New information received from the investigational site includes: start date of dasatinib updated, stop date of dasatinib, additional serious event (bilateral pleural effusion) and non-serious event (Cardiac decompensation), relevant tests and investigations, medical history, treatment of the events, outcome and causality of the new events. Due to the new reported events, the case was upgraded to serious.

Follow-up (11Mar2019): Follow-up attempts are completed. No further information is expected.

Follow-up (16Jan2020): New information received includes Medical history, concomitant drug details, reaction data (onset date of events "hypotension, tachycardia, hepatic fibrosis" updated, resolve date of events "hypotension, Inflammatory syndrome, tachycardia, weight loss" updated, added new events "lower limbs oedema, folate deficit, hypercalcemia, and hyperkalemia", deleted events "Pleural effusion, heart decompensation, and pulmonary hypertension"), causality of tachycardia (provided as "unrelated"). The case has been upgraded due to new event hyperkalemia.

Follow-up (17Jan2020): New information received from the CRO included: onset date and recovered date of event hypercalcemia, action taken with bosutinib regarding the event hyperkalemia, causality assessment of event hyperkalemia for concomitant drug.

Follow-up (25Apr2023): This is a non-interventional study follow-up report received from the CRO. Updated information included: Patient's initials updated. Previously reported information also amended: event hyperkalemia downgraded to non-serious as reported by investigator and event details for hyperkalemia updated.

Follow-up (15Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information included: dasatinib monohydrate start date, asthenia onset date, gynecomastia outcome.

Case Comment: The reported events lower limbs oedema, folate deficit, hypercalcemia, gynecomastia, asthenia, hepatic fibrosis, tachycardia, hepatomegaly, and dyspnea exertional are considered unrelated to bosutinib. The other events including hyperkalemia are considered related to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	23-OCT-2018	Auscultation	anomaly	
2	23-OCT-2018	Body temperature	38 Centigrade	
3	24-AUG-2016	White blood cell count	19.21 x10 9/l	
4	22-FEB-2017	White blood cell count	14.54 x10 9/l	

Mfr. Control Number: 2017372690

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
5		X-ray	right pleurisy	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #2	300 mg, daily; Unknown	Unknown	07-JUL-2016 / 13-JUL-2016; 7 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	400 mg, daily; Unknown	Unknown	14-JUL-2016 / 23-AUG-2016; 41 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	300 mg, 1x/day; Unknown	Unknown	24-AUG-2016 / 21-JUN-2017; 302 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#1) COVERAM (AMLODIPINE BESILATE, PERINDOPRIL ARGININE) ; 2014 / 23-AUG-2016

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);
15-MAR-2016 to Ongoing	Relevant Med History	Mass (Mass);
Unknown	Relevant Med History	Cirrhosis liver (Hepatic cirrhosis);
Unknown	Relevant Med History	Alcohol abuse (Alcohol abuse);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		DEC	1963	53 Years	Male	91.00 kg	12	APR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Nephritic colic [Renal colic]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL, Center ID/Subject ID 13|02.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 300 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 10-MAY-2016 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) PLAVIX (CLOPIDOGREL BISULFATE) ; 2004 / Ongoing
#2) XANAX (ALPRAZOLAM) ; MAR-2011 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017385530

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 53-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration, from 10May2016 at 300 mg daily, for an unspecified indication. The subject had no medical history. Concomitant medications included clopidogrel bisulfate (PLAVIX) ongoing since 2004 at 75 (unspecified unit) per day for peripheral arterial disease, alprazolam (XANAX) ongoing since Mar2011 at 1.5 (unspecified unit) per day for depressive syndrome, both were ongoing at the onset of the event. On 12Apr2017, the subject developed nephritic colic, rated grade 1 and non-serious. The action taken with bosutinib was dose not changed. The subject received an symptomatic treatment of the event nephritic colic included ketoprofen (PROFENID) and paracetamol (unspecified trade name) as needed. The subject recovered from the event on 19Apr2017. The cause of the event was not identified.

The investigator considered there was not a reasonable possibility that the event was related to study drug bosutinib and or to concomitant medication.

Follow-up (03Oct2017): New information received from the investigational site includes: Treatment for the event, and that the cause of the event was not identified.

Follow-up (19Oct2017): New information received from the investigational site includes: Updated Start date of the event nephritis colic to 12Apr2017 (from 25Jul2017), and the investigator initial aware date of this event.

Follow-up (10Aug2018): New information reported includes concomitant medications information.

Follow-up (14Nov2023). This follow-up is received from the clinical team in the context of reconciliation.
Updated information included: Updated end date (updated to 19Apr2017)

Follow-up attempts are completed. No further information is expected.

Case Comment: Based on the information currently provided, the company concurs with the causality assessment provided by the investigator, considering there was not a reasonable possibility that the reported nephritic colic was related to study drug bosutinib. The follow up information received does not alter the previous company clinical evaluation.

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1948	69 Years	Male	112.00 kg	06	OCT	2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Cardiac failure [Cardiac failure]
Renal insufficiency [Renal failure]
Myocardial infarction [Myocardial infarction]
Bronchitis [Bronchitis]
Bilateral pleural effusion [Pleural effusion]
Pruritus [Pruritus]
Diarrhea [Diarrhoea]
Pleural effusion [Pleural effusion]
Asthenia [Asthenia]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) GLIVEC (IMATINIB MESILATE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 200 mg, 1x/day
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown
#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 06-OCT-2016 / 09-JAN-2018
#2) 08-AUG-2018 / Ongoing

19. THERAPY DURATION
#1) 461 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) BISOPROLOL (BISOPROLOL) ; 25-AUG-2017 / Ongoing
#2) ALLOPURINOL (ALLOPURINOL) ; 1994 / Ongoing
#3) TAHOR (ATORVASTATIN CALCIUM) ; 25-AUG-2017 / Ongoing
#4) MOPRAL /00661201/ (OMEPRAZOLE) ; Unknown
#5) BRILIQUE (TICAGRELOR) ; 25-AUG-2017 / Ongoing
#6) VALSARTAN (VALSARTAN) ; 15-NOV-2017 / Ongoing
(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1987 to Unknown	Relevant Med History	Renal colic (Renal colic)
1994 to Ongoing	Relevant Med History treated since 1994.	Gout (Gout)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017402512

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
- ☒ STUDY
- ☐ LITERATURE
- ☒ HEALTH PROFESSIONAL
- ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
- ☒ INITIAL
- ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Dyspnea [Dyspnoea]
alteration of general condition [General physical health deterioration]
Renal lithiasis [Nephrolithiasis]
Cough [Cough]
Joint pain [Arthralgia]
Herpes [Herpes zoster]
Infectious episode [Infection]
Insomnia [Insomnia]
fecaloma [Faecaloma]
dry skin [Dry skin]
Forget take medication [Product dose omission issue]
Forget take medication two times [Product dose omission issue]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
A 69-year-old male patient received bosutinib (BOSULIF), first regimen from 06Oct2016 to 09Jan2018 at 200 mg, 1x/day and second regimen from 12May2018 to 26Jul2018 at 300 mg daily; imatinib mesilate (GLIVEC), since 08Aug2018 (ongoing) (Batch/Lot number: unknown), oral for chronic myeloid leukaemia; acetylsalicylic acid (ASPIRINE), since 25Aug2017 (Batch/Lot number: unknown) at 100 mg 1x/day, oral for thrombosis prophylaxis. The patient's relevant medical history included: Renal colic, start date:1987, stop date:1987; Gout-start date:1994 (ongoing), notes: treated since 1994; pleural effusion-start date:2016 (unknown if ongoing). Concomitant medication(s) included: BISOPROLOL oral taken for cardiac failure, hypertension, start date:25Aug2017 (ongoing); ALLOPURINOL oral taken for gout, start date:1994 (ongoing); TAHOR oral taken for blood cholesterol, hypertension, start date:25Aug2017 (ongoing); MOPRAL /00661201/; BRILIQUE oral taken for infarction, thrombosis prophylaxis, start date:25Aug2017 (ongoing); VALSARTAN oral taken for hypertension, start date:15Nov2017 (ongoing); AMLOR oral taken for hypertension, start date:15Nov2017; FUROSEMIDE oral taken for pleural effusion, start date:15Nov2017; ESOMEPRAZOLE oral taken for gastrooesophageal reflux disease; PARIET; TICAGRELOR; ATORVASTATIN.
On 19Aug2017,the subject experienced myocardial infarction, which was assessed serious (medically significant) from medical standpoint and required hospitalization. The subject also experienced the following: insomnia in Oct2016, pruritus on 27Apr2017 and diarrhea in Mar2017, pleural effusion in Nov2017 for which no seriousness criterion was reported, general condition alteration on 31May2018, joint pain for which no seriousness criterion was reported on 06Oct2016, herpes and infectious episode for which no seriousness criterion was reported on 26Oct2016, cough for which no seriousness criterion was reported in Oct2016, bronchitis, onset date 10Sep2017, grade 2, requiring hospitalization, renal lithiasis on an unspecified date in Aug2017, and cardiac failure grade 3 on 30Dec2017 which required hospitalization. The subject underwent lab tests and procedures which included: electrocardiogram was performed on 19Aug2017 (result not provided); Pulmonary X-ray (frontal) on lying position performed on 19Aug2017 (Indication: infarction): no pleural or pulmonary opacity, mild hilar hyperplasia of vascular aspect; Lab tests of 19Aug2017 10.36 pm: Troponin T Hs 0.404 ng/mL (N<0.014) (probable myocardial infarction was suspected for values >0.05 ng/mL); Lab tests of 19Aug2017: Prothrombin ratio 100%, White blood cells (N:4.00-11.00 G/L) 14.02, Red blood cells N:4.28-6.00 T/L) 5.43, Hemoglobin (N:13.0-18.0 g/dL) 15.4, Hemoglobin (N:130-180 g/L) 154, Hematocrit (N:39-53%) 46, Platelets (N:150-400 G/L) 194, Neutrophils (N:1.40-7.70 G/L) 7.35, Eosinophils (N:0.02-0.63 G/L) 1.23, Basophils (N:0.00-0.11 G/L) 0.08, Lymphocytes (N:1.00-4.80 G/L) 4.37, Monocytes (N:0.18-1.00 G/L) 0.98, eGFR (CKD-EPI) 42 mL/min (N >90), eGFR (MDRD) 42 mL/min, CRP 5.8 mg/L (N< 5.0), Sodium 141 mmol/L (N:136-145), Potassium 3.89 mmol/L (N: 3.40-4.50), Chloride 103 mmol/L (N:98-107), Total CO2 21.7 mmol/L (N: 22.0-29.0), Proteins 78.4 g/L (N: 64.0-83.0), Glucose 7.20 mmol/L (N: 4.56-6.38), Urea 8.2 mmol/L (N: 2.5-7.5), creatinine 146 µmol/L (N: 59-104), troponin Hs 0.029 ng/mL (N< 0.014), troponin Hs 29 ng/L (N<14); Lab tests of 20Aug2017 09.03 am: Calculated LDL 1.39 g/L, Troponin T Hs 0.481 ng/mL (N<0.014), fasting blood glucose level 0.86 g/L (N: 0.70-1.15), sodium 143 mmol/L (N:136-145), plasma potassium 4.4 mmol/L (N:3.4-4.5), urea 0.42 g/L (N: 0.17-0.49), creatinine 14.9 mg/L (N:6.7-11.7); Lab tests of 20Aug2017 02.15 pm: Troponin T Hs 0.339 ng/mL (N<0.014); Lab tests of 21Aug2017 08.33 am: Sodium 141 mol/L (N:136-145), plasma potassium 4.2 mmol/L (N: 3.4-4.5), creatinine 15.4 mg/L (N:6.7-11.7).Troponin was measured on 22Aug2017(results not provided). A coronary catheterization and angioplasty were performed on 23Aug2017 with the following conclusion: success of angioplasty of middle part of the proximal anterior interventricular artery. Insertion of 1 drug-eluting stent. ECG recording (29Aug2017): Heart rate 61 bpm, PR interval 166 ms, QRS duration 78 ms, QT/QTc 408/410 ms, P-R-T axis 43 48 44, Average RR 982 ms, QTcB 411 ms, QTcF 410 ms.
On 25Sep2017, the subject developed cough / bronchopathy rated grade 2. The subject was not hospitalized as he was only admitted to emergency department from 02:00 p.m. to 07:15 p.m. Trans-thoracic echography showed no pericardic effusion on 25Sep2017. The subject was treated with amoxicillin / clavulanate potassium (AUGMENTIN) for 7 days. Following hospital record was provided:"Emergency report of 25Sep2017 at 02.06 pm: the patient visited to emergency department for bilateral pleural effusion, bronchopathy for 15 days. The patient was under corrective treatment but no improvement was observed. General health deterioration was also reported with pre-syncope. Admission for bronchitis. Disease history: For 15 days, the patient experienced loose cough without fever (no body temperature was recorded). No chills were reported. Fifteen days earlier, general practitioner recommended to perform chest CT-scan and administered roxithromycin (unspecified trade name). Transient improvement was observed. On 25Sep2017the patient visited again his general practitioner due to further general health deterioration (very severe cough during the week-end) associated with repeat vagal episode sensation. Ultrasound disclosed bilateral pleural effusion and pericardial effusion was suspected. The patient was addressed to emergency department for bad tolerance of pleural

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

effusion.Medical history: acute coronary syndrome (no more details) in Aug2017 with 2 stents insertion. Treatment upon admission: bisoprolol fumarate (BISOCE), bosutinib (unspecified trade name), allopurinol (unspecified trade name), esomeprazole (unspecified trade name), atorvastatin (unspecified trade name), ticagrelor (unspecified trade name). Clinical examination: No fever, stable hemodynamic parameters. Pneumological examination: eupneic in ambient air, general condition alteration, NYH classe III, cough, Decreased vesicular murmur (right lower third more important than left side),No sign of deep vein thrombosis.Cardiological examination: No chest pain, No palpitation, Regular heart sound, No murmur, No sign of heart failure. Abdominal examination: No dysfunction symptoms, abdomen soft, no guarding or tenderness. Normal peristalsis. Neurological examination: Glasgow coma scale 15, No delirium tremens,No sensorimotor deficit of four limbs. Computer-assisted tomography for bilateral pleural effusion partially tolerated in a context of chronic myeloid leukemia in remission. ECG: RSR ventricular complex, Normal axis, No repolarization disorder, No focus, No confirmed pleurisy after reassessment by the pulmonologist.Laboratory work-up: Systemic inflammation: White blood cells 18.41 (no unit provided), neutrophils 14.88 (no unit provided), CRP44 (no unit provided), troponin 19 (no unit provided), BNP 316 clearance 45 (no unit provided). Pulmonologist advice: bronchitis without oxygen dependence, amoxicillin / potassium clavulanate (AUGMENTIN).Cardiologist advice: Transthoracic echocardiogram revealed no effusion, pericarditis, non-dilated left ventricle, inferior hypokinesia, Ejection fraction 50-55%, Normal left ventricular filling pressure, Right chambers not dilated, inferior vena cava well compliant, systolic pulmonary arterial pressure 35 mmHg. Conclusion: Shuffling bronchitis, no pleurisy, amoxicillin / potassium clavulanate (AUGMENTIN) for 7 days, No chest CT-scan after pulmonological advice, Visit if no improvement. On medical advice, the patient was discharged on 25Sep2017 at 07.15 pm."No action was taken on study drug bosutinib despite the events bronchitis and myocardial infarction, neither dosing modification nor interruption. Visit in cardiology was scheduled by the end of November. Cardiac rehabilitation was scheduled from 02Oct2017. On 15Nov2017, the subject presented with bilateral pleural effusion (grade 2) which was considered as non-serious by the investigator. On 15Nov2017, valsartan (unspecified trade name) and amlodipine besilate (AMLOR) were introduced on15Nov2017 by oral route for hypertension arterial. On this date, roxithromycin was introduced on 15Nov2017 at 150 mg twice daily for 10 days, furosemide was started by oral route at 20 mg for pleural effusion and prednisolone was introduced at 60 mg on 15Nov2017 then, at 40 mg on 16Nov2017. On 19Dec2017,blood test was performed (result not provided) and creatinine was 259 umol/l (normal between 59 and 103). On 30Dec2017 the subject presented with renal insufficiency which required hospitalization/prolongation of hospitalization. On 02Nov2017, the subject experienced asthenia grade 3 assessed as non-serious event. As a result of the event the study drug was withdrawn temporarily. On an unspecified date in May2017, the subject forgot to take study drug, this event was assessed as non-serious. In Nov2017, the subject forgot to take study drug two times, and the event was assessed as non-serious.No action was taken on the study drug bosutinib, as a result of the events infectious episode, pleural effusion (10Sep2017), general condition alteration, lithiasis.The action taken in response to the study drug bosutinib, as a result of events cough and dyspnea was temporarily withdrawn. The study drug bosutinib was permanently discontinued as a result of the event cardiac failure. On 31May2018, the subject experienced general condition alteration and considered as not serious.In Jul2019, the subject experienced fecaloma in 2019, reported as non-serious and rated grade 2. No action was taken with study drug. The subject experienced dry skin, non-serious, grade 1 in Sep2018. Action taken with bosutinib in response to asthenia was temporarily withdrawn. Reporter comment: alteration of general condition: aggravation of respiratory disorders on pleural effusion: pain, cough, dyspnea, asthenia as well as the presence of hematuria. Definitive discontinuation of bosutinib on 26Jul2018. As of 28Feb2023 it was reported that the treatment initiated with prednisone 60mg on 15Nov2017, prednisone 40mg on 16Nov2017, roxithromycin 150 mg 2x day for 10 days, furosemide 20mg. The last action taken for bosulif was temporarily withdrawn on 26Jul2018, for imatinib mesylate was unknown and acetylsalicylic acid was dose not changed. The outcome of events cardiac failure was recovered on 05Jan2018, event myocardial infarction was recovered on 23Aug2017, event bronchitis was recovered on 07Dec2017, pruritus was recovered on 21Sep2017, diarrhea was recovered on 21Sep2017, pleural effusion was recovered in Sep2017, asthenia was recovered on 22Feb2018, alteration of general condition recovered on 06Sep2018, renal lithiasis was recovered on 31May2018, cough was recovered on Dec2016, joint pain was recovered in Dec2016, herpes recovered in Dec2016, infectious episode recovered on 02Nov2016, insomnia recovered on 05Oct2017, fecaloma recovered in 2019, dyspnea recovered on 22Feb2018, dry skin recovered on 06Dec2018 and bilateral pleural effusion was recovered on Nov2017. Event renal insufficiency was recovering, "forgot to take study drug" onset May2017 recovered on 22Jun2017 and "forgot to take study drug two times" had unknown outcome.

The investigator considered there was not a reasonable possibility that the event 'myocardial infarction' was related to the study drug, bosutinib, or concomitant drug. Also the event bronchitis was unrelated to study drug and to concomitant drugs. The reporter did consider the event insomnia, pruritus, diarrhea as unrelated to concomitant medications. The investigator considered the event insomnia as unrelated to the study drug, bosulif, or concomitant medications. According to the investigator, the events bilateral pleural effusion, diarrhea, renal insufficiency and asthenia grade 3 were related to bosutinib but not related to concomitant medication.

The investigator considered there was not a reasonable possibility that the event infectious episode was related to the study drug, bosutinib, or concomitant drug. The investigator considered there was a reasonable possibility that the event pleural effusion (10Sep2017) was related to the study drug bosutinib. The investigator considered there was not a reasonable possibility that the event renal lithiasis was related to the study drug, bosutinib, but related to concomitant drug acetylsalicylic acid (ASPIRINE). As of 24Mar2023, it was reported that renal lithiasis with hematuria also related to anticoagulant drugs.

The investigator considered general condition alteration and cardiac failure as related to study drug bosutinib and unrelated to concomitant medications. According to the reporter, the event fecaloma was unrelated to study drug and to concomitant drugs.

The investigator considered dry skin unrelated to study drug and related to GLIVEC. Cough and dyspnea was considered unrelated to bosutinib.

The reporter's assessment of the causal relationship of "pruritus", "joint pain", "herpes" and "insomnia" with the suspect product(s) bosutinib was not provided at the time of this report. Since no determination has been received, the case is managed based on the

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

company causality assessment.

Follow-up (22Sep2017): New information received from investigational site includes: relevant medical history, concomitant medications, lab data, therapeutic measures, and clinical course details.

Follow-up (02Oct2017): New information received includes: Concomitant medications start date, indication, and route of administration and additional concomitant medications (BRILIQUE, ASPIRINE), new additional event "cough / bronchopathy rated grade 2" and treatment, outcome, causality assessment, additional medical history (chronic lymphocytic leukemia) and hospital report with lab and test results.

Follow-up (10Oct2017): New information received includes: action taken for bosutinib and subject was not hospitalized as he was only admitted to emergency department from 02:00 p.m. to 07:15 p.m.

Follow-up (24Nov2017): follow-up attempts completed. No further information expected.

Follow-up (12Jan2018): New information received includes: lab data and concomitant medication, new events bilateral pleural effusion and renal insufficiency added.

Follow-up (16Jan2018): New information received from CRO includes:medical history (added pleural effusion), product data (updated dose and frequency), concomitant medication (updated concomitant medication details and added esomeprazole), and reaction data (added insomnia, pruritus, diarrhea, renal lithiasis leading to hematuria, cough, dyspnea, joint pain, herpes, infectious episode, pleural effusion, and cardiac failure).

Follow-up (18Jan2018) additional information received from investigational site:updated the dose of bosutinib, additional medical history (myocardial infarction), stop date of medical history renal colic, additional concomitant medications, added daily dose of several concomitant medications, updated event cardiac failure (updated start date from 30Dec2016 to 30Dec2017, updated outcome from unknown to recovered on 05Jan2018), updated event renal lithiasis leading to hematuria (updated start date from unknown to Aug2017, updated outcome from unknown to recovering), updated outcome of the event dyspnea (from not recovered to recovering), updated action taken of bosutinib for events, added causality of the events (infectious episode, pleural effusion (10Sep2017) and renal lithiasis leading to hematuria), and updated concomitant drug acetylsalicylic acid as suspect drug.

Follow-up (23Feb2018 and 26Feb2018): new information received from CRO includes: new events (asthenia grade3, forgot to take study drug, and forgot to take study drug two times), action taken in response to event asthenia grade3, outcome and causality of event asthenia grade 3.

Follow-up (11Apr2018): New information received from the study site upon the query includes:confirmed that the subject had never received acetyl salicylate lysine (KARDEGIC), he was only treated with acetylsalicylate (ASPIRINE) at 100 mg daily since 25Aug2017.

Follow-up (14Sep2018): New information received from the CRO includes additional event dyspnea.

Follow-up (18Sep2019): New information received from CRO includes: new adverse event (fecaloma, reported as non-serious), additional concomitant medication (imatinib mesilate).

Follow-up (20Dec2019): New reported information from CRO included grade of "renal lithiasis leading to hematuria" with updated outcome and grade of cardiac failure with causality provided

Follow-up (31May2022 , 01Jun2022, and 04Jun2022): New information received provided information regarding the subject's clinical course, updating renal lithiasis leading to hematuria to lithiasis, dyspnea to general condition alteration, cough/bronchopathy grade 2 to bronchitis, providing new information dates of therapy for bosutinib, information regarding event causality assessment, updates to action taken and event outcome.

Follow-up (07Jun2022): This is a follow-up to a non-interventional study for protocol B1871047.Updated information: Action taken on bosutinib in response to the events cough and dyspnea is temporarily withdrawn.

No follow-up attempt initiated. No further information expected.

Follow-up (09Feb2023): This is a non-interventional study follow-up report from investigational site via CRO for protocol B1871047.Updated information included:updated recovery date for cough and pruritus, updated outcome for dyspnea and renal lithiasis, updated onset/recovery dates for insomnia and diarrhea.

Follow-up (28Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.Updated information included:Onset and outcome of the event "bilateral pleural effusion" and additional information regarding treatment.

Follow-up attempts are completed. No further information is expected.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (24Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047.Updated information: reaction data (stop date/outcome of event renal lithiasis) and causality factor of Renal lithiasis with hematuria.

Follow-up (23May2023): This is a follow-up of non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.Updated information included: bosutinib second dosing regimen start date and Stop date for event Cough updated.

Follow-up (06Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047.Updated information: dosage of study drug Bosulif.

Follow-up (31Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047.Updated information:start date and information regarding event causality assessment of event insomnia.

Follow-up (14Nov2023). This follow-up is received from the clinical team in the context of reconciliation:Updated information includes:End date of event 'forget take medication' of May2017 was reported as 22Jun2017.

Case Comment: Cardiac failure is unlisted in the single reference safety document of bosutinib and unrelated per Company assessment.

Based on the temporal association and known product safety profile, the events renal insufficiency, pleural effusion, pruritus, diarrhea, asthenia, dyspnea, and alteration of general condition are assessed as related to bosutinib.

Based on currently available information, the Company considers there is not enough evidence suggesting that the reported events myocardial infarction, cardiac failure, alteration of general condition were related to bosutinib (BOSULIF); patient significant medical history included cardiac insufficiency, on concomitant medication atorvastatin for cholesterol, acetyl salicylate lysine (KARDEGIC) for infarction, valsartan and amlodipine besilate (AMLOR) for arterial hypertension and renal colic. Other events cough, bronchitis, insomnia, joint pain, herpes, infectious episode, fecaloma and dry skin and Nephrolithiasis are assessed as unrelated to bosutinib. Missed dose (2 episodes) are intercurrent medical conditions, unrelated to the suspect drug. The follow-up information received does not alter the previous company clinical evaluation.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	19-AUG-2017	Basophil count	0.08 x10 9/l	0.11 0
2	19-AUG-2017	Blood chloride	103 mmol/L	107 98
3	19-AUG-2017	Blood creatinine	146 umol/l	104 59
4	20-AUG-2017	Blood creatinine	14.9 mg/l	11.7 6.7
5	21-AUG-2017	Blood creatinine	15.4 mg/l	11.7 6.7
6	19-DEC-2017	Blood creatinine	259 umol/l	103 59
7	19-AUG-2017	Blood glucose	7.2 mmol/L	6.38 4.56
8	20-AUG-2017	Blood glucose	0.86 g/l	1.15 0.7
9	19-AUG-2017	Blood potassium	3.89 mmol/L	4.5 3.4
10	20-AUG-2017	Blood potassium	4.4 mmol/L	4.5 3.4
11	21-AUG-2017	Blood potassium	4.2 mmol/L	4.5 3.4

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
12	19-AUG-2017	Blood sodium	141 mmol/L	145 136
13	20-AUG-2017	Blood sodium	143 mmol/L	145 136
14	21-AUG-2017	Blood sodium	141 mmol/L	145 136
15	19-DEC-2017	Blood test	Not provided	
16	19-AUG-2017	Blood urea	8.2 mmol/L	7.5 2.5
17	20-AUG-2017	Blood urea	0.42 g/l	0.49 0.17
18	25-SEP-2017	Brain natriuretic peptide	316	
19	19-AUG-2017	C-reactive protein	5.8 mg/ml	5
20	25-SEP-2017	C-reactive protein	44	
21	19-AUG-2017	Carbon dioxide	21.7 mmol/L	29 22
22	25-SEP-2017	Cardiovascular examination	No chest pain,No palpitation,Regular heart sound	
		No chest pain, No palpitation, Regular heart sound, No murmur, No sign of heart failure		
23	25-SEP-2017	Coma scale	15	
24	25-SEP-2017	Creatinine renal clearance	45	
25	25-SEP-2017	Echocardiogram	no pericardic effusion	
		pericarditis, non-dilated left ventricle, inferior hypokinesia, Ejection fraction 50-55%, Normal left ventricular filling pressure, Right chambers not dilated, inferior vena cava well compliant, systolic pulmonary arterial pressure 35 mmHg.		
26	19-AUG-2017	Electrocardiogram	result not provided	
27	29-AUG-2017	Electrocardiogram	Heart rate 61 bpm, PR interval 166 ms	
		Heart rate 61 bpm, PR interval 166 ms, QRS duration 78 ms, QT/QTc 408/410 ms, P-R-T axis 43 48 44, Average RR 982 ms, QTcB 411 ms, QTcF 410 ms.		
28	25-SEP-2017	Electrocardiogram	RSR ventricular complex, Normal axis, No repolariz	
		RSR ventricular complex, Normal axis, No repolarization disorder, No focus, No confirmed pleurisy.		
29	19-AUG-2017	Eosinophil count	1.23 x10 9/l	0.63 0.02
30	19-AUG-2017	Glomerular filtration rate	42 ml/min	90
31	19-AUG-2017	Glomerular filtration rate	42 mL	
32	19-AUG-2017	Haematocrit	46 %	53

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
				39
33	25-SEP-2017	Haemodynamic test	stable	
34	19-AUG-2017	Haemoglobin	154 g/l	180 130
35	19-AUG-2017	Haemoglobin	15.4 g/dl	18 13
36	25-SEP-2017	Heart rate	61	
37	20-AUG-2017	Low density lipoprotein	1.39 g/l	
38	19-AUG-2017	Lymphocyte count	4.37 x10 9/l	4.8 1
39	19-AUG-2017	Monocyte count	0.98 x10 9/l	1 0.18
40	25-SEP-2017	Neurological examination No delirium tremens, No sensorimotor deficit of four limbs.	No delirium tremens, No sensorimotor deficit	
41	19-AUG-2017	Neutrophil count	7.35 x10 9/l	7.7 1.4
42	25-SEP-2017	Neutrophil count	14.88	
43	25-SEP-2017	Physical examination	no fever	
44	25-SEP-2017	Physical examination No dysfunction symptoms, abdomen soft, no guarding or tenderness, Normal peristalsis.	No dysfunction symptoms, abdomen soft, no guarding	
45	19-AUG-2017	Platelet count	194 x10 9/l	400 150
46	19-AUG-2017	Protein total	78.4 g/l	83 64
47	19-AUG-2017	Prothrombin time ratio	100 %	
48	25-SEP-2017	Pulmonary arterial pressure	35 mmHg	
49	25-SEP-2017	Pulmonary physical examination eupneic in ambient air, dyspnea on slightest effort, NYH classe III, cough, Decreased vesicular murmur (right lower third more important than left side), No sign of deep vein thrombosis.	eupneic in ambient air,dyspnea on slightest effort	
50	19-AUG-2017	Red blood cell count	5.43 x10 12/l	6 4.28
51	19-AUG-2017	Troponin	results not provided	
52	19-AUG-2017	Troponin	29	14
53	19-AUG-2017	Troponin 29 ng/L (N < 14)	0.029 ng	0.014

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
54	19-AUG-2017	Troponin	0.404 ng	0.014
55	20-AUG-2017	Troponin	0.481 ng	0.014
56	20-AUG-2017	Troponin	results not provided	
57	20-AUG-2017	Troponin	0.339 ng	0.014
58	22-AUG-2017	Troponin	results not provided	
59	25-SEP-2017	Troponin	19	
60	19-AUG-2017	White blood cell count	14.02 x10 9/l	11 4
61	25-SEP-2017	White blood cell count	18.41	
62	19-AUG-2017	X-ray	no pleural or pulmonary opacity, mild hilar hyperp no pleural or pulmonary opacity, mild hilar hyperplasia of vascular aspect	
63	19-AUG-2017	X-ray	result not provided	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Unknown	12-MAY-2018 / 26-JUL-2018; 2 months 15 days
#3) ASPIRINE (ACETYLSALICYLIC ACID) ; Regimen #1	100 mg, 1x/day; Oral	Thromboembolism prevention (Thrombosis prophylaxis)	25-AUG-2017 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) AMLOR (AMLODIPINE BESILATE) ; 15-NOV-2017 / Unknown

#8) FUROSEMIDE (FUROSEMIDE) ; 15-NOV-2017 / Unknown

#9) ESOMEPRAZOLE (ESOMEPRAZOLE) ; Unknown

#10) PARIET (RABEPRAZOLE SODIUM) ; Unknown

#11) TICAGRELOR (TICAGRELOR) ; Unknown

#12) ATORVASTATIN (ATORVASTATIN) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2016 to Unknown	Relevant Med History	Pleural effusion (Pleural effusion);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		AUG	1943	73 Years	Male	73.00 kg	16	APR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea grade 1 [Diarrhoea]
Diarrhea grade 2 [Diarrhoea]
Intermittent diarrhea [Diarrhoea]
Abdominal pain [Abdominal pain]
Diarrhea grade 2 [Diarrhoea]
Diarrhea [Diarrhoea]
Bronchitis grade 2 [Bronchitis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 24-MAR-2017 / 07-APR-2017	#1) 15 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CRESTOR (ROSUVASTATIN CALCIUM) ; NOV-2012 / Ongoing
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; NOV-2012 / Ongoing
#3) TRIATEC /00885601/ (RAMIPRIL) ; NOV-2012 / Ongoing
#4) PARIET (RABEPRAZOLE SODIUM) ; NOV-2012 / Ongoing
#5) SPASFON [PHLOROGLUCINOL] (PHLOROGLUCINOL) ; 21-JUN-2018 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
29-NOV-2012 to 29-NOV-2012	Relevant Med History	Myocardial infarction (Myocardial infarction) persistent myocardial infarction
1959 to 1959	Relevant Med History	Appendectomy (Appendicectomy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017418654

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
02-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE.

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. This is a Non-Interventional Study report with non-serious events only.

A 73-year-old male subject started to receive bosutinib (BOSULIF, film-coated tablets) via an unspecified route of administration from 24Mar2017 to 07Apr2017 at 100 mg once a day, from 08Apr2017 to 22Apr2017 at 200 mg once a day, from 23Apr2017 to an unspecified date at 300 mg once a day, from 22Jun2018 to an unspecified date at 400 mg once a day, and then since 20Dec2018 (ongoing) at 300 mg daily for chronic myeloid leukaemia. Medical history included persistent myocardial infarction on 29Nov2012, appendectomy in 1959 and hernia repair in 1949. Concomitant medication included rosuvastatin calcium (CRESTOR), acetylsalicylate lysine (KARDEGIC) and ramipril (TRIATEC), all ongoing since Nov2012 and orally for infarction, and rabeprazole sodium (PARIET) ongoing from Nov2012 orally for gastric protection. On 16Apr2017, the subject experienced diarrhea (CTCAE grade 1), assessed as non-serious. The action taken in response to the event diarrhea for bosutinib was dose not changed. The clinical outcome of the event diarrhea was recovered on 20Apr2017. On 01May2017, the subject experienced diarrhea (CTCAE grade 2), assessed as non-serious. The action taken in response to the event diarrhea for bosutinib was dose not changed. The clinical outcome of the event diarrhea was recovered on 14May2017. On 01Sep2017, the subject presented with intermittent diarrhea which was considered as non-serious. No action was taken with the study drug. This intermittent diarrhea was not recovered. In Dec2017, the subject experienced abdominal pain which was considered as non-serious and rated grade 1. In response to the event, dose of bosutinib was not changed. Therapeutic measures taken as result of abdominal pain included oral phloroglucinol (SPASFON) from 21Jun2018. The subject had recovered from abdominal pain on an unspecified date in Jun2018. In Jun2018, the subject experienced diarrhea grade 2 (non-serious). The patient received racecadotril (TIORFAN) as corrective treatment of diarrhea by oral route from Jun2018 to ongoing. He recovered from the event diarrhea (onset date Jun2018) on 14Jan2019. On 18Jun2018, the subject experienced bronchitis (non-serious). In result of the event, bosutinib was continued at the same dose (at 400 mg daily, ongoing since 22Jun2018) and the subject was treated with racecadotril (TIORFAN) via oral route for diarrhea, ongoing from Jun2018 and amoxicillin trihydrate clavulanate potassium (AUGMENTIN), via oral route for bronchitis, ongoing from 18Jun2018. On 09Dec2019, the subject developed a new episode of diarrhea rated grade 2 and assessed as non-serious. Dose of bosutinib was decreased on 20Dec2018 from 400 mg to 300 mg in response to the event diarrhea (Jun2018), while no action was taken in response to the event diarrhea (09Dec2019). Last action taken with bosutinib was dose not changed. On 13Dec2019, the subject recovered from diarrhea onset 09Dec2019. The outcome of the event diarrhea grade 2 (onset Jun2018) was recovered on 14Jan2019. The outcome of the event bronchitis grade 2 was recovered in Dec2018. The patient had recovered from abdominal pain on an unspecified date in Jun2018.

According to the reporter, the events abdominal pain and the episodes of diarrhea (onset dates 16Apr2017, 01May2017, 01Sep2017, 09Dec2019) were related to bosutinib and unrelated to concomitant drugs. The investigator considered the episode of diarrhea grade 2 (onset date Jun2018), as possibly related to the study drug bosutinib. The investigator considered the event, bronchitis, as not related to the study drug bosutinib.

Follow-up (27Jun2018): New information received from the Site includes: new AE (abdominal pain).

Follow-up (04Jul2018): New information received from investigator includes: the investigator confirmed phloroglucinol was a corrective treatment for the event abdominal pain and not a concomitant drug.

Follow-up (01Feb2019): New information received from investigator includes details on bosutinib administration, clinical course with new events (bronchitis and new episode of diarrhea).

Follow-up (15Feb2019): New information received from the study site includes: reaction data (added intermittent diarrhea with onset date of 01Sep2017).

Follow-up (11Apr2019): Follow-up attempts completed. No further information expected.

Follow-up (04Aug2020): New information received from investigator via the CRO includes clinical course details, additional episode of diarrhea.

Follow-up (10May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047. Updated information included: outcome of the events diarrhea (onset date Jun2018), abdominal pain and intermittent diarrhea; details on bosutinib and treatments received.

Follow-up (12Jul2023) New information received from investigator included: clinical details (the dose of bosutinib was decreased from 400 to 200 mg because of this event).

Follow-up (07Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047. Updated information included: Action taken detail and dosage (300 mg) since 20Dec2018.

Mfr. Control Number: 2017418654

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Amendment: This follow-up report is being submitted to amend previous information: bronchitis grade 2 outcome updated to recovered and stop date added Dec2018.

Case Comment: Considering the plausible drug-event temporal association and the consistency of these events with the known safety profile of the suspect product, a reasonable possibility that the reported episodes of diarrhea and abdominal pain are related to bosutinib administration cannot be excluded. Conversely, the reported bronchitis is deemed an intercurrent and self-supporting episode of lung infection, unrelated to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	08-APR-2017 / 22-APR-2017; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	23-APR-2017 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	22-JUN-2018 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	20-DEC-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1949 to 1949	Relevant Med History	Hernia repair (Hernia repair);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		OCT	1945	71 Years	Male	88.00 kg	15	JUN	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Right coxarthrosis [Osteoarthritis]
Diarrhea [Diarrhoea]
Diarrhea [Diarrhoea]
flatulence [Flatulence]
Anaemia [Anaemia]
Gastroenteritis [Gastroenteritis]
Coxarthrosis [Osteoarthritis]
COPD WORSENING [Chronic obstructive pulmonary disease]
Chronic renal failure [Chronic kidney disease]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 03-JUN-2017 / 16-JUN-2017	#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing
#2) ADANCOR (NICORANDIL) ; OCT-2004 / Ongoing
#3) VERAPAMIL (VERAPAMIL) ; OCT-2004 / Ongoing
#4) KENZEN (CANDESARTAN CILEXETIL) ; OCT-2004 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
OCT-2004 to Ongoing	Relevant Med History	Ischemic cardiomyopathy (Ischaemic cardiomyopathy)
06-FEB-2017 to Ongoing	Relevant Med History	COPD (Chronic obstructive pulmonary disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017418881

24c. DATE RECEIVED BY MANUFACTURER
17-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 71-year-old male patient received bosutinib (BOSULIF), first regimen from 03Jun2017 to 16Jun2017 at 100 mg 1x/day, second regimen from 17Jun2017 to 30Jun2017 at 200 mg 1x/day, third regimen from 01Jul2017 to 15Sep2017 at 300 mg 1x/day and fourth regimen since 16Sep2017 (ongoing) at 400 mg 1x/day. The patient's relevant medical history included: "ischemic cardiopathy", start date: Oct2004 (ongoing); "COPD", start date: 06Feb2017 (ongoing); "hypercholesterolemia" (ongoing); "arterial hypertension", start date: Oct2004 (ongoing). Concomitant medication(s) included: TAHOR oral taken for hypercholesterolaemia (ongoing); ADANCOR oral taken for cardiomyopathy, start date: Oct2004 (ongoing); VERAPAMIL oral taken for cardiomyopathy, start date: Oct2004 (ongoing); KENZEN oral taken for hypertension, start date: Oct2004 (ongoing).
On 15Jun2017, the subject developed diarrhea, rated grade 1 and non-serious. No action was taken with bosutinib. The subject had recovered from the event on 10Jul2017. On 01Sep2017, the subject developed diarrhea and flatulence, both rated grade 1 and assessed as non-serious. No action was taken with bosutinib in response to these events. At the time of the report, diarrhea (onset date 01Sep2017) and flatulence were resolving. On an unspecified date in Nov2018, the subject experienced coxarthrosis grade 2. On 15Feb2019, gastroenteritis grade 3. Despite the events, the suspect drug bosutinib was pursued unchanged. On 20Feb2019, the subject recovered from gastroenteritis. The event coxarthrosis was ongoing. On 09Dec2019, the subject experienced anaemia considered non-serious and rated grade 3 and right coxarthrosis rated grade 3 and led to hospitalization. History of disease included the subject experienced right coxarthrosis which becoming invalidating. The subject experienced pains increasingly invalidating in right lower limb with significative stiffness at right hip movement. A lumbar spine CT scan disclosed degenerative spondylolisthesis on L3-L4 with stenosis extended from L3 to sacral bone. The subject received several epidural infiltrations as corrective treatment, but they were ineffective. The clinical presentation was in favor of right coxarthrosis. The X-ray found significative coxo-femoral pinching and scintigraphy found hyperfixation on femoral head. A total right hip prosthesis was prescribed. Treatment at admission, salbutamol (AIROMIR AUTOHALER 100ug/dose) 2 puffs thrice a day; umeclidinium bromide (INCRUSE 55ug) 1 puff in the morning; fluticasone furoate, vilanterol trifenatate (RELVAR ELLIPTA 92 ug/22ug) 1 puff in the evening; silodosin (UROREC 4mg) 1 capsule in the evening; bosutinib (BOSULIF 100 mg) 400 mg in the evening; candesartan cilexetil; hydrochlorothiazide (COKENZEN 16mg/12.5mg) 1 tablet in the morning; acetylsalicylate lysine (KARDEGIC 75 mg) 1 bag in the morning; verapamil (VERAPAMIL SANDOZ 120 mg) 1 tablet in the evening; atorvastine (ATORVASTATINE ACCORD 10 mg) 1 tablet in the evening and, nicorandil (NICORANDIL ALMUS 10 mg) 1 tablet in the morning and 1 tablet in the evening. A total hip arthroplasty via postero-external route was performed. Diosmectite (SMECTA) was administered orally from 17Feb2019 to 20Feb2019 for gastroenteritis. Investigator initial aware date for events coxarthrosis grade 2 and gastroenteritis grade 3 were 21Mar2019. As of 17Jul2023, it was reported Coxarthrosis on 09Dec2019 was grade 3. AMOXICILIN was not a concomitant drug, was received for infection prophylaxis from 19Mar2019 to 20Mar2019. Anemia recovered on 10Dec2019. The patient experienced additional events COPD WORSENING on 17Apr2020, grade 2, non-serious. Chronic renal failure on 21Mar2019, grade 2, non-serious. No action was taken for bosutinib in response to these events. No action was taken for bosutinib in response to events right coxarthrosis and anaemia. The outcome of event anemia was resolved on 10Dec2019 and of right coxarthrosis was resolved on 19Dec2019. The outcome of events COPD WORSENING and Chronic renal failure was not resolved.

The investigator considered there was a reasonable possibility that the events (diarrhea (two episodes) and flatulence) were related to study drug and unrelated to concomitant drugs.
The investigator considered there was a reasonable possibility that the events gastroenteritis, coxarthrosis, anaemia and right coxarthrosis were unrelated to study drug bosutinib and concomitant drugs.
The investigator considered that COPD worsening and Chronic renal failure were unrelated to bosutinib or to any concomitant drug.

Follow-up (23Nov2017): Follow-up attempts completed. No further information expected.

Follow-up (27Jun2018): New information received from the investigator included new dose for bosutinib and new events diarrhea (second episode) and flatulence.

Follow-up (22Jul2019): New information received from CRO includes: new events (coxarthrosis grade 2 and gastroenteritis grade 3) added.

Follow-up (04May2020): New information received from CRO includes: new events (anaemia and right coxarthrosis) added, lab data and treatment at admission added.

Follow-up (15May2020): new information received from investigational: some drugs were confirmed was started after onset of the event right coxartrhrosis: salbutamol (AIROMIR AUTOHALER); umeclidinium bromide (INCRUSE); fluticasone furoate, vilanterol trifenatate (RELVAR ELLIPTA); silodosin (UROREC 4mg); candesartan cilexetil, hydrochlorothiazide (COKENZEN); acetylsalicylate lysine (KARDEGIC); verapamil (VERAPAMIL SANDOZ); atorvastine (ATORVASTATINE) and nicorandil (NICOR).

Follow-up (14May2023): This is a non-interventional study report received from investigational site via CRO for protocol B1871047. Updated information: treatment for gastroenteritis added, and concomitant drug amoxicillin added.

Mfr. Control Number: 2017418881

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (17Jul2023): This is a non-interventional study report from the investigational site via the CRO. Updated information includes: Coxarthrosis on 09Dec2019 was grade 3. AMOXICILIN was not a concomitant drug, was received for infection prophylaxis from 19Mar2019 to 20Mar2019. Anemia recovered on 10Dec2019. Additional events COPD WORSENING and Chronic renal failure.

Case Comment: Based on plausible drug-event temporal association and known drug safety profile, the event diarrhea (both episodes) is considered related to bosutinib. Similarly, the reported flatulence is considered possibly related to bosutinib. Osteoarthritis, gastroenteritis, anaemia, right coxarthrosis, COPD WORSENING and Chronic renal failure are deemed unrelated the suspect medication.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Computerised tomogram	degenerative spondylolisthesis with stenosis degenerative spondylolisthesis on L3-L4 with stenosis extended from L3 to sacral bone	
2		Radioisotope scan	hyperfixation on femoral head	
3		X-ray	significative coxo-femoral pinching	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	Unknown	17-JUN-2017 / 30-JUN-2017; 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Unknown	Unknown	01-JUL-2017 / 15-SEP-2017; 77 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, 1x/day; Unknown	Unknown	16-SEP-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
OCT-2004 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1969	47 Years	Female	62.00 kg		JAN	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
abdominal pain [Abdominal pain]
Loss of weight [Weight decreased]
Intermittent Constipation [Constipation]
Depression [Depression]
Diffuse pain [Pain]
Anorexia aggravation [Decreased appetite]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) DUROGESIC (FENTANYL) **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, 1x/day	#1) Oral
#2) UNK	#2) Transdermal

17. INDICATION(S) FOR USE
#1) Unknown
#2) pain (Pain) **(Continued on Additional Information Page)**

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 12-DEC-2016 / 19-FEB-2017	#1) 2 months 8 days
#2) FEB-2017 / Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LOXETINE (FLUOXETINE HYDROCHLORIDE) ; 2017 / Ongoing
#2) DOLIPRANE (PARACETAMOL) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2016 to Ongoing	Relevant Med History	Lumbalgia (Back pain)
12-DEC-2016 to Unknown	Relevant Med History	Lumbalgia (Back pain)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017424792

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
02-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE.

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 47-year-old female patient received bosutinib (BOSULIF), first regimen from 12Dec2016 to 19Feb2017 at 200 mg 1x/day, oral, second regimen from 20Feb2017 to 06Jun2017 at 100 mg 1x/day, oral and third regimen since 07Jun2017 (ongoing) at 200 mg daily; fentanyl (DUROGESIC), since Feb2017 (ongoing) (Batch/Lot number: unknown), transdermal for pain, back pain; ponatinib hydrochloride (ICLUSIG), (Batch/Lot number: unknown). The patient's relevant medical history included: "lumbalgia", start date: 2016 (ongoing); "Reappearance of lumbalgia", start date: 12Dec2016 (unknown if ongoing); "anorexia", start date: Oct2016 (unknown if ongoing), notes: grade 2; "ciatica pain and cruralgia related to lumbago", start date: 09Dec2016 (unknown if ongoing); "Reappearance of lumbalgia", start date: Jan2017, stop date: 12Feb2018. Concomitant medication(s) included: LOXETINE oral taken for depression, start date: 2017 (ongoing); DOLIPRANE oral taken for pain.
On 09Dec2016, the subject presented with persistent sciatica pain and hyperalgic cruralgia related to lumbago which had not improved despite corrective treatment. So according to the investigator, the reappearance of these pains then started before the introduction of bosutinib on 12Dec2016. In Dec2016, the subject developed reappearance of lombalgia. The action taken in response to this event and causality of this event were not provided. The subject presented with lumbalgia in Jan2017 which was a medical history which recurred. In the follow-up, it was reported that the reappearance of lumbalgia was a medical history and not an adverse event since it occurred before the first administration of bosutinib. The subject presented with loss of weight, depression and intermittent constipation on 20Feb2017. These events were non-serious. In response to these events, bosutinib was decreased or temporarily discontinued and loxetine was introduced for depression. There was no action taken in response to the weight loss. In Feb2017, the subject experienced grade 2 diarrhea which was considered as non-serious by the investigator. On 07Jun2017, the subject presented with diffuse bone pain grade 3 which was considered as non-serious. The action taken in response to the event diffuse bone pain was reported as not applicable. In Jan2017, the subject experienced abdominal pain rated grade 3 which was considered as non-serious event. In response to the event, bosutinib was withdrawn. The final action taken with bosutinib was permanently withdrawn on 20Nov2017. The action taken with Duragesic in repose to the event was the dose was reduced. It was also reported that the bosutinib was withdrawn due to the constipation and the subject received HEPAR water (with high concentration of magnesium) as therapeutic measure. The subject received antidepressant therapy as therapeutic measure for depression. The clinical outcome of the events weight loss, abdominal pain, anorexia, diffuse bone pain were resolved on 12Feb2018. Diarrhea resolved on 20Feb2017. Depression resolved on 18Dec2017. The clinical outcome of the constipation was not recovered. As of 06Jul2023, The subject presented with anorexia aggravation grade 2 on 20Feb2017. Clinical outcome of anorexia aggravation was recovered on 12Feb2018.Event diffuse pain was related to study drug and unrelated to concomitant treatment. Action taken in response to the event diffuse pain was permanently withdrawn.There was no action taken in response to the weight loss was dose reduced. There was no action taken in response to the depression was dose not changed.

According to the investigator, grade 2 diarrhea, abdominal pain and anorexia (onset date: Oct2016) were related to study drug bosutinib and unrelated to concomitant drugs.
According to the investigator, constipation was related to bosutinib and was related to concomitant drugs ponatinib HCL(ICLUSIG) and fentanyl (DUROGESIC).
According to the investigator, the loss of weight was related to bosutinib and was related to concomitant drug.
According to the investigator, depression was related to bosutinib and unrelated to concomitant drug.
According to the investigator, anorexia aggravation on 20Feb2017 was related to study drug bosutinib.
Event diffuse pain was related to study drug and unrelated to concomitant treatment.

The reporter's assessment of the causal relationship of diffuse bone pain with the suspect product was not provided at the time of this report. Since no determination has been received, the case is managed based on the company causality assessment.

Follow-up (10Oct2017): New information included: drug data and outcome of event

Follow-up (04Jan2018): New information included additional event pain updated concomitant medications, updated action taken with BOSULIF.

Follow-up (16Jan2018): New information received includes: reaction data (added non-serious events anorexia, lumbalgia, loss of weight, depression, constipation, and diffuse bone pain which), product data (updated dosage regimen), patient data, and clinical details.

Follow-up (18Jan2018): New information reported includes: drug data, add new events: anorexia (onset date: Oct2016) and reappearance of lombalgia (onset date: Dec2016).

Follow-up (16Feb2018): New information received from investigational site includes: Additional therapy dates/dosage for bosutinib, stop date for bosutinib provided (20Nov2017), Clinical data (event of anorexia was removed and added as medical history since it was confirmed to have occurred prior to bosutinib introduction), event term "important pain" was updated to "abdominal pain"), therapeutic measures (for the events constipation and depression) and Clinical outcome.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (07Mar2018): new information received from investigational site includes: product data (duration of bosutinib updated), event data (event outcome updated, stop date updated) and clinical course details.

Follow-up (30Mar2018): New information received from investigational site is as follows: patient data (medical history updated).

Follow-up (25May2018): New information received from investigational site is as follows: medical history details.

Follow-up (31May2022) :New information was received from the non-interventional study for protocol B1871047 updating medical history anorexia, first dosage regimen of bosutinib provided, constipation reported as intermittent, information regarding causality, and action taken with suspect products.

Follow-up (28Feb2023) : This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: depression outcome (resolved) and causality (related to bosutinib).

Amendment: This follow-up report is being submitted to amend previously reported information: patient's date of birth was added.

Follow-up (06Jul2023): This is a follow-up report received from the CRO.
Updated information included: 2nd and 3rd reporter, suspect drug Bosulif details (dose/units on 11Dec2016, ongoing), new events of Decreased appetite, event Abdominal pain details (onset date).Dechallenge for Bosulif: Positive. Causality assessment.

Follow-up (31Jul2023). This follow-up is received from the investigational site via CRO:Bosulif was administered from 12Dec2016 to 19Feb2017 at 200mg x1/day, from 20Feb2017 to 06Jun2017 at 100 mg x1/day and at 200 mg 1x/day from 07Jun2017 and ongoing.Fentanyl unit 12.5 ug added. Verbatim Grade 2 diarrhea corrected to Diarrhea. Causality of diffuse pain

Follow-up attempts are completed. No further information is expected.

Amendment: This follow-up report is being submitted to amend previous information: Recovery date of event depression amended in event tab (previous 12Feb2018).

Case Comment: Due to a plausible drug-event temporal association, and the known safety profile of the suspect drug, the company concurs with the investigator, considering diarrhea, abdominal pain, loss of weight, decreased appetite were related to bosutinib. Event diffuse pain is most likely due to underlying condition and unrelated to bosutinib. Event depression most likely represents an intercurrent mood instability for this subject had malignancy and unrelated to bosutinib. Event constipation was unrelated to the suspect drug bosutinib and likely attributed to concomitant pain medications. The follow up information does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, 1x/day; Oral	Unknown	20-FEB-2017 / 06-JUN-2017; 108 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	07-JUN-2017 / Ongoing; Unknown
#2) DUROGESIC (FENTANYL) ; Regimen #1	UNK; Transdermal	pain (Pain) Lumbalgia (Back pain)	FEB-2017 / Ongoing; Unknown
#3) ICLUSIG (PONATINIB HYDROCHLORIDE) ; Regimen #1	; Unknown	Unknown	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
OCT-2016 to Unknown	Relevant Med History grade 2	Anorexia (Decreased appetite);
09-DEC-2016 to Unknown	Relevant Med History	Lumbago (Back pain);

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ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
JAN-2017 to 12-FEB-2018	Relevant Med History	Lumbalgia (Back pain);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1943	74 Years	Female	111.00 kg	03	OCT	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

increase in ALT [Alanine aminotransferase increased]
increase in AST [Aspartate aminotransferase increased]
increase in Gamma GT [Gamma-glutamyltransferase increased]
increase in creatinine [Blood creatinine increased]
increase in AST [Aspartate aminotransferase increased]
increase in ALT [Alanine aminotransferase increased]
Cephalgia [Headache]
Dark urines [Chromaturia]
Nausea [Nausea]
Allergies to the wrists [Hypersensitivity]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☒ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)
#1) 23-AUG-2017 / 06-OCT-2017

19. THERAPY DURATION
#1) 44 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) FUROSEMIDE (FUROSEMIDE) ; Ongoing
#2) ATACAND (CANDESARTAN CILEXETIL) ; Ongoing
#3) ALDACTONE (SPIRONOLACTONE) ; Ongoing
#4) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Unknown / 29-SEP-2017
#5) AVAMYS (FLUTICASONE FUROATE) ; 2017 / Ongoing
#6) AERIUS (DESLORATADINE) ; Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Obesity (Obesity)
Unknown to Ongoing	Relevant Med History	COPD (Chronic obstructive pulmonary disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017444870

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
21-FEB-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Fatigue [Fatigue]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 74-year-old female patient received bosutinib (BOSULIF), first regimen from 23Aug2017 to 06Oct2017 at 400 mg daily and second regimen from 23Oct2017 to 15Nov2017 at 200 mg daily for chronic myeloid leukaemia. The patient's relevant medical history included: "obesity" (ongoing); "COPD" (ongoing); "Arterial hypertension" (ongoing); "hypothyroidism" (ongoing); "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: FUROSEMIDE taken for hypertension (ongoing); ATACAND taken for hypertension (ongoing); ALDACTONE taken for hypertension (ongoing); LEVOTHYROX taken for hypothyroidism, stop date: 29Sep2017; AVAMYS taken for chronic obstructive pulmonary disease, start date: 2017 (ongoing); AERIUS taken for chronic obstructive pulmonary disease (ongoing); ALLOPURINOL taken for prophylaxis, start date: 26Sep2016 (ongoing); EUTHYRAL taken for hypothyroidism, start date: 29Sep2017 (ongoing); NATI K taken for hypokalaemia, start date: 29Sep2017 (ongoing); INFLUENZINUM taken for antiviral prophylaxis, start date: 29Sep2017, stop date: 29Dec2017; INNOVAIR taken for chronic obstructive pulmonary disease, start date: 29Sep2017 (ongoing). Past drug history included: Glivec, start date: 2016, reaction(s): "liver toxicity".
The following information was reported: ALANINE AMINOTRANSFERASE INCREASED (non-serious) with onset 03Oct2017, outcome "recovered" (28Oct2017), ALANINE AMINOTRANSFERASE INCREASED (non-serious) with onset 30Oct2017, outcome "recovered" (26Dec2017) and all described as "increase in ALT"; ASPARTATE AMINOTRANSFERASE INCREASED (non-serious) with onset 03Oct2017, outcome "recovered" (16Oct2017), ASPARTATE AMINOTRANSFERASE INCREASED (non-serious) with onset 30Oct2017, outcome "recovered" (05Dec2017) and all described as "increase in AST"; GAMMA-GLUTAMYLTRANSFERASE INCREASED (non-serious) with onset 10Oct2017, outcome "recovered" (09Jan2018), described as "increase in Gamma GT"; HYPERSENSITIVITY (non-serious) with onset Oct2017, outcome "recovered" (22Nov2017), described as "Allergies to the wrists"; BLOOD CREATININE INCREASED (non-serious) with onset 28Oct2017, outcome "recovered" (12Jan2018), described as "increase in creatinine"; HEADACHE (non-serious) with onset 15Nov2017, outcome "recovered" (17Nov2017), described as "Cephalgia"; CHROMATURIA (non-serious) with onset 15Nov2017, outcome "recovered" (17Nov2017), described as "Dark urines"; FATIGUE (non-serious) with onset Nov2017, outcome "recovered" (12Apr2018); NAUSEA (non-serious) with onset Nov2017, outcome "recovered" (12Apr2018). Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was reported as temporarily withdrawn on 15Nov2017. Rechallenge of bosutinib was performed and "increase in ast", "increase in alt" reoccurred.
Additional information: On 03Oct2017, the subject developed increase in ALT, rated grade 2 and non-serious, and increase in AST, rated grade 3 and non-serious. In Oct2017, the subject developed allergies to the wrists rated grade 1 and considered as a non-serious event. There was no modification of bosutinib in response to the event allergies to the wrists. In Nov2017, the subject developed nausea rated grade 1 and fatigue rated grade 1, both considered as a non-serious events. There was no modification of bosutinib in response to the events nausea and fatigue. On 07Nov2017, the subject developed increase in Gamma GT and increase in creatinine, both rated grade 2 and considered non-serious by the reporter. On 07Nov2017, the subject also developed increase in AST and increase in ALT, both rated grade 3 and considered non-serious by the reporter. On 15Nov2017, the subject developed cephalgia and dark urines, both rated grade 2 and considered non-serious by the investigator. The subject underwent lab tests which included Liver function tests before the introduction of bosutinib treatment on 11Jul2017, AST was 20 IU/l (normal values <32), ALT was 24 IU/l (normal values <32); Liver function tests on 25Sep2017, AST was 24 IU/l, and ALT was 25 IU/l; Liver function tests on 10Oct2017, AST was 184 IU/l, ALT was 433 IU/l, and GGT was 118 IU/l (normal values < 38); on 14Nov2017: AST was 356 IU/l (normal range 0-34); ALT was 592 IU/l (normal range 0-49); and Gamma GT was 126 IU/l (normal range 0-38); and Liver function tests were performed on 20Mar2018, AST was 22 IU/l, and ALT was 29 IU/l. The treatment was temporarily withdrawn on 06Oct2017 in response to the events (increase in ALT grade 2 and increase in AST, rated grade 3). Bosutinib was resumed on 24Oct2017 at a decreased dose of 200 mg. In response to the events increase in Gamma GT and increase in creatinine, bosutinib was temporarily withdrawn. In response to these events increase in AST and increase in ALT, bosutinib was withdrawn on 15Nov2017 (it had been interrupted from 06Oct2017 to 24Oct2017 due to previous occurrences of these events and resumed on 24Oct2017 at a decreased dose of 200 mg). Action taken with bosutinib in response to these events (cephalgia and dark urines) was not reported. The events (increase in ALT grade 2 and increase in AST, rated grade 3) resolved on 23Oct2017. At the report time, the subject had not yet recovered from the events increase in Gamma GT, increase in creatinine, increase in AST and increase in ALT. At the report time, the subject had recovered from cephalgia on 17Nov2017. The outcome of the event dark urines was not reported. The outcome of allergies to the wrists was recovered on 22Nov2017. The event nausea was resolving at the report time. The subject was not recovered from fatigue. The subject discontinued bosutinib as requested by protocol and was under sprycel. On consultation of 12Apr2018 it was noted fever (probable bronchial superinfection), on consultation of 15May2018 another fever. On ultrasound done on 12Jun2018 for abdominal pains. On consultation of 25Jun2018 it was noted diarrhea and nausea, as of 24Aug2018 pseudo membranous colitis. On 02Oct2018 subject went to emergency for lower limbs edema from 15 days, erythema at leg level, hematoma of lip following a fall. On consultation of 30Sep2010 (as reported) the subject was complaining of weight gain. In response to increase in ALT and increase in AST, bosulif was temporarily withdrawn and events reappeared with the reintroduction of the product. AST and ALT on 14Nov2017 were rated grade 3. The action taken in response to the events cephalgia and dark urines was reported as dose not changed for the study drug BOSULIF. In response to increase in AST and increase in ALT on 30Oct2017, bosutinib was temporarily withdrawn and resumed on 24Oct2017, events reappeared, bosulif interrupted again on 15Nov2017. Investigator Initial

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Aware Date of the events Gamma GT and Creatinine increase: 10Oct2017, events Nausea and Fatigue: 11Dec2017, event Allergies to the wrists: 30Oct2017, events ASAT and ALAT increase: 30Oct2017.

The reporter considered "increase in alt", "increase in ast", "increase in gamma gt", "increase in creatinine" and "cephalgia" related to bosutinib. The reporter considered "nausea", "allergies to the wrists" and "fatigue" not related to bosutinib. The reporter considered "dark urines" unrelated to bosutinib and unrelated to concomitant drug.

Follow-up (08Nov2017): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information reported includes: product data, medical history data and concomitant medication data.

Follow-up (17Nov2017): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from CRO includes: reaction data (added new events increase in Gamma GT, increase in creatinine, increase in AST, increase in ALT, cephalgia and dark urines), clinical course details.

Follow-up (09Feb2018): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from CRO includes: reaction data (added events allergies to the wrists, nausea, and fatigue) and product data (indication and updated dosage regimens for bosutinib).

Follow-up (16May2018):This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from CRO includes: concomitant medications data (furosemide updated to 2 times/day; proprietary names; onset date fluticasone (2017), frequency desloratadine; onset date, frequency and indication allopurinol; levothyroxine sodium / liothyronine sodium dose updated, new concomitant medications (INFLUENZINUM, beclomethasone dipropionate, formoterol fumarate)), previous drug history (imatinib), causality assessment (allergies to wrists unrelated to concomitant medications); lab data added.

Follow-up (28Jan2022): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from CRO includes: Patient consultation information after discontinuation of bousitinib and start of Sprycel.

Follow-up (29Jul2022): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. Updated information: the recovery date of event AST increased changed from 23Oct2017 to 16Oct2017; the recovery date of event ALT increased changed from 23Oct2017 to 28Oct2017.

Follow-up (21Feb2023, 23Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: start date of first regimen and second regimen of BOSULIF, medical history includes ongoing chronic myeloid leukemia, events nausea and fatigue: stop date added,outcome updated,
events ASAT increase and ALAT increased: onset date updated to 30Oct2017 (previously 07Nov2017), stop date added (05Dec2017), onset date updated to 30Oct2017 (previously 07Nov2017), event Gamma GT increase: onset date updated to 10Oct2017 (previously 07Nov2017), event creatinine increase onset date updated to 28Oct2017 (previously 07Nov2017), stop date added (12Jan2018); events stop dated added and outcome updated; outcome and causality assessment (unrelated) for the event dark urines, clinical course.

Case Comment: The events AST and ALT increased were related to study drug bosutinib (BOSULIF). Furthermore, also increase in Gamma GT, increase in creatinine, cephalgia were possibly related with the suspect drug. The event allergies to the wrists and dark urines are attributed to intercurrent medical conditions and unrelated to bosutinib. The events nausea and fatigue are considered associated with underlying malignancy and unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	11-JUL-2017	Alanine aminotransferase	24 IU/l	32
2	25-SEP-2017	Alanine aminotransferase	25 IU/l	32
3	03-OCT-2017	Alanine aminotransferase	increase grade 2 IU/l	49 0
4	10-OCT-2017	Alanine aminotransferase	433 IU/l	32
5	14-NOV-2017	Alanine aminotransferase grade 3	592 IU/l	49 0
6	20-MAR-2018	Alanine aminotransferase	29 IU/l	32
7	11-JUL-2017	Aspartate aminotransferase	20 IU/l	32

Mfr. Control Number: 2017444870

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8	25-SEP-2017	Aspartate aminotransferase	24 IU/l	32
9	03-OCT-2017	Aspartate aminotransferase	increase grade 3 IU/l	340
10	10-OCT-2017	Aspartate aminotransferase	184 IU/l	32
11	14-NOV-2017	Aspartate aminotransferase grade 3	356 IU/l	340
12	20-MAR-2018	Aspartate aminotransferase	22 IU/l	32
13	10-OCT-2017	Gamma-glutamyltransferase	118 IU/l	380
14	14-NOV-2017	Gamma-glutamyltransferase	126 IU/l	380

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	23-OCT-2017 / 15-NOV-2017; 24 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) ALLOPURINOL (ALLOPURINOL) ; 26-SEP-2016 / Ongoing

#8) EUTHYRAL (LEVOTHYROXINE SODIUM, LIOTHYRONINE SODIUM) ; 29-SEP-2017 / Ongoing

#9) NATI K (POTASSIUM TARTRATE) ; 29-SEP-2017 / Ongoing

#10) INFLUENZINUM (HOMEOPATHICS NOS) ; 29-SEP-2017 / 29-DEC-2017

#11) INNOVAIR (BECLOMETASONE DIPROPIONATE, FORMOTEROL FUMARATE) ; 29-SEP-2017 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism);
2016 to Unknown	Past Drug Event	GLIVEC (GLIVEC); Drug Reaction: Hepatotoxicity (Hepatotoxicity)
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		APR	1969	47 Years	Male	83.00 kg		APR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

30 minutes post-prandial abdominal pain [Abdominal pain]
Intermittent constipation [Constipation]
episode of flu [Influenza]
nausea [Nausea]
Erection disorder [Erectile dysfunction]
Abdominal pain [Abdominal pain]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 06-JAN-2017 / 19-MAR-2017	#1) 2 months 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) PANTOPRAZOLE (PANTOPRAZOLE) ; JAN-2016 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2015 to Unknown	Relevant Med History	
JUN-2015 to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017498747

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
25-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 47-year-old male patient received bosutinib (BOSULIF), first regimen from 06Jan2017 to 19Mar2017 at 100 mg daily and second regimen since 20Mar2017 (ongoing) at 200 mg daily. The patient's relevant medical history included: "Peripheral arterial disease", start date: 2015 (unknown if ongoing); "Diabetes", start date: Jun2015 (ongoing); "dyslipidemia", start date: 2016 (ongoing); "epigastric pain", start date: 2016 (ongoing); "intermittent constipation", start date: Jan2017, stop date: Jan2017, notes: rated grade 1, non-serious. Concomitant medication(s) included: PANTOPRAZOLE, start date: Jan2016 (ongoing).
The following information was reported: ABDOMINAL PAIN (non-serious) with onset Apr2017, outcome "recovered" (09Jan2018), described as "30 minutes post-prandial abdominal pain"; CONSTIPATION (non-serious) with onset 21Jun2017, outcome "recovered" (25Sep2017), described as "Intermittent constipation"; INFLUENZA (non-serious) with onset 14Jan2019, outcome "recovered" (21Jan2019), described as "episode of flu"; NAUSEA (non-serious) with onset May2019, outcome "recovered" (27Jan2020); ERECTILE DYSFUNCTION (non-serious) with onset 2019, outcome "not recovered", described as "Erection disorder"; ABDOMINAL PAIN (non-serious) with onset Dec2019, outcome "recovered" (Dec2019). The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of abdominal pain, influenza.

Additional information: In Apr2017, the subject developed abdominal pain which was considered as non-serious. The subject experienced for about 2 months abdominal pain (grade CTCAE: 1) occurring half an hour after the meal, with periombilical and epigastric localizations which lasted for 3 to 4 hours associated with meteorism sensation. There was no diarrhea or heartburn. This pain was sometime associated to nausea. According to the reporter, nausea should not be considered as an additional event. Pantoprazole was increased to 40 mg once daily (increased dose after the adverse event) and sodium alginate/sodium bicarbonate (GAVISCON) was introduced during pain. The subject had to consult if the symptoms would not improve within 2 weeks. The action taken in response to the event abdominal pain for bosutinib was dose not changed (continued at the same posology). The pain resolved with proton-pump inhibitor therapy. The ongoing dose of pantoprazole (unspecified trade name) was increased, while bosutinib was continued. On the last visit on 25Sep2017, the subject did not report any more complaint. According to the investigator, nausea was part of the event abdominal pain. The clinical outcome of the event abdominal pain was resolved on 09Jan2018. On 21Jun2017, the subject developed intermittent constipation, rated grade 1 which was considered as non-serious. No action was taken with bosutinib in response to this event. The event resolved on 25Sep2017. On 14Jan2019 the subject experienced an episode of flu, CTCAE grade 2, assessed as non-serious. No action was taken with study drug in response to the event. Event resolved on 21Jan2019. It was reported that since the 'consolation' in Oct2018 the subject reported nothing of particular, except an episode of flu allure/flu-like episode on last week, with cough and fever for 48 hours. Subject received antibiotic therapy for 5 days (subject did not know which one) and had sick leave of one week, was going to resume work on 21Jan2019. Doctor notified of the event on 21Jan2019. The subject experienced erection disorder in 2019. The event was assessed as non-serious and of grade 1. It was reported in the consultation report on 20May2019 that 'the subject reported erection disorder/erectile dysfunction for a few months' before this report. In response to the event, bosutinib continued at the same dose. At the time of reporting, the event erection disorder had not resolved. On an unspecified date in May2019, the subject experienced nausea rated non-serious and grade 1. The subject reported epigastric pain from time to time after nausea and vomiting. This event occurred two to three time per month. At the time of this report, the event was not resolved. Despite the event, bosutinib was pursued unchanged. In Dec2019 the subject experienced abdominal pain, grade 1, non-serious, which resolved in Dec2019. Nausea resolved on 27Jan2019. In consultation report of 27Jan2020, the subject reported having abdominal pain several days before the celebrations. No action was taken with study drug in response to abdominal pain.

According to the investigator, the events abdominal pain, intermittent constipation were related to bosutinib and the events flu, erection disorder, nausea and abdominal pain of Dec2019 were unrelated to bosutinib. All events were unrelated to concomitant medications.

Follow-up (27Nov2017): New information received from investigational site includes: action taken (updated from unknown to dose not changed), medical history, clinical outcome (updated from unknown to recovered), and treatment details.

Follow-up (08Jan2018): New information received from the investigator includes: relevant medical history, suspect product data (start date and dosing added), concomitant medication, reaction data (confirmation nausea should not be considered an additional event), and clinical course details.

Follow-up (20Apr2018): New information received from the CRO includes: patient details (month of birth was corrected, height), medical history, new events (intermittent constipation).

Follow-up (23Jan2019). new information reported includes new event flu.

Follow-up (07Jun2019): New information received from the CRO included new event erection disorder.

Follow-up (29Oct2019): New information received from CRO includes reaction data (added new event 'nausea'), and dosage regimens of bosutinib.

Mfr. Control Number: 2017498747

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (31Jan2019): New information reported includes an additional event (abdominal pain with onset date Dec2019), outcome of nausea (recovered).

Follow-up (07Jun2022): This is a follow-up to a non-interventional study for protocol B1871047. Updated information: recovery date of some events (nausea and two episodes of abdominal pain).
No follow-up attempt initiated. No further information expected.

Follow-up (25Jul2023 and 26Jul2023): This is a follow-up to a non-interventional study for protocol B1871047.
Updated information: Dosage Regimen start and drug stop dates, clinical course modified.

Case Comment: Based on the information currently available, in agreement with investigator, a possible contributory role of bosutinib to the reported event abdominal pain (both episodes) cannot be completely excluded based on temporal association and known drug safety profile. The two episode of intermittent constipation are considered related to bosutinib based on temporal association. The reported nausea is considered related to bosutinib based on temporal association and known safety profile of suspect drug. The reported flu is deemed an intercurrent infectious episode, unrelated to bosutinib. Similarly, the reported erection disorder is unlikely related to bosutinib.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	Unknown	20-MAR-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2015 to Unknown	Relevant Med History	Peripheral arterial disease (Peripheral arterial occlusive disease);
2016 to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);
2016 to Ongoing	Relevant Med History	Epigastric pain (Abdominal pain upper);
JAN-2017 to JAN-2017	Relevant Med History rated grade 1, non-serious	Constipation (Constipation);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1972	45 Years	Female	Unk	28	AUG	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Dental abscess grade 3 [Tooth abscess]
Increase in hepatic transaminases grade 1 [Transaminases increased]
flu grade 2 [Influenza]
diarrhea grade 1 [Diarrhoea]
vesicular murmur decrease grade 1 [Breath sounds abnormal]
depressive state grade 1 [Depression]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) AUGMENTIN [AMOXICILLIN;CLAVULANIC ACID] (AMOXICILLIN, **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Oral
#2) UNK	#2) Intravenous

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) tooth anti-inflammatory (Pulpitis dental)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 15-MAY-2017 / Unknown	#1) Unknown
#2) 19-SEP-2017 20:19:00 / 22-SEP-2017 11:30:00	#2) 2 days 15 hrs

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) AMOXYCILLIN (AMOXICILLIN) ; 14-SEP-2017 / Unknown
#2) APRANAX [NAPROXEN SODIUM] (NAPROXEN SODIUM) ; 14-SEP-2017 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History during a first pregnancy at the age of 16 years	Phlebitis (Phlebitis)
Unknown	Relevant Med History first pregnancy at the age of 16 years	Pregnancy (Pregnancy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017499332

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
27-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. A 45-year-old female subject was recruited in the above study and started to receive bosutinib (BOSULIF), first regimen since 15May2017 at 300 mg daily, oral, second regimen from 16May2017 to 12Jun2017 at 100 mg daily, third regimen from 13Jun2017 to 11Jul2017 at 200 mg daily and fourth regimen since 12Jul2017 (ongoing) at 300 mg daily for chronic myeloid leukaemia. The most recent dose before the event was 300 mg daily. Concomitant suspect drugs included amoxicillin/ clavulanic acid (AUGMENTIN) first regimen from 19Sep2017 at 20:19 to 22Sep2017 at 11:30, intravenous and second regimen since 27Sep2017 for tooth anti-inflammatory. Medical history included chronic myeloid leukemia (ongoing), phlebitis during a first pregnancy at the age of 16 years, hypothyroidism, surgery for shoulder rupture and glaucoma. Concomitant medication(s) included: AMOXYCILLIN oral taken for tooth infection, start date: 14Sep2017; APRANAX [NAPROXEN SODIUM] oral taken for pulpitis dental, start date: 14Sep2017.
On 28Aug2017, the subject developed increase in hepatic transaminases, rated grade 1 and considered as a non-serious event. There was a slight increase in ALT at 69 on an unknown date in Aug2017 (previous value was 49 on an unknown date), in AST at 36 on an unknown date in Aug2017 (previous value was 34 on an unknown date) and in GGT at 47 on an unknown date in Aug2017 (previous value was 38 on an unknown date) (no units provided for the lab data). It was reported that during a few weeks prior to the onset of the event, the subject had a more significant consumption of wine and aperitive drinks but that it would not last at back to school. A repeat liver work-up was performed 15 days after and was normalized. Bosutinib dose was not changed in response to the event increase in hepatic transaminases, it was continued at the dose of 300 mg daily. On 28Aug2017, hepatic transaminases reached highest value, due to alcohol consumption (wine and aperitive drinks) during the previous week. This consumption was punctual and was not considered as a relevant medical history as no alcoholism was noted in the subject medical record.
On 14Sep2017, the subject developed dental abscess grade 3 (also reported as dental problem (wisdom tooth)), event reported as serious, was hospitalized from 19Sep2017 to 22Sep2017. It was further clarified that the subject was admitted to emergency unit on 19Sep2017 at 09:19 pm but she was really taken care only after midnight (on 20Sep2017). The patient has been treated since 14Sep2017 with amoxicillin and Apranax for a painful decayed wisdom tooth (#48). Antibiotherapy with oral amoxicillin and oral naproxene (APRANAX) as tooth anti-inflammatory were prescribed, apparently without success as the infection progressed. Upon examination, inflammatory and indurated swelling of the right mandibular angle fluctuating, not descending to the cervical was found. There was no pus to the tooth neck and no abscess to the buccal or pharyngeal floor. There is no pus at the collar from the tooth. There is no abscess of the mouth or pharyngeal floor. Patient is afebrile. She was apiretic and presented with laboratory signs of inflammation with CRP of 138 and leucocyte count of 14000 on an unknown date in Sep2017. The orthopantomogram found an apical reaction of tooth 48. The subject was hospitalized with intravenous antibiotic therapy by amoxicillin sodium, clavulanic acid (AUGMENTIN) from 19Sep2017 08:19 pm to 22Sep2017 11:30 am. A flash of corticosteroids was performed at D1. On 21Sep2017, the subject was surgered for evacuation of dental abscess and extraction of tooth 48 under general anesthetic. The subject was discharged on day 1 after the surgery amoxicillin, clavulanic acid for 10 days and analgesics. The subject should see her dentist within 10 days. Action taken with bosutinib in response to the event dental abscess was dose not changed. The subject experienced diarrhea on an unspecified date in Sep2017, rated grade 1 and reported as non-serious. No action was taken with bosutinib and Augmentin. Medical report of 09Oct2017: the subject lost some weight, diarrhea with amoxicillin, clavulanic acid, resumed work on 27Sep2017. Bosutinib was not withdrawn, diarrhea improved. In Dec2017, the subject experienced flu considered as non-serious and rated grade 2. The subject reported in medical notes that she had flu a month before the report which made her very tired (symptom of the flu). No action was taken with Bosutinib in response to the event flu. The subject experienced vesicular murmur decreased without shortness of breath or cough on 16Jan2018, rated grade 1 and reported as non-serious. No action was taken with bosutinib. The subject experienced depressive state due to family problems and work overload on an unspecified date in Apr2018, rated grade 1 and reported as non-serious. No action was taken with bosutinib. As of 12Jul2023, In the report of 09Oct2017: 'Lost a little weight, diarrhea, under Augmentin, returned to work on 27Sep. There was no interruption of Bosulif. Diarrhea is improving, in the report of 16Jan2018: 'Decrease in bladder murmure, no shortness of breath or coughing', rated grade 1. In the medical report of 25Apr2018: reactionary depressive state family problems and work overload. The events Diarrhea, Breath sounds decreased and Depression reappeared after reintroduction of the suspect drug were reported as not applicable. The last action taken for bosutinib and for amoxicillin/ clavulanic acid was dose not changed. The subject had recovered from the event hepatic transaminases increased on 09Oct2017, from dental abscess and flu on 16Jan2018, from diarrhea on 09Oct2017. The outcome of event vesicular murmur decreased was not recovered, for event depressive state was recovering.

According to the investigator, the events dental abscess, increase in hepatic transaminases, flu, vesicular murmur decreased and depressive state were unrelated to study drug bosutinib and to concomitant drug.
According to the reporter, the event diarrhea was unrelated to bosutinib but related to drug amoxicillin/ clavulanic acid (AUGMENTIN).

Follow-up (24Nov2017): New information received from the Site includes details on hospitalization, and clarification on surgery performed on 21Sep2017.

Follow-up (07Dec2017): New information received from investigational site includes: investigator initial aware date (added 09Oct2017), and clinical course details.

Follow-ups (17Apr2018): New information received from investigational site includes additional event (flu, non-serious and unrelated) and updated onset of dental abscess (from 20Sep2017 to 19Sep2017).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (29May2018): New information received from the investigational site includes: tiredness was a symptom of the flu but not an event.

Amendment: This follow-up report is being submitted to amend previously reported information: last action taken with bosutinib in response to the events was dose not changed.

Follow-up (10Jul2018 and 11Jul2018): New information received from the CRA site includes: clinical course, event onset date for Dental abscess.

Follow-up (08Aug2018): New information received from the investigational site via the clinical team includes medical history, start date, route and indication of bosutinib.

Follow-up (22Oct2018): Follow-up attempts completed. No further information expected.

Follow-up (05Apr2019): New information from the clinical team includes grade of the event Increase in hepatic transaminases (rated grade 1).

Follow-up (07Nov2019): New information received from CRO includes: updated resolved date of event dental abscess (16Jan2018), updated the causality for event increase in hepatic transaminases (unrelated to bosutinib), new events (diarrhea, vesicular murmur decreased and depressive state), and new suspect drug (amoxicillin/ clavulanic acid).

Follow-up (12Nov2019): New information received from CRO includes: patient's height.

Follow-up (23May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.
Updated information: new reporter, outcome of event vesicular murmur decreased updated to recovered with recover date (previous not recovered).
Follow-up attempts completed. No further information expected.

Follow-up (12Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.
Updated information: clinical course details.

Follow-up (27Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.
Updated information: suspect drugs information (new dosage regimen of Bosulif and Augmentin, route of administration and action taken of Augmentin), new medical history (chronic myeloid leukemia), new concomitant medications, events details (outcome of the event breath sounds decreased).

Case Comment: Based on the clinical information currently provided, the company concurs with the causality assessment expressed by the investigator, considering dental abscess, flu, increase in hepatic transaminases, vesicular murmur decreased and depressive state unrelated to the suspect drug bosutinib. Event diarrhea is most likely related to an intercurrent or underlying condition or amoxicillin, clavulanic acid and unrelated to suspect drug.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Alanine aminotransferase	49	
2	AUG-2017	Alanine aminotransferase	69	
3		Aspartate aminotransferase	34	
4	AUG-2017	Aspartate aminotransferase	36	
5	SEP-2017	Body temperature	Apiretic	
6	SEP-2017	C-reactive protein	138	
7	SEP-2017	Dental examination	inflammatory and indurated swelling of the right mandibular angle non-fluctuating, not descending to the cervical. No pus to the tooth neck. No abscess to the buccal or pharyngeal floor	

Mfr. Control Number: 2017499332

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8		Gamma-glutamyltransferase	38	
9	AUG-2017	Gamma-glutamyltransferase	47	
10	2017	Liver function test	normalized (15 days after event onset)	
11	28-AUG-2017	Transaminases	highest value	
12	SEP-2017	White blood cell count	14000	
13	SEP-2017	X-ray dental	apical reaction of tooth 48	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	16-MAY-2017 / 12-JUN-2017; 28 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	13-JUN-2017 / 11-JUL-2017; 29 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	12-JUL-2017 / Ongoing; Unknown
#2) AUGMENTIN [AMOXICILLIN;CLAVULANIC ACID] (AMOXICILLIN, CLAVULANIC ACID) ; Regimen #1	UNK; Intravenous	tooth anti-inflammatory (Pulpitis dental)	19-SEP-2017 20:19:00 / 22-SEP-2017 11:30:00; 2 days 15 hrs
#2) AUGMENTIN [AMOXICILLIN;CLAVULANIC ACID] (AMOXICILLIN, CLAVULANIC ACID) ; Regimen #2	UNK; Unknown	tooth anti-inflammatory (Pulpitis dental)	27-SEP-2017 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hypothyroidism (Hypothyroidism);
Unknown	Relevant Med History	Surgery (Surgery);
Unknown	Relevant Med History	Limb injury (Limb injury);
Unknown	Relevant Med History	Glaucoma (Glaucoma);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1954	63 Years	Male	Unk	09	FEB	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Chills [Chills]
Epigastric pain [Abdominal pain upper]
Diarrhea [Diarrhoea]
irregular mole [Melanocytic naevus]
Nasal secretions [Rhinorrhoea]
Actinic keratosis of the skull [Actinic keratosis]
Cramps [Muscle spasms]
fever 3 days [Pyrexia]
Transaminases increase [Transaminases increased]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) PARACETAMOL (PARACETAMOL)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, daily
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Oral
#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 26-JAN-2017 / 08-FEB-2017
#2) 26-MAY-2017 / 28-MAY-2017

19. THERAPY DURATION
#1) 14 days
#2) 3 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia)
1998 to Unknown	Relevant Med History	Autograft (Transplant)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017506699

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
27-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 63-year-old male patient received bosutinib (BOSULIF), first regimen from 26Jan2017 to 08Feb2017 at 100 mg daily, oral, second regimen from 09Feb2017 to 05Mar2017 at 200 mg daily, oral, third regimen from 06Mar2017 to 29Mar2017 at 300 mg daily, oral, fourth regimen from 28Apr2017 to 01Jun2017 at 300 mg daily, oral, fifth regimen since 30Jun2017 (ongoing) at 100 mg daily, oral, sixth regimen since 04Oct2018 (ongoing) at 200 mg cyclic (200 mg, cyclic, every other day) and seventh regimen since 04Oct2018 (ongoing) at 300 mg cyclic (300 mg, cyclic, every other day); paracetamol (PARACETAMOL), from 26May2017 (Batch/Lot number: unknown) to 28May2017. The patient's relevant medical history included: "Chronic myeloid leukemia" (ongoing); "Autograft", start date: 1998 (unknown if ongoing); "Seborrheic keratosis" (ongoing). The patient's concomitant medications were not reported.
The following information was reported: CHILLS (non-serious) with onset 09Feb2017, outcome "recovered" (09Feb2017); ACTINIC KERATOSIS (non-serious) with onset 21Apr2017, outcome "recovered" (25Jan2019), described as "Actinic keratosis of the skull"; MUSCLE SPASMS (non-serious) with onset May2017, outcome "recovered" (01Jun2017), described as "Cramps"; TRANSAMINASES INCREASED (non-serious) with onset 29May2017, outcome "recovered" (29Jun2017), described as "Transaminases increase"; MELANOCYTIC NAEVUS (non-serious) with onset 09May2018, outcome "recovered" (25Jan2019), described as "irregular mole"; RHINORRHOEA (non-serious) with onset 22Nov2018, outcome "recovered" (14Feb2019), described as "Nasal secretions"; PYREXIA (non-serious) with onset Mar2019, outcome "recovered" (Mar2019), described as "fever 3 days"; DIARRHOEA (non-serious) with onset Sep2019, outcome "recovered" (14May2020), described as "Diarrhea"; ABDOMINAL PAIN UPPER (non-serious) with onset Sep2019, outcome "recovered" (14May2020), described as "Epigastric pain". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for paracetamol was dosage not changed. The action taken for bosutinib was temporarily withdrawn. Therapeutic measures were not taken as a result of chills, melanocytic naevus. Therapeutic measures were taken as a result of actinic keratosis, muscle spasms.

The reporter considered "chills", "epigastric pain", "diarrhea" and "transaminases increase" related to bosutinib. The reporter considered "irregular mole", "nasal secretions", "actinic keratosis of the skull", "cramps" and "fever 3 days" not related to bosutinib.

Additional information: The patient received bosutinib at 100 mg daily from 26Jan2017 then at 200 mg daily from 09Feb2017 and at 300 mg daily from 06Mar2017. From 30Mar2017 to 27Apr2017, bosutinib was temporarily withdrawn. On 01Jun2017, bosutinib was discontinued until 29Jun2017.
On 09Feb2017, the patient developed chills with cold feeling, assessed as non-serious and grade 1. These events lasted for several hours. No action was taken with bosutinib which was pursued at the same dose. Chills with cold feeling spontaneously resolved on 09Feb2017 and did not recur thereafter. The investigator considered the events chills with cold feeling as related to bosutinib and unrelated to a concomitant medication.
The patient experienced Actinic keratosis of the skull on 21Apr2017, which was assessed as non-serious. Action taken with bosutinib in the result of the event, actinic keratosis of the skull, was reported as dose not changed. The investigator considered the event actinic keratosis of the skull as not related to the study drug bosutinib.
The patient experienced cramps in May2017 (non serious) which resolved on 01Jun2017. In medical record dated 01Jun2017: 'Intake of paracetamol 1 g on 26, 27 and 28May after walking in mountain'. The patient had cramps following walks in mountain. Physician informed on the day of consultation (01Jun2017). No action was taken with bosutinib in response to this event. The investigator did not consider that the event was related to study drug.
The patient experienced "Transaminases increase" on 29May2017, rated as grade 3 (non-serious). Laboratory analysis was done (neither units nor normal values were provided) and found aspartate aminotransferase (AST) at 30 on 30Mar2017, 43 at 27Apr2017, 140 on 29May2017, 154 on 01Jun2017, 128 on 15Jun2017, 61 on 29Jun2017, 99 on 12Jul2017, 94 on 20Jul2017, 80 on 26Jul2017, 66 on 08Aug2017, 79 on 16Aug2017, 71 on 23Aug2017, 65 on 06Sep2017, 59 on 19Sep2017, 52 on 05Oct2017, 55 on 07Nov2017 and 49 on 07Dec2017. Alanine aminotransferase (ALT) was at aspartate aminotransferase at 19 on 30Mar2017, 33 at 27Apr2017, 231 on 29May2017, 260 on 01Jun2017, 45 on 15Jun2017, 89 on 29Jun2017, 123 on 12Jul2017, 111 on 20Jul2017, 102 on 26Jul2017, 81 on 08Aug2017, 99 on 16Aug2017, 93 on 23Aug2017, 74 on 06Sep2017, 72 on 19Sep2017, 60 on 05Oct2017, 57 on 07Nov2017 and 51 on 07Dec2017. On 29May2017, AST increased and ALT increased were grade 2. On 01Jun2017, AST increased and ALT increased were at grade 3 and came back to grade 2 on 15Jun2017 and to grade 1 on 29Jun2017. Liver ultrasound was in Jun2017 was normal Jun2017. Bosutinib was then resumed at the dose of 100 mg, daily. This event was related to bosutinib and concomitant drug paracetamol. No action was taken with paracetamol in response to this event.
On 09May2018, the patient presented with an irrregular mole. On 09May2018, presence of irregular beauty spots noted in the report; the patient saw the dermatologist on 25Jan2019 who treated the actinic keratosis of the skull with liquid nitrogen. For the pigmented lesions on the back, the dermatologist indicated that these were benigneous lesions left in place, no treatment needed. The event was considered as non-serious and assessed as grade I. No action was taken with bosutinib in response to this event. The investigator considered the event irregular mole as unrelated to bosutinib and unrelated to a concomitant medication.
On 22Nov2018 the patient experienced feeling of congested nose and nasal secretions assessed as non-serious. No action was taken with study drug in response to the event. According to the investigator the event was not related to study drug or to concomitant treatment.
The patient also experienced fever for 3 days rated grade 1 and reported as non-serious. The reporter stated: reported on medical report on 07May2019: experienced an episode of fever in Mar2019 for 3 days without any symptom with outcome spontaneously

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

favourable. In response to the event, no action was taken with bosutinib. According to the reporter, the event was unrelated to study drug and to concomitant drugs.
In Sep2019, the patient experienced diarrhea and epigastric pain, which were assessed as non-serious and with a grade 1. In the result of the events, no action was taken with the study drug. The patient developed several times gastrointestinal disorders including diarrhea and epigastric pain. The investigator considered that there was a reasonable possibility that the events were related to the study drug bosutinib but not related to concomitant medication.

Follow-up (12Dec2017): This is a follow up report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. Update information: dosage regimens, lab data, event outcome.

Follow-up (20Apr2018): New information received from the investigator via the CRO is as follows:
The subject's date of birth was corrected. Subject's height was provided. New event (chills with cold feeling).

Follow-up (07Jun2018): This is a follow-up to a non-interventional clinical study case reporting non-serious event only. New information: new event (irrregular mole).
Follow-up (03Jul2018): This is a follow-up to a non-interventional clinical study case reporting non-serious event only. New information reported includes: The patient had not been seen by his dermatologist yet.

Follow-up (17Aug2018): Follow-up attempts are completed. No further information is expected.

Follow-up (04Dec2018). This follow-up is received from the investigator via CRO. New information includes: new event (feeling of congested nose and nasal secretions).

Follow-up (20Feb2019): New information received the CRO is as follows: new event (Actinic keratosis of the skull).

Follow-up (26Feb2019): New information received from the study sites upon query includes: The actinic keratosis of the skull occurred on 25Jan2019 (previously reported as 09Feb2019).

Follow-up (16Apr2019): New information received from CRO included: New event (Cramps).

Follow-up (22May2019): Additional information includes medical history of ongoing seborrheic keratosis, new event "fever".

Follow-up (17Jan2020): New information received from the CRO includes reaction data (event 'chills with cold feeling' was changed to 'chills').

Follow-up (31Jan2020): New information received from the CRO includes updated reaction data (event term feeling of congested nose and nasal secretions was changed to nasal secretions).

Follow-up (03Feb2020): New information received from the CRO. New events (diarrhea and epigastric pain).

Follow-up (08Jun2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

Updated information included: Outcome of the event 'AST increased' (resolved on 29Jun2017). The action taken in response to the event 'AST increased' for the study drug was dose not changed.

Follow-up (23Aug2022): This is a non-interventional study follow-up report from the investigator for protocol B1871047.
Updated information included: patient data (initials changed from UNKNWON to PRIVACY), lab data, suspect drug data (start date of dose regimen 100mg changed, ongoing checked), concomitant medication Paracetamol added.

Follow-up (22May2023): This is a non-interventional study follow-up report from the investigator via CRO for protocol B1871047.
Updated information includes: Epigastric pain and diarrhea resolved on 14May2020.

Follow-up (11Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: event Actinic keratosis of the skull onset data.

Follow-up (25Jul2023 and 26Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: dosages started on 04Oct2018, outcome of event "mole of skin", no treatment for this event.

Amendment: This follow-up report is being submitted to amend previously reported information: outcome of the event nasal secretions updated to recovered on 14Feb2019.

Follow-up (27Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: Event terms "ALT increased" and "AST increased" were updated to "Transaminases increase" with onset date 29May2017, updated 'paracetamol' as co-suspect drug.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Comment: Based on FU information events ALT, AST increased were updated to transaminase increased.

Based on the available data, there is no reasonable possibility that the adverse events irregular mole, Actinic keratosis of the skull, nasal secretions, cramps and fever were related to bosutinib use. They are more likely intercurrent medical conditions.
ALT, AST increased, Chills, Epigastric pain, and diarrhea are considered related to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	04-OCT-2016	Alanine aminotransferase	normal	49 0
2	25-JAN-2017	Alanine aminotransferase	normal	49 0
3	26-JAN-2017	Alanine aminotransferase	normal	49 0
4	09-FEB-2017	Alanine aminotransferase	normal	49 0
5	27-FEB-2017	Alanine aminotransferase	normal	49 0
6	06-MAR-2017	Alanine aminotransferase	normal	49 0
7	28-MAR-2017	Alanine aminotransferase	normal	49 0
8	30-MAR-2017	Alanine aminotransferase	19	49 0
9	27-APR-2017	Alanine aminotransferase	33	49 0
10	29-MAY-2017	Alanine aminotransferase	231	49 0
11	01-JUN-2017	Alanine aminotransferase	260	49 0
12	2017	Alanine aminotransferase	decreased	49 0
13	15-JUN-2017	Alanine aminotransferase	4 ULN	49 0
14	15-JUN-2017	Alanine aminotransferase	45	49 0
15	15-JUN-2017	Alanine aminotransferase	245	49 0
16	29-JUN-2017	Alanine aminotransferase	89	49 0
17	12-JUL-2017	Alanine aminotransferase	123	49 0
18	20-JUL-2017	Alanine aminotransferase	111	49 0
19	26-JUL-2017	Alanine aminotransferase	102	49 0
20	08-AUG-2017	Alanine aminotransferase	81	49 0
21	16-AUG-2017	Alanine aminotransferase	99	49 0
22	23-AUG-2017	Alanine aminotransferase	93	49 0
23	06-SEP-2017	Alanine aminotransferase	74	49 0

Mfr. Control Number: 2017506699

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
24	19-SEP-2017	Alanine aminotransferase	72	49 0
25	05-OCT-2017	Alanine aminotransferase	60	49 0
26	07-NOV-2017	Alanine aminotransferase	57	49 0
27	07-DEC-2017	Alanine aminotransferase	51	49 0
28	04-OCT-2016	Aspartate aminotransferase	normal	34 0
29	25-JAN-2017	Aspartate aminotransferase	normal	34 0
30	26-JAN-2017	Aspartate aminotransferase	normal	34 0
31	09-FEB-2017	Aspartate aminotransferase	normal	34 0
32	27-FEB-2017	Aspartate aminotransferase	normal	34 0
33	06-MAR-2017	Aspartate aminotransferase	normal	34 0
34	28-MAR-2017	Aspartate aminotransferase	normal	34 0
35	30-MAR-2017	Aspartate aminotransferase	30	34 0
36	27-APR-2017	Aspartate aminotransferase	43	34 0
37	29-MAY-2017	Aspartate aminotransferase	140	34 0
38	01-JUN-2017	Aspartate aminotransferase	154	34 0
39	15-JUN-2017	Aspartate aminotransferase	128	34 0
40	15-JUN-2017	Aspartate aminotransferase	3 ULN	34 0
41	2017	Aspartate aminotransferase	decreased	34 0
42	29-JUN-2017	Aspartate aminotransferase	61	34 0
43	12-JUL-2017	Aspartate aminotransferase	99	34 0
44	20-JUL-2017	Aspartate aminotransferase	94	34 0
45	26-JUL-2017	Aspartate aminotransferase	80	34 0
46	08-AUG-2017	Aspartate aminotransferase	66	34 0
47	16-AUG-2017	Aspartate aminotransferase	79	34 0
48	23-AUG-2017	Aspartate aminotransferase	71	34 0
49	06-SEP-2017	Aspartate aminotransferase	65	34 0

Mfr. Control Number: 2017506699

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
50	19-SEP-2017	Aspartate aminotransferase	59	34 0
51	05-OCT-2017	Aspartate aminotransferase	52	34 0
52	07-NOV-2017	Aspartate aminotransferase	55	34 0
53	07-DEC-2017	Aspartate aminotransferase	49	34 0
54	JUN-2017	Ultrasound liver	Normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	Unknown	09-FEB-2017 / 05-MAR-2017; 25 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	Unknown	06-MAR-2017 / 29-MAR-2017; 24 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	300 mg, daily; Oral	Unknown	28-APR-2017 / 01-JUN-2017; 1 month 5 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	100 mg, daily; Oral	Unknown	30-JUN-2017 / Ongoing; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	200 mg, cyclic, every other day; Unknown	Unknown	04-OCT-2018 / Ongoing; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	300 mg, cyclic, every other day; Unknown	Unknown	04-OCT-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Seborrheic keratosis (Seborrhoeic keratosis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1958	59 Years	Male	71.00 kg	28	MAR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
malaria crisis [Malaria]
Diarrhea [Diarrhoea]
diarrhea [Diarrhoea]
diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 28-MAR-2017 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LERCAN (LERCANIDIPINE HYDROCHLORIDE) ; 23-MAR-2017 / Ongoing
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 23-MAR-2017 / Ongoing
#3) ATORVASTATIN (ATORVASTATIN) ; 23-MAR-2017 / Ongoing
#4) LANSOPRAZOLE (LANSOPRAZOLE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Atherosclerosis (Arteriosclerosis)
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017507864

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 59-year-old male patient received bosutinib (BOSULIF), since 28Mar2017 (ongoing) at 400 mg 1x/day. The patient's relevant medical history included: "Atherosclerosis" (ongoing); "Hypertension arterial" (ongoing); "dermatosis" (ongoing); "dyslipidemia" (ongoing). Concomitant medication(s) included: LERCAN oral taken for hypertension, start date: 23Mar2017 (ongoing); KARDEGIC oral taken for arteriosclerosis, prophylaxis, start date: 23Mar2017 (ongoing); ATORVASTATIN oral taken for dyslipidaemia, start date: 23Mar2017 (ongoing); LANSOPRAZOLE oral taken for abdominal pain upper (ongoing).
On 28Mar2017, the subject experienced diarrhea (grade 2) which was reported as non-serious event. Despite the event diarrhea, bosutinib was ongoing at the reporting time. However, it was also reported that an adverse event reoccurred after study drug bosutinib was resumed. Loperamide (IMODIUM) was received as therapeutic measure. The subject recovered on 04Apr2017. The subject experienced diarrhea rated grade 1 in Jul2017. The event was considered as non-serious. The subject received loperamide (IMODIUM) as therapeutic measure. No action taken was taken with study drug bosutinib in response to the diarrhea grade 1. The diarrhea grade 1 (onset Jul2017) was recovered in Jul2017. On 23Feb2018, the subject experienced a new episode of diarrhea grade 2, assessed as non-serious. No action was taken with bosutinib in response to diarrhea grade 2. Corrective measure consisted of initiation of loperamide (IMODIUM). The subject had fully recovered on 28Feb2018. On Aug2018, the subject experienced malaria crisis assessed grade 2 and serious: medically significant, and the patient was required a visit to the emergency room. Thick smear test performed on 19Aug2018 was positive and revealed malaria crisis. In response to the event atovaquone/ proguanil hydrochloride (MALARONE) was initiated and bosutinib dose was not changed. The event recovered on Aug2018. Systolic murmur was noted at consultation on 14Dec2018. Systolic murmur is not clinically significant.

The investigator considered that the episodes of diarrhea (onset dates: 28Mar2017, Jul2017 and 23Feb2018) as related to bosutinib, but not related to concomitant drug. The investigator considered that there was not a reasonable possibility that the events malaria crisis and parasitic infection were related to study drug or to a concomitant drug.

Follow-up (19Dec2017): New information received from investigational site includes updated start date of bosutinib, updated medical history, concomitant medications, new episode of diarrhea and relevant assessment.

Follow-up (26Mar2018): Follow-up attempts completed. No further information expected.

Follow-up (08Jun2018): New information received from the investigator includes: Reaction data (previously reported event diarrhea with onset date of 18Jul2017 was updated from grade 2 to grade 1; added new episode of diarrhea with onset of 23Feb2018) and update for causality assessment for diarrhea with onset date of 18Jul2018 (from unrelated to related to bosutinib).

Follow-up (11Sep2018): New information received included start date of bosutinib updated, new event added (malaria crisis), lab data provided.

Follow-up (21Dec2018): New information received includes: patient's clinical course, new event 'Systolic murmur', and additional lab test.

Follow-up (14Feb2019): New information received includes: updated details (trade name, indication, start date) of concomitant medications, and new event (parasitic infection) added.

Follow-up (06Mar2019): Follow-up attempts completed. No further information expected.

Follow-up (09Mar2023 and 13Mar2023): This is a non-interventional study follow up report received from the investigational site via the CRO.
Updated information includes: the event parasitic infection was removed.

Follow-up (13Apr2023): This is a non-interventional study follow up report received from the investigational site via the CRO.
Updated information includes: investigator initial aware date, seriousness criteria of event Malaria updated.

Amendment: This follow-up report is being submitted to amend previous information: Event malaria crisis onset date was updated from 19Aug2018 to Aug2018 and stop date was updated from 22Aug2018 to Aug2018.

Follow-up (14Nov2023). This follow-up is received from the clinical team in the context of reconciliation:

Updated information: Event systolic murmur deleted and onset date of diarrhea updated as Jul2017 (previously reported as 18Jul2017).

Case Comment: Based on the temporal association, and the known safety profile of bosutinib, a causal relationship between the event diarrhea (all three episodes) and bosutinib is possible. In concurrence with the reporting investigator, the reported malaria crisis is unlikely related to bosutinib.The follow up information does not alter the previous company clinical evaluation.

Mfr. Control Number: 2017507864

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	14-DEC-2018	Auscultation	systolic murmur	
2	19-AUG-2018	Smear test	positive and revealed malaria crisis	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Dermatosis (Dermatosis);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		AUG	1943	74 Years	Female	90.00 kg	13	SEP	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

LOWER LIMB PAIN [Pain in extremity]
Auricular fibrillation [Atrial fibrillation]
Auricular fibrillation [Atrial fibrillation]
Hepatic cytolysis [Hepatic cytolysis]
Vomiting [Vomiting]
Hepatic pain [Hepatic pain]
Constipation [Constipation]
Pruriginous skin eruption [Rash pruritic]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) TASIGNA (NILOTINIB HYDROCHLORIDE) **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, daily	#1) Unknown
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 31-MAY-2017 / 15-SEP-2017	#1) 108 days
#2) 31-JAN-2018 / Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) METFORMINE (METFORMIN HYDROCHLORIDE) ; MAR-2016 / Ongoing
#2) ALTIZIDE W/SPIRONOLACTONE (ALTIZIDE, SPIRONOLACTONE) ; Ongoing
#3) ASPIRINE (ACETYLSALICYLIC ACID) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
MAR-2016 to Ongoing	Relevant Med History treated	Type II diabetes mellitus (Type 2 diabetes mellitus)
Unknown	Relevant Med History	Hypertension (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017508316

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
28-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 74-year-old female subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 31May2017 to 15Sep2017 at 400 mg daily, from 06Dec2017 to 26Dec2017 at 200 mg, daily, for chronic myeloid leukemia. Additional suspect medication included nilotinib hydrochloride (TASIGNA) orally from 31Jan2018 and ongoing for chronic myeloid leukemia. Medical history included treated type II diabetes mellitus ongoing from Mar2016. The subject had a relevant medical history which also included hypertension and it was unknown if the subject had any familial history of liver disease. Concomitant medication included ongoing metformin hydrochloride (METFORMINE) for type II diabetes mellitus from Mar2016, altizide/ spironolactone ongoing as thiazide diuretic and diuretic potassium cleaner in association for arterial hypertension, and acetylsalicylic acid (ASPIRINE) ongoing for prevention of complication.
On 13Sep2017, the subject developed increase in AST (event term AST superior than 5 UNL), rated grade 3 and non-serious, and increase in ALT (event term ALT superior than 10 UNL), rated grade 3 and non-serious. There was no liver function testing done in the years prior to commencing bosutinib. However, liver function testing was performed at start of therapy, to obtain baseline, during therapy and after therapy. The subject underwent lab tests and procedures which included: Liver function testing performed on 12Jul2017 revealed AST was 22 IU/L (normal range less than 35), ALT was 23 IU/L (normal range less than 35), Gamma-glutamyltransferase (GGT) was 26 IU/L (normal range less than 38), total bilirubin was 10.9 umol/L (normal range less than 21), and conjugated total bilirubin was 2.1 umol/L (normal range less than 3.4), On 26Jul2017, AST was 25 IU/L, ALT was 31 IU/L, GGT was 27 IU/L, total bilirubin was 10.1 umol/L, and conjugated total bilirubin was 1.9 umol/L. On 09Aug2017, AST was 23 IU/L, ALT was 28 IU/L, GGT was 27 IU/L, total bilirubin was 7.0 umol/L, and conjugated bilirubin was 1.4 umol/L. On 23Aug2017, AST was 55 IU/L, ALT was 110 IU/L, GGT was 29 IU/L, total bilirubin was 7.7 umol/L, and conjugated total bilirubin was at 1.4 umol/L. On 13Sep2017, AST was 177 IU/L, ALT was 411 IU/L, and GGT was 38 IU/L. On 26Sep2017, AST was 122 IU/L, ALT was 277 IU/L, GGT was 40 IU/L, total bilirubin was 8.9 umol/L, and conjugated total bilirubin was 2.1 umol/L. On 04Oct2017, AST was 83 IU/L, ALT was 194 IU/L, and GGT was 47 IU/L. On 11Oct2017, AST was 48 IU/L, ALT was 98 IU/L, and GGT was 42 IU/L. On 18Oct2017, AST was 33 IU/L, ALT was 52 IU/L, GGT was 38 IU/L, total bilirubin was 10.3 umol/L, and conjugated total bilirubin was 2.1 umol/L. On 31Oct2017, AST was 134 IU/L, ALT was 125IU/L, and GGT was 33 IU/L. On 06Nov2017, AST was 79 IU/L, ALT was 183 IU/L, GGT was 40 IU/L, total bilirubin was 10.1 umol/L, and conjugated total bilirubin was 1.7 umol/L. On 20Nov2017, AST was 87 IU/L, ALT was 157 IU/L, GGT was 37 IU/L, total bilirubin was 10.3 umol/L, and conjugated total bilirubin was 1.9 umol/L. On 23Aug2017, the patient presented with an increase in ALT at 110 IU/L and an increase in AST at 55 IU/L that were rated grade 1; however, no action was taken by the physician regarding the study drug as these events were rated grade 1. It was reported that why 23Aug2017 should not be used as onset date according to the investigational site. The treatment was withdrawn on 15Sep2017 in response to the events. Action taken with bosutinib in response to these events was reported as "stopped (temporary or permanent or dose changed)". The subject experienced constipation Grade 1 in Oct2017 (non serious, grade1, Investigator awareness date for this event was 06Dec2017). No action was taken with study drug in response to the event constipation Grade 1. The subject received bosutinib (BOSULIF) at 200 mg daily from 06Dec2017 to 26Dec2017. On an unspecified date in Dec2017, the subject experienced vomiting and hepatic pain which were assessed as non-serious events. As a result of both events the study drug was withdrawn permanently or temporarily. The subject received as concomitant drug nilotinib (TASIGNA) by oral route ongoing from 31Jan2018 for chronic myeloid leukemia. The subject experienced on 07Feb2018 pruriginous skin eruption which was reported as non-serious and rated grade 1. No action was taken with nilotinib in response to this event. On 14Oct2018 the subject experienced traffic accident, CTCAE grade2, which led to hospitalization/prolongation of hospitalization. Following the traffic accident paroxytic auricular fibrillation was evidenced. Subject was admitted to emergency on 14Oct2018 following traffic accident. On the same day the subject experienced auricular fibrillation, rated grade2. Event was described as paroxytic auricular fibrillation. During the hospitalization the subject described sensation of occasional palpitations since the treatment with nilotinib hydrochloride was started. Role of nilotinib hydrochloride was not retained but a cardiologic monitoring was requested. The subject experienced grade 2 lower limb pain on 13Oct2018, serious as hospitalization or prolongation of hospitalization. No action was taken for study drug in response to the event. The subject experienced auricular fibrillation on 10Oct2019, which required hospitalization or prolongation of hospitalization rated grade 2 and resolved on 11Oct2019. Subject underwent radiofrequency ablation of paroxysmal atrial fibrillation on 10Oct2019 which required hospitalization and resolved on 11Oct2019. She was diagnosed with paroxysmal atrial fibrillation on a healthy heart in Oct2018, which had led to a hospitalization. Since then, different drug strategies had been tried, including betablocking agents and then flecainide acetate (FLECAINE). Unfortunately, the treatment turned out to be generally poorly tolerated, so that she had been on amiodarone for some time, which did not completely control the rhythmic situation. In these conditions, it had of course been agreed that a removal procedure would be carried out. The operation took place under good conditions on 10Oct2019. Hepatic cytolysis (reported as non-serious by investigator) caused nausea, vomiting, liver pains. Hepatic cytolysis fluctuating according to withdrawals and intakes of treatment > intermittent grade 3 which stems from the intakes of treatment. No action was taken with study drug bosutinib in response to the event traffic accident and auricular fibrillation. The subject recovered from the event constipation Grade 1 on 23Oct2017. The outcome of the events (AST superior then 5 UNL and ALT superior then 10 UNL) was recovered on 31Jan2018. On 31Jan2018, the subject recovered from vomiting and hepatic pain. The event pruriginous skin eruption resolved on 12Sep2018. The event lower limb pain was recovered on 17Oct2018, event auricular fibrillation (10Oct2019) was recovered on 11Oct2019.

The investigator considered it possible that these events (increase in AST, increase in ALT, vomiting and hepatic pain) were related to study drug bosutinib and unrelated to concomitant medications.
The investigator considered there was not reasonable possibility that the events (constipation Grade 1, auricular fibrillation

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

(14Oct2018 and 10Oct2019), lower limb pain) were related to study drug or to concomitant treatments.
The investigator considered pruriginous skin eruption unrelated to bosutinib and related to nilotinib.

Follow-up (11Dec2017): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from investigational site included: reaction data (non-serious events Aspartate aminotransferase (AST) superior than 5 UNL, and Alanine aminotransferase (ALT) superior than 10 UNL), lab data, relevant medical history, and concomitant medications.

Follow-up (30Jan2018): This is a follow-up report of a non-interventional clinical study case reporting non-serious events only. New information received from investigational site was as follows: confirmation and rationale for start date of events ALT and AST increased.

Follow-up (23Feb2018): New additional information received from CRO includes: reaction data (added non-serious events vomiting and hepatic pain), product data, medical history data and concomitant medication data.

Follow-up (01Mar2018): This follow-up is received from the investigator via CRO. New information was as follows: reaction data (added non-serious event constipation Grade 1).

Follow-up (28Mar2018): This follow-up report is received from the study coordinator. New information was as follows: confirmation the event constipation was confirmed non serious, grade1 and not related to study treatment.

Follow-up (28Sep2018): New information received from CRO includes: product data, added suspect concomitant mediation nilotinib, reaction data (added non-serious event pruriginous skin eruption), and clinical details.

Follow-up (01Feb2019). New information received from the CRO includes: reaction data (added serious event traffic accident), concomitant mediation data, and clinical details. The case became serious with this follow up.

Follow-up (22Feb2019). New information includes new event auricular fibrillation.

Follow-up (30Apr2019): Follow-up attempts completed. No further information expected.

Follow-up (23Dec2019): New information received from the study site includes: clinical course (subject underwent radiofrequency ablation of paroxysmal atrial fibrillation).

Follow-up (29Nov2021): New information received included: new event auricular fibrillation (with onset on 10Oct2019) added.

No follow-up attempts are initiated. No further information is expected.

Follow-ups (29Nov2021, 03Dec2021, and 07Dec2021): New information received included updated patient's height, and new event (lower limb pain).

Follow-up (27May2022): New information received included suspect drug data (start date of bosutinib at 200 mg daily updated to Sep2017) and additional information.

Follow-up (17Nov2022): This is a follow-up to a Non-Interventional Study report received from the study site for Protocol B1871047. Updated information bosutinib start date was updated, PRURIGINOUS SKIN ERUPTION was removed from events as occurred 28 days after the end of bosutinib treatment.

Follow-up (22Jun2023): This is a follow-up to a Non-Interventional Study report received from the study site for Protocol B1871047. Updated information includes: The event Pruriginous skin eruption (07Feb2018) which was previously deleted should be kept as every events should be kept until the date of end of study, for any imputability and, even those occurring after 28 days after the end of study treatment.

Follow-up (14Nov2023): This is a follow-up to a non-interventional study for protocol B1871047 received from the clinical team following reconciliation. Updated information includes: event details (ALT superior than 10x ULN rated grade 3, onset date of events ALT Superior than 10x UNL and AST superior than 5x UNL updated and outcome updated) and clinical course details.

No follow-up attempts is needed. No further information is expected.

Follow-up (28Nov2023 and 28Nov2023) : This is a follow-up to a non-interventional study for protocol B1871047 received from the investigator site in response to query and via the CRO. Updated information included : reaction data (added hepatic cytolysis), removed events ALT Superior than 10x UNL and AST superior than 5x UNL and subsumed under hepatic cytolysis.

No follow-up attempts is needed. No further information is expected.

Case Comment: The event lower limb pain is unrelated to bosutinib. Based on the information available, the Company cannot exclude that the suspect drug bosutinib contributed to the development of the reported vomiting, hepatic cytolysis (AST/ALT increased) and

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

hepatic pain. Conversely, the reported constipation is unlikely related to bosutinib. The Company considers the reported two episodes of auricular fibrillation are unrelated to suspect drug bosutinib but more likely due to underlying or inter-current medical condition in this 74-year-old female subject with medical history of diabetes mellitus and hypertension. The Company considers the reported event Pruriginous skin eruption is unrelated to suspect drug bosutinib but more likely related to nilotinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12-JUL-2017	Alanine aminotransferase	23 IU/l	35
2	26-JUL-2017	Alanine aminotransferase	31 IU/l	35
3	09-AUG-2017	Alanine aminotransferase	28 IU/l	35
4	23-AUG-2017	Alanine aminotransferase	110 IU/l	35
5	13-SEP-2017	Alanine aminotransferase	411 IU/l	35
6	15-SEP-2017	Alanine aminotransferase	INCREASED IU/l	35
7	26-SEP-2017	Alanine aminotransferase	277 IU/l	35
8	04-OCT-2017	Alanine aminotransferase	194 IU/l	35
9	11-OCT-2017	Alanine aminotransferase	98 IU/l	35
10	18-OCT-2017	Alanine aminotransferase	52 IU/l	35
11	31-OCT-2017	Alanine aminotransferase	125 IU/l	35
12	06-NOV-2017	Alanine aminotransferase	183 IU/l	35
13	20-NOV-2017	Alanine aminotransferase	157 IU/l	35
14	12-JUL-2017	Aspartate aminotransferase	22 IU/l	35
15	26-JUL-2017	Aspartate aminotransferase	25 IU/l	35
16	09-AUG-2017	Aspartate aminotransferase	23 IU/l	35
17	23-AUG-2017	Aspartate aminotransferase	55 IU/l	35
18	13-SEP-2017	Aspartate aminotransferase	177 IU/l	35
19	15-SEP-2017	Aspartate aminotransferase	INCREASED IU/l	35
20	26-SEP-2017	Aspartate aminotransferase	122 IU/l	35
21	04-OCT-2017	Aspartate aminotransferase	83 IU/l	35
22	11-OCT-2017	Aspartate aminotransferase	48 IU/l	35
23	18-OCT-2017	Aspartate aminotransferase	33 IU/l	35
24	31-OCT-2017	Aspartate aminotransferase	134 IU/l	35

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
25	06-NOV-2017	Aspartate aminotransferase	79 IU/l	35
26	20-NOV-2017	Aspartate aminotransferase	87 IU/l	35
27	12-JUL-2017	Bilirubin conjugated	2.1 umol/l	3.4
28	26-JUL-2017	Bilirubin conjugated	1.9 umol/l	3.4
29	09-AUG-2017	Bilirubin conjugated	1.4 umol/l	3.4
30	23-AUG-2017	Bilirubin conjugated	1.4 umol/l	3.4
31	26-SEP-2017	Bilirubin conjugated	2.1 umol/l	3.4
32	18-OCT-2017	Bilirubin conjugated	2.1 umol/l	3.4
33	06-NOV-2017	Bilirubin conjugated	1.7 umol/l	3.4
34	20-NOV-2017	Bilirubin conjugated	1.9 umol/l	3.4
35	12-JUL-2017	Blood bilirubin	10.9 umol/l	21
36	26-JUL-2017	Blood bilirubin	10.1 umol/l	21
37	09-AUG-2017	Blood bilirubin	7.0 umol/l	21
38	23-AUG-2017	Blood bilirubin	7.7 umol/l	21
39	26-SEP-2017	Blood bilirubin	8.9 umol/l	21
40	18-OCT-2017	Blood bilirubin	10.3 umol/l	21
41	06-NOV-2017	Blood bilirubin	10.1 umol/l	21
42	20-NOV-2017	Blood bilirubin	10.3 umol/l	21
43	12-JUL-2017	Gamma-glutamyltransferase	26 IU/l	38
44	26-JUL-2017	Gamma-glutamyltransferase	27 IU/l	38
45	09-AUG-2017	Gamma-glutamyltransferase	27 IU/l	38
46	23-AUG-2017	Gamma-glutamyltransferase	29 IU/l	38
47	13-SEP-2017	Gamma-glutamyltransferase	38 IU/l	38
48	26-SEP-2017	Gamma-glutamyltransferase	40 IU/l	38
49	04-OCT-2017	Gamma-glutamyltransferase	47 IU/l	38
50	11-OCT-2017	Gamma-glutamyltransferase	42 IU/l	38

Mfr. Control Number: 2017508316

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
51	18-OCT-2017	Gamma-glutamyltransferase	38 IU/l	38
52	31-OCT-2017	Gamma-glutamyltransferase	33 IU/l	38
53	06-NOV-2017	Gamma-glutamyltransferase	40 IU/l	38
54	20-NOV-2017	Gamma-glutamyltransferase	37 IU/l	38

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	06-DEC-2017 / 26-DEC-2017; 21 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	UNK; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	Unknown; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		SEP	1950	67 Years	Female	Unk		NOV	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Cardiac decompensation [Cardiac failure]
Atrial fibrillation [Atrial fibrillation]
Tachyarrhythmia on atrial fibrillation [Tachyarrhythmia]
Bilateral pleural effusion [Pleural effusion]
Escherichia coli infection [Escherichia infection]
Staphylococcus aureus infection [Staphylococcal infection]
Helcococcus kunzii infection [Bacterial infection]
Acute respiratory distress [Acute respiratory distress syndrome]
Systolic heart failure [Left ventricular failure]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) OXYNORM (OXYCODONE HYDROCHLORIDE)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 300 mg, daily
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Oral
#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 14-SEP-2017 / 02-JUL-2018
#2) Unknown

19. THERAPY DURATION
#1) 292 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) BACTRIM FORTE (SULFAMETHOXAZOLE, TRIMETHOPRIM) ; 21-
#2) RIFADINE (RIFAMPICIN) ; 15-SEP-2017 / 17-DEC-2017
#3) ACUPAN (NEFOPAM HYDROCHLORIDE) ; 28-SEP-2017 / 17-DEC-2017
#4) OXYCONTIN LP (OXYCODONE HYDROCHLORIDE) ; MAY-2017 / Unknown
#5) OXYNORMORO (OXYCODONE HYDROCHLORIDE) ; MAY-2017 / Ongoing
#6) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; 19-JUN-2001 / Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Cyst removal (Cyst removal)
Unknown to Ongoing	Relevant Med History With ongoing treatment	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017527651

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Bilateral pleural effusions [Pleural effusion]
Lower limb oedema (cardiac failure) [Oedema peripheral]
Biological inflammation signs with cutaneous origin [Dermatitis]
Wound on the back of the left foot [Limb injury]
Wound on the back of the left foot [Limb injury]
Thrombopenia [Thrombocytopenia]
Depressive syndrome [Depression]
Urinary infection [Urinary tract infection]
Klebsiella infection [Klebsiella infection]
Vaginal mycosis [Vulvovaginal mycotic infection]
somnolence [Somnolence]
Creatinine increased [Blood creatinine increased]
Vomiting [Vomiting]
Nausea [Nausea]
Fever with cutaneous origin [Pyrexia]
Intertrigo at vaginal folds [Intertrigo]
Hemorrhoids [Haemorrhoids]
Bronchopulmonary syndrome [Bronchopulmonary disease]
dyspnea [Dyspnoea]
Severe arteriopathy [Arterial disorder]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 67-year-old female patient received bosutinib (BOSULIF), first regimen from 14Sep2017 to 02Jul2018 at 300 mg daily, oral and second regimen from 16Aug2018 to 18Jun2019 at 300 mg daily for chronic myeloid leukaemia; oxycodone hydrochloride (OXYNORM), (Batch/Lot number: unknown). The patient's relevant medical history included: "Left breast cyst removal" (unspecified if ongoing); "Hypothyroidism" (ongoing), notes: With ongoing treatment; "diabetes mellitus" (ongoing), notes: With ongoing treatment; "Pleural effusion" (unspecified if ongoing); "Arterial hypertension" (ongoing), notes: With ongoing treatment; "Obliterative arteriopathy of the inferior limbs" (ongoing), notes: With ongoing treatment; "Left femoral popliteal bypass" (ongoing), notes: With ongoing treatment; "Heel pressure sores" (ongoing), notes: With ongoing treatment; "Staphylococcus aureus and Enterococcus osteitis" (ongoing), notes: Staphylococcus aureus and Enterococcus osteitis with ongoing treatment; "Paroxysmal atrial fibrillation" (ongoing), notes: With ongoing treatment; "Legs pain" (ongoing), notes: With ongoing treatment; "Anxiety" (ongoing), notes: With ongoing treatment; "Pain" (unspecified if ongoing), notes: Indication of nefopam hydrochloride (ACUPAN) and Pregabalin.; "gastroesophageal reflux" (unspecified if ongoing), notes: Indication of esomeprazole; "staphylococcal auerus" (unspecified if ongoing), notes: Staphylococcus aureus and Enterococcus osteitis; "enterocccus" (unspecified if ongoing), notes: Staphylococcus aureus and Enterococcus osteitis; "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: BACTRIM FORTE taken for osteitis, start date: 21Aug2017, stop date: 17Dec2017; RIFADINE taken for osteitis, start date: 15Sep2017, stop date: 17Dec2017; ACUPAN taken for pain, start date: 28Sep2017, stop date: 17Dec2017; OXYCONTIN LP taken for pain in extremity, start date: May2017; OXYNORMORO taken for pain in extremity, start date: May2017 (ongoing); LEVOTHYROX taken for hypothyroidism, start date: 19Jun2001 (ongoing); GLICLAZIDE taken for diabetes mellitus, start date: 04Feb2016 (ongoing); JANUVIA (ongoing); KARDEGIC (ongoing); ESOMEPRAZOLE taken for gastrooesophageal reflux disease (ongoing); LOXEN L P (ongoing); MACROGOL (ongoing); ESCITALOPRAM taken for anxiety, stop date: 17Dec2017; ALPRAZOLAM taken for anxiety, stop date: 29Dec2017; PREGABALIN taken for pain, start date: 28Dec2017 (ongoing); TARDYFERON taken for anxiety, stop date: 17Dec2017; FOLIC ACID, stop date: 17Dec2017; XARELTO taken for atrial fibrillation, start date: 25Jul2017 (ongoing); EPREX (ongoing); DOLIPRANE taken for pain (ongoing); AMOXICILLINE taken for osteitis, start date: 27Jul2017, stop date: Nov2017.
On 29Nov2017, the subject presented with systolic heart failure, acute respiratory distress (reported as acute respiratory distress suspicious of a systolic heart failure, grade 3) and bilateral pleural effusions (grade 3) which required hospitalization/prolongation of hospitalization. The subject went to emergency with blood pressure of 180/100 (unit not provided) and oxygen saturation of 75 %. Bacteriological samples were negatives. Non-invasive ventilation, exploratory pleural puncture, pulmonary computerized tomography were performed. Broad spectrum antibiotic therapy was introduced. In Nov2017, ciprofloxacin (CIFLOX) was introduced at 100 (unspecified unit) daily for osteitis. On 30Nov2017, ciprofloxacin was discontinued and piperacillin/tazobactam (TAZOCILLINE) was introduced until 06Dec2017 for infection and pleural effusion. In Nov2017, the subject experienced Klebsiella infection and urinary infection (reported as Klebsiella urinary infection) and vaginal mycosis, both rated grade 2 and considered as non-serious events. On 30Nov2017, the patient experienced lower limb oedema (cardiac failure), requiring hospitalization from 14Dec2017 to 29Dec2017. On 04Dec2017, investigator's advice was requested, it was decided to continue bosutinib and etiology of pleural effusion should be search elsewhere than by hematological treatment. Consultation with a pneumologist should be planned. The subject was discharged on 06Dec2017. In Dec2017, the subject experienced somnolence rated grade 2 and considered as non-serious. On 14Dec2017, the subject presented with depressive syndrome (grade 3) which was considered as non-serious. The subject was still hospitalized either at hospital or at home. She was hospitalized from 14Dec2017 to 29Dec2017 for lower limbs oedema. On 14Dec2017, some treatments were introduced: sotalol at 160 (unspecified unit) daily for tachycardia (ongoing), furosemide (LASILIX) at 125 (unspecified

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

unit) daily for oedema (ongoing) and mortazapine (NORSET) daily for depressive syndrome (ongoing). She did not respect her low-sodium diet, therefore furosemide was increased and oedemas resolved.
On 19Feb2018, the subject presented with creatinine increased at 145.1 umol/l (N: 49 - 90) rated grade 2 at and assessed as non-serious. On 06Mar2018, the subject was seen on consultation but did not provide previous blood cell count to the investigator. On 06Mar2018, creatinine was still rated grade 2 at 151 umol/l (N: 45 - 84). CRP was 231 mg/l (normal between 0 and 5) on 31May2018. Upon follow up on 15Jun2018, it was reported that the patient experienced wound on the back of the left foot from 01Mar2018 which was considered as non-serious (grade 2). She recovered on 31Mar2018. On an unspecified date, she presented with wound on the back of the left foot which required hospitalization (grade 4). Since 01May2018, the subject was hospitalized for left foot injury which required amputation in 2 times: on 22May2018 and 01Jun2018. Escherichia coli was found on biopsy on 14May2018, Staphylococcus aureus on 22May2018 and stopped 11Jun2018 and Helcococcus kunzii (considered serious for medically significant) was found on 01Jun2018; all requiring hospitalization. The subject experienced on Nov2017 intertrigo at vaginal folds, grade 2, assessed as non-serious. The action taken as a result of the events for bosutinib was dose not changed, for oxycodone hydrochloride was unknown. Treatment received for the events included: Non-invasive ventilation, exploratory pleural puncture, broad spectrum antibiotic therapy, ciprofloxacin (CIFLOX), piperacillin/tazobactam (TAZOCILLINE), sotolol, furosemide, mortazapine (NORSET); amputation of the 2 first radius of left foot on 22May2018; and transmetatarsal amputation of left foot on 01Jun2018. The patient had to the consultation on 12Jun2018. Awareness by the investigator of the hospitalization on 01May2018 of the patient for wound on the back of the left foot requiring amputation in 2 stages on 22May2018 and 01Jun2018. The subject underwent Trans P1 amputation of the 2 first radius of left foot on 22May2018 (grade 4) and transmetatarsal amputation of left foot on 01Jun2018 (grade 4), which required hospitalization and were considered as a medically significant condition. Cause of trans P1 amputation of the 2 first radius of left foot on 22May2018 (grade 4) and transmetatarsal amputation of left foot on 01Jun2018 (grade 4) was the severe arteriopathy (unknown onset date and outcome). On 31May2018, the subject presented with biological inflammatory signs with cutaneous origin which was considered as a medically significant condition (grade 4) and fever with cutaneous origin (grade 2) which was considered as non-serious. On 06Jun2018, the subject presented with nausea and vomiting which were considered as non-serious (grade 3). The subject presented with thrombopenia on 02Jul2018 which was considered as non-serious and rated as grade 3. In response to this event, bosutinib was discontinued temporarily on 02Jul2018. The patient came at the consultation on 12Jun2018 with the investigator, which was aware at that time of the hospitalization of the patient since 01May2018 for wound on the back of the left foot, requiring amputation in 2 phases : on 22May2018 and 01Jun2018. Thrombopenia resolved on 16Aug2018. This event did not reoccur after reintroduction of study drug. Bosutinib was temporarily withdrawn from 02Jul2018 to 16Aug2018 and then resumed on 16Aug2018 at 300 mg daily. On 09Aug2018, the subject experienced hemorrhoids, rated grade 2 and reported as non-serious. No action was taken with bosutinib in response to the events. The outcome of the events acute respiratory distress suspicious of a systolic heart failure was resolved on 06Dec2017, bilateral pleural effusions resolved on 27Dec2017, lower limb oedema resolved on 29Dec2017, klebsiella urinary infection resolved in Nov2017, vaginal mycosis resolved on 29Dec2017, somnolence resolved in Dec2017, while depressive syndrome was not recovered. The nausea, vomiting, biological inflammatory signs with cutaneous origin and fever with cutaneous origin resolved on 11Jun2018. Escherichia coli infection resolved on 13Jun2018. The subject recovered from Staphylococcus aureus on 11Jun2018 and from Helcococcus kunzii and wound on the back of the left foot grade 4 on 13Jun2018. The subject recovered from the amputations. Event intertrigo at vaginal folds grade2 was recovered in Nov2017. Thrombopenia resolved on 16Aug2018. The event hemorrhoids resolved on 20Mar2019.
On 10Jun2019, the subject presented bronchopulmonary syndrome and dyspnea both considered non-serious and assessed grade 3. Dyspnea was increasing. No relevant laboratory data was performed. No action was taken for bosutinib in response to the events. Bronchopulmonary syndrome and dyspnea recovered on 24Jun2019. On 17Jun2019, the subject experienced cardiac decompensation and atrial fibrillation (reported as cardiac decompensation on atrial fibrillation), Tachyarrhythmia on atrial fibrillation and bilateral pleural effusion, all requiring hospitalization and assessed grade 3. The subject had atrial fibrillation higher than usual value. She gone to the emergency unit and cardiac decompensation was diagnosed. Chest x-Ray confirmed bilateral pleural effusion, pleural puncture was performed and given the persistence of pleural effusion, the subject was transferred to pneumology department. The patient was hospitalized from 17Jun2019 in emergency unit then she was transferred to continuing care pneumology department, then a brief stay on pneumology department and finally she was hospitalized in follow-up care and rehabilitation unit and was not yet discharged. The patient underwent the following laboratory tests and procedures: Aspiration pleural cavity: (unspecified date) Result not provided; Bacterial test: (unspecified date) Negative; Biopsy: (14May2018) S.aureus, E. coli; (01Jun2018) Staph aureus, E coli, Helicoccus kunzi; Blood creatinine (45-84): (06Mar2018) 151 umol/l, notes: grade 2; Blood creatinine (49-90): (19Feb2018) 145.1 umol/l, notes: grade 2; Blood pressure measurement: (unspecified date) 180/100; Chest X-ray: (unspecified date) confirmed bilateral pleural effusion; Computerised tomogram thorax: (unspecified date) Result not provided; C-reactive protein (0-5): (31May2018) 231 mg/l; Oxygen saturation: (unspecified date) 75 %. The investigator saw the patient during consultation on 09Jul2019. It was reported that investigator's initial aware date for Bronchopulmonary disease and dyspnea is 09Jul2019. In response to events cardiac decompensation on atrial fibrillation and Tachyarrhythmia on atrial fibrillation bosutinib was withdrawn. Bosutinib was received at 300 mg, daily until 18Jun2019, when it was stopped. No action taken in response to Bilateral pleural effusions and Lower limb oedema (cardiac failure). No action taken in response to the events intertrigo at vaginal folds and Escherichia coli infection. In response to somnolence (Dec2017), analgesic drugs were pursued without modification. Cardiac decompensation on atrial fibrillation and Tachyarrhythmia on atrial fibrillation resolved on 24Jun2019. Bilateral pleural effusion resolved on 31Mar2020, blood creatinine increased recovered on 15Apr2020.

The investigator considered that there was a reasonable possibility that the events thrombopenia, cardiac decompensation on atrial fibrillation and Tachyarrhythmia on atrial fibrillation and bilateral pleural effusion (on 17Jun2019) was related to bosutinib, but not related to concomitant medication.
The investigator considered that there was not a reasonable possibility that the events acute respiratory distress suspicious of a systolic heart failure, bilateral pleural effusions, lower limbs oedema, depressive syndrome, Klebsiella urinary infection, vaginal mycosis, nausea, vomiting, foot amputation, inflammation, fever, Escherichia coli infection, staphylococcus infection, bacterial infection, hemorrhoids and foot injury, creatinine increased and intertrigo at vaginal folds grade2, bronchopulmonary syndrome and

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

dyspnea were related to bosutinib or to a concomitant drug.
The investigator considered that it was not reasonably possible that the event somnolence was related to bosutinib but related to antalgic concomitant drug oxycodone hydrochloride (OXYNORM).
The reporter's assessment of the causal relationship of the event "severe arteriopathy" with the suspect product bosutinib was not provided at the time of this report. Since no determination has been received, the case is managed based on the company causality assessment.

Follow-up (24Jan2018 and 25Jan2018): New information received from the investigator upon the query includes: new events (lower limbs edema and depressive syndrome), updated outcome of event bilateral pleural effusions as recovered (previously "recovering"), dose regimen of bosutinib, medical history, and concomitant medications.

Follow-up (08Feb2018): New information reported from the investigator includes: reaction data (added Klebsiella urinary infection, vaginal mycosis, and somnolence).

Follow-up (08Mar2018): New information reported from the site includes: lab data, product details (indication), reaction data (additional event "creatinine increased"), outcome of event and clinical course details.

Follow-up (14May2018): New information reported from the investigator via CRO includes: product details (oral route of administration for bosutinib) and new suspect product (oxycodone HCL (OXYNORM) including causality related for event somnolence).

Follow-up (15Jun2018): New information received from the study site includes: laboratory data (CRP); new events (nausea, vomiting, inflammation, fever, Escherichia coli infection, staphylococcus aureus infection, bacterial infection, and foot injury); treatment received (amputation for foot injury); clinical course, and causality assessment (the events nausea, vomiting, foot amputation, inflammation, fever, Escherichia coli infection, staphylococcus infection, bacterial infection, and foot injury), were not related to study drug or concomitant drug).

Follow-up (07Sep2018): New information received includes: new event intertrigo at vaginal folds grade 2 added.

Follow-up (16May2019): New information received from CRO included dates when bosutinib was temporarily withdrawn and date when it was resumed, new non-serious event hemorrhoids.

Follow-up (23May2019): New information received from the study site includes: additional non-serious event (thrombocytopenia), action taken for the new event, causality per reporter.

Follow-up (16Jul2019): New information received from the investigational site via the CRO includes: new events (bronchopulmonary syndrome, dyspnea, cardiac decompensation on atrial fibrillation, Tachyarrhythmia on atrial fibrillation and bilateral pleural effusion) added, and lab data (chest X-ray) added.

Follow-up (16Sep2019): New information received from the investigational site included confirmed event bilateral pleural effusion had not recovered yet.

Follow-up (08Jan2020): New information received from CRO includes: separate event acute respiratory distress suspicious of a systolic heart failure into 2 events systolic heart failure and acute respiratory distress, event Klebsiella urinary infection into 2 events Klebsiella infection and urinary infection, event cardiac decompensation on atrial fibrillation into 2 events cardiac decompensation and atrial fibrillation; updated onset date of events respiratory distress suspicious of a systolic heart failure and bilateral pleural effusions (from 31Oct2017 to 29Nov2017).

Follow-up (30Sep2020): New information received from CRO includes updated outcome for the events pleural effusion (occurred on 17Jun2019) and creatinine increased (both from not recovered to recovered) and recovery date.

Follow-up (07Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from study site for protocol B1871047. Updated information: medical history of ongoing chronic myeloid leukemia, onset date of left foot injury grade 4, updated event verbatim updated for lower limb oedema (cardiac failure) and onset date, event verbatim updated for Helcococcus kunzii infection, event verbatim for Staphylococcus aureus infection and onset and recovery dates (22May2018 to 11Jun2018)., recovery date for vaginal mycosis, action taken in response to bilateral pleural effusions, lower limb oedema (cardiac failure), intertrigo at vaginal folds and Escherichia coli infection and treatment for somnolence (Dec2017).

Follow-up (10May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from study site for protocol B1871047. Updated information: updated stop date of the event Escherichia coli infection from 11Jun2018 to 13Jun2018, clinical course updated.

Follow-up (20Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047. Updated information: description updated and hospitalization added for Escherichia coli infection, hospitalization added and stop date changed for Staphylococcus infection, hospitalization and medically significant criteria added for Bacterial infection (Helcococcus kunzii infection).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (02Aug2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (other HCP) for protocol B1871047. Updated information: new event (severe arteriopathy).

Follow-up (19Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (other HCP) for protocol B1871047 updating lab data , staphylococcus aureus infection stop date, and additional details regarding the patient's wound and treatment.

Follow-up (14Nov2023): This is a follow-up to a non-interventional study for protocol B1871047 received from the clinical team. Updated information included: event "Left foot injury" from 01Mar2018 to 31Mar2018 was updated to "wound on the back of the left foot" rated grade 2. Event "left foot injury grade 4" updated to "wound on the back of the left foot" requiring hospitalization and resolved on 13Jun2018.

No follow-up attempt is needed. No further information is expected.

Case Comment: Events cardiac decompensation, atrial fibrillation, tachyarrhythmia are unlisted in SRSD of bosutinib and related per Company assessment.

The company concurs with the investigator and considered that there was a reasonable possibility that the events cardiac failure, atrial fibrillation, tachyarrhythmia, bilateral pleural effusion (Onset date: 17-JUN-2019), and thrombopenia were related to bosutinib, based on temporal association, and known product profile. Conversely, the events Escherichia coli infection, Staphylococcus aureus infection, Helcococcus kunzii infection, Acute respiratory distress, Systolic heart failure, bilateral pleural effusion (onset: 29-NOV-2017), Lower limb oedema, Wound on the back of the left foot (onset: 01-MAY-2018), skin inflammation, Wound on the back of the left foot (onset: 01-MAR-2018), Depressive syndrome, Urinary infection, Klebsiella infection, Vaginal mycosis, somnolence, creatinine increased, Vomiting, Nausea, Fever with cutaneous origin, Intertrigo at vaginal folds, hemorrhoids, Bronchopulmonary syndrome, dyspnea and arteriopathy were not related to bosutinib. The underlying medical history of diabetes mellitus, hypertension, paroxysmal atrial fibrillation may explain the occurrence of left ventricular heart failure which consequently led to development of pleural effusion, peripheral oedema, and acute respiratory distress. The potential of immunosuppressive state induced by the underlying malignancy was the contributor to the reported infections.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to regulatory authorities, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Aspiration pleural cavity	Result not provided	
2		Bacterial test Negative	Negative	
3	14-MAY-2018	Biopsy	S.aureus, E. coli	
4	01-JUN-2018	Biopsy	Staph aureus, E coli, Helicoccus kunzi	
5	19-FEB-2018	Blood creatinine grade 2	145.1 umol/l	90 49
6	06-MAR-2018	Blood creatinine grade 2	151 umol/l	84 45
7		Blood pressure measurement	180/100	
8	31-MAY-2018	C-reactive protein	231 mg/l	5 0
9		Chest X-ray	confirmed bilateral pleural effusion	
10		Computerised tomogram thorax	Result not provided	
11		Oxygen saturation	75 %	

Mfr. Control Number: 2017527651

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	16-AUG-2018 / 18-JUN-2019; 307 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#1) BACTRIM FORTE (SULFAMETHOXAZOLE, TRIMETHOPRIM) ; 21-AUG-2017 / 17-DEC-2017

#7) GLICLAZIDE (GLICLAZIDE) ; 04-FEB-2016 / Ongoing

#8) JANUVIA (SITAGLIPTIN PHOSPHATE) ; Ongoing

#9) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing

#10) ESOMEPRAZOLE (ESOMEPRAZOLE) ; Ongoing

#11) LOXEN L P (NICARDIPINE HYDROCHLORIDE) ; Ongoing

#12) MACROGOL (MACROGOL) ; Ongoing

#13) ESCITALOPRAM (ESCITALOPRAM) ; Unknown / 17-DEC-2017

#14) ALPRAZOLAM (ALPRAZOLAM) ; Unknown / 29-DEC-2017

#15) PREGABALIN (PREGABALIN) ; 28-DEC-2017 / Ongoing

#16) TARDYFERON (FERROUS SULFATE) ; Unknown / 17-DEC-2017

#17) FOLIC ACID (FOLIC ACID) ; Unknown / 17-DEC-2017

#18) XARELTO (RIVAROXABAN) ; 25-JUL-2017 / Ongoing

#19) EPREX (EPOETIN ALFA) ; Ongoing

#20) DOLIPRANE (PARACETAMOL) ; Ongoing

#21) AMOXICILLINE (AMOXICILLIN TRIHYDRATE) ; 27-JUL-2017 / 10-OCT-2017

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History With ongoing treatment	Diabetes mellitus (Diabetes mellitus);
Unknown	Relevant Med History	Pleural effusion (Pleural effusion);
Unknown to Ongoing	Relevant Med History With ongoing treatment	Hypertension arterial (Hypertension);
Unknown to Ongoing	Relevant Med History With ongoing treatment	Peripheral obliterative arteriopathy (Peripheral arterial occlusive disease);

Mfr. Control Number: 2017527651

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History With ongoing treatment	Femoropopliteal artery bypass (Peripheral artery bypass);
Unknown to Ongoing	Relevant Med History With ongoing treatment	Pressure sore (Decubitus ulcer);
Unknown to Ongoing	Relevant Med History	Osteitis (Osteitis); Staphylococcus aureus and Enterococcus osteitis with ongoing treatment
Unknown to Ongoing	Relevant Med History With ongoing treatment	Paroxysmal atrial fibrillation (Atrial fibrillation);
Unknown to Ongoing	Relevant Med History With ongoing treatment	Leg pain (Pain in extremity);
Unknown to Ongoing	Relevant Med History With ongoing treatment	Anxiety (Anxiety);
Unknown	Relevant Med History	Pain (Pain); Indication of nefopam hydrochloride (ACUPAN) and Pregabalin.
Unknown	Relevant Med History Indication of esomeprazole	Gastroesophageal reflux (Gastrooesophageal reflux disease);
Unknown	Relevant Med History Staphylococcus aureus and Enterococcus osteitis	Staphylococcal infection (Staphylococcal infection);
Unknown	Relevant Med History Staphylococcus aureus and Enterococcus osteitis	Enterococcal infection (Enterococcal infection);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		SEP	1948	69 Years	Male	60.00 kg	20	OCT	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Alteration of the general status in a patient with fragile general status (given the comorbidities) [General physical health deterioration]
fistula bleeding [Haemorrhage]
Malaise at the connection for dialysis session [Malaise]
diarrhea/diarrhea-nausea [Diarrhoea]
Nausea [Nausea]
Diarrhea [Diarrhoea]
Vomiting [Vomiting]
Recurrence of bullous eruption on the back of the hands [Dermatitis **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 02-MAR-2019
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☒ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) Levofloxacin (LEVOFLOXACIN) Unknown **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, 1x/day	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 21-SEP-2017 / 2017	#1) Unknown
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) HYDREA (HYDROXYCARBAMIDE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
JUL-2014 to Ongoing	Relevant Med History with dialysis	Chronic renal failure (Chronic kidney disease)
JUL-2014 to Ongoing	Relevant Med History	Dialysis (Dialysis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2017550776

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
27-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

bullous]
Sliding syndrome [General physical health deterioration]
Bronchitis [Bronchitis]
Stenosis of the drainage vein used for dialysis [Venous stenosis]
Inflammatory comedo in the back [Acne]
Burn of the 2nd phalanx of the 4th finger of the right hand [Thermal burn]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 69-year-old male patient received bosutinib (BOSULIF), first regimen from 21Sep2017 to 2017 at 300 mg 1x/day, oral, second regimen from 11Oct2017 to Oct2017 at 400 mg 1x/day, oral, third regimen from 20Oct2017 to Oct2017 at 500 mg 1x/day, oral, fourth regimen from 26Oct2017 to 29Oct2017 at 400 mg 1x/day, oral, fifth regimen from 05Dec2017 to Dec2017 at 300 mg 1x/day, oral, sixth regimen from 28Dec2017 to 30Dec2017 at 400 mg 1x/day, oral, seventh regimen from 04Jan2018 to Jan2018 at 400 mg 1x/day, oral, eighth regimen from 18Jan2018 to 20Jan2018 at 400 mg 1x/day, oral, ninth regimen since 24Jan2018 at 400 mg 1x/day, oral, tenth regimen since 02Mar2018 at 200 mg daily, oral, eleventh regimen from May2018 to 24May2018 at daily (200 mg day before dialyses and 300 mg a day other days), oral, twelfth regimen from 03May2018 to 05Jun2018 at 200 mg daily (rotation) and thirteenth regimen since 04Jun2018, oral for chronic myeloid leukaemia; levofloxacin (LEVOFLOXACIN). The patient's relevant medical history included: "Chronic renal failure", start date: Jul2014 (ongoing), notes: with dialysis; "Dialysis", start date: Jul2014 (ongoing); "bullous eruption" (unspecified if ongoing), notes: known before the introduction of bosutinib; "Type 2 diabetes mellitus", start date: 2014 (ongoing); "amputation of the left knee", start date: 2008, stop date: 2008, notes: following an arteriopathy of the lower limbs; "arteriopathy of the lower limbs" (unspecified if ongoing), notes: complicated by a perforating disorder; "amputation of the right toe", start date: 17May2015, stop date: 17May2015, notes: following Methicillin-resistant Staphylococcus aureus infection; "Methicillin-resistant Staphylococcus aureus infection" (unspecified if ongoing). Concomitant medication(s) included: HYDREA.
The subject experienced diarrhea rated grade 2 on 20Oct2017 which was considered as non-serious event. The subject developed diarrhea following bosutinib dose increased to 500 mg. In response to the event, bosutinib dose was reduced to 400 mg once a day. The subject was also treated with loperamide (unspecified trade name). The event reoccurred after drug reintroduction. It was also reported that the subject experienced another episode of diarrhea grade 2 in the same period of time from 05Dec2017 to Jun2018. The subject experienced nausea rated grade 2 on 05Dec2017 which was considered as non-serious event. The subject developed diarrhea and nausea following reintroduction of bosutinib at 300 mg once a day. The investigator confirmed that two events of diarrhea were one event which reoccurred after drug reintroduction. Bosutinib was temporarily withdrawn by the subject following bubbling skin eruptions which was already present in Jun2017 due to pseudo-porphyry associated to subject's dialysis. According to the investigator, this did not challenge the study drug treatment. The investigator confirmed that bubble skin eruption was not an adverse event or serious adverse event. Dermatologist evaluation: the subject presented with post bubble erosion of back of hands. Course of the event and clinical data were in favor of pseudo porphyry associated to subject dialysis. It was not compatible with hematological therapeutics. However, if they were responsible, they would be a photoxicity reaction and not a toxidermal reaction. Dosage of blood porphyrins and stool porphyrin were in progress. The subject's file would be discussed again with results. Photoprotection had been recommended. There were no contraindications to resume bosutinib. No action was taken with bosutinib in response to the event nausea. The events diarrhea rated grade 2 (onset 20Oct2017) was recovered on 08Feb2018 and nausea rated grade 2 (onset 05Dec2017) was recovered on 30Apr2018. According to the investigator, the event diarrhea (onset date 20Oct2017) and nausea were related to bosutinib. Less nausea on reduction of bosutinib to 200 mg on 02Mar2018. On 27Oct2017, the subject developed recurrence of bullous eruption on the back of the hands, rated grade 1. In response to this event, bosutinib was temporarily withdrawn by the subject. Bosutinib was resumed on 05Dec2017 and the event did not reappear. The event Recovered/Resolved with Sequel on 22Dec2017. These bullous eruptions were known before installing bosulif; Registered with sequelae because sometimes patient had skin eruptions. The subject was advised to photoprotect, as these bullous eruptions were known before the introduction of bosutinib. The investigator considered recurrence of bullous eruption on the back of the hands as unrelated to study drug bosutinib. According to the hematologist and the dermatologist, this skin eruption was potentially due to pseudoporphyria of the dialyzed subjects, therefore not in relation with the study treatment. On 21Dec2017, the subject developed inflammatory comedo in the back, rated grade 1 and considered as non-serious. The comedo was noted in the hospital report of 21Dec2017, then not noted in further medical reports. The event resolved in Apr2018. No action was taken with bosutinib in response to the event. The investigator considered the event as unrelated to study drug bosutinib and concomitant drug. On 01Feb2018, the subject developed alteration of the general status in a patient with fragile general status (given the comorbidities), rated grade 5. In the hospital report of 01Feb2018, the nephrologist mentioned a deterioration of the patient without any details. In the report of the multidisciplinary consultation meeting in Mar2018, it was mentioned an alteration of the general status (weight loss and comorbidities). In the hematology report dated 09Apr2018, it was noted an objective emaciation. The subject was progressively in an altered general status. It was noted that this event was the follow-up of the event sliding syndrome. No action was taken with bosutinib in response to the event. The event alteration of the general status in a patient with fragile general status (given the comorbidities) had not resolved, the general status was precarious. The event was serious for hospitalization and was fatal. The investigator considered the event as unrelated to study drug bosutinib and concomitant drug. The clinical course of this event was as follows: 01Feb2018: grade 2; 24Jul2018: grade 3 (context of denutrition); 07Feb2019: grade 4 - hospitalization for aggravation of the alteration of the general condition; (context of denutrition with cachexia and negligence) leading to death - grade 5 - 02Mar2019. On

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

15Feb2018, the subject developed stenosis of the drainage vein used for dialysis, rated grade 3 and considered as non-serious. Following a control of the fistula (used for dialysis) on 15Feb2018, it was noted a reduction of the flow of arteriovenous fistula due to a narrow stenosis well perceived under the skin, close to the division of the superficial radial vein to an extern branch (the more significant one) and an intern branch which becomes atretic. This was to be discussed during staff meeting. A therapeutic proposal of angioplasty was made on 20Feb2018. On 28Feb2018, angioplasty of the lesion was performed with a balloon of 6mmx20mm. The surgery and the after-surgery were simple. The event resolved on 28Feb2018. No action was taken with bosutinib in response to the event. The investigator considered the event as unrelated to study drug bosutinib and concomitant drug. On 25Mar2018, the subject developed burn of the 2nd phalanx of the 4th finger of the right hand, rated grade 1 and considered as non-serious. On the medical report dated 05Apr2018, it was noted that the patient presented with a healing lesion on the 2nd phalanx of the 4th finger of the right hand following an accidental burn at home which occurred around 10 days prior to the report. No action was taken with bosutinib in response to the event. The event resolved in 2018. The investigator considered the event as unrelated to study drug bosutinib and concomitant drug. On 03Apr2018 the subject experienced loss of response, grade 2, assessed non-serious. Action was taken with study drug in response to the event was dose increased. Event was not recovered. According to the investigator the event loss of response was not related to study drug or to concomitant treatment. BCR/ABL dosage on 03Apr2018 was at 39.3 %. Caryotype analysis showed no mutation. Bosutinib dosage was increased to 200 mg day before dialyses and 300 mg a day other days. However the subject followed that prescription approximately from 15May2018. On 03May2018, the subject experienced fistula bleeding, grade 4, which led to hospitalization and was assessed as life threatening. The event description was as follow: on 03May2018, during dialysis the subject did not feel well, the needle mismatched, the repositioning was impossible because of clotting in needle circuit. Therefore, the needle was removed immediately and the subject received filling of 500 ml of potassium chloride and then he was transferred in nephrology ward. The subject lost about 500 ml and 1000 ml. Laboratory analysis was done on blood on branch point and found haemoglobin at 122 g/l on 03May2018 and at 91 g/l on 05May2018 (as it was up to 90 g/l, no transfusion was necessary). The subject stayed at hospital during 48 hours for monitoring and on 05May2018 he was discharged without modification of his daily treatment. Action taken of bosutinib was dose not changed. The subject was considered recovered from 'fistula bleeding' on 05May2018. According to the investigator the event fistula bleeding was not related to study drug and concomitant medication. On 19May2018, the subject experienced bronchitis, which was assessed of grade 1 and non-serious. During the physician visit to dialysis room, the subject presented with picture of bronchitis, which was treated with levofloxacin from 19May2018 for 7 days. The subject had recovered from the event on 30Jun2018. The investigator considered the event bronchitis as not related to the study drug bosutinib and to concomitant medications. On 09Feb2018 the subject experienced diarrhea, grade 1, assessed as non-serious. Study drug was temporarily withdrawn in response to the event. Diarrhea recovered on 10Aug2018. The event diarrhea was under antibiotics and treated with loperamide (unspecified trade name). The subject did not take bosutinib as he experienced diarrhea following the antibiotic treatment for bronchitis, bosutinib was dose not changed. According to the investigator the event diarrhea (with event onset date 09Feb2018) was related to bosutinib and to concomitant treatment levofloxacin. The investigator considered levofloxacin was only related to the AE diarrhea (onset date 09Feb2018), and not related to any other AEs. He tried to take bosutinib on 04Jun2018 and that caused vomiting following the intake. On 04Jun2018, the subject experienced vomiting, which was assessed of grade 2 and non-serious. The subject resumed bosutinib at the beginning of the week of 04Jun2018. Following the intake, the subject developed vomiting. In result of the event, bosutinib was withdrawn. The subject was not taking bosutinib following that digestive intolerance. Vomiting recovered on 05Jun2018. The investigator considered the event vomiting not related to study drug or concomitant medications. On 07Jun2018, the subject experienced sliding syndrome, which was assessed as non-serious. The event was assessed of grade 2. The investigator was aware of this event on 07Jun2018. During the visit, the subject recognized that she presented with sliding syndrome. He decided to be admitted to the rest home on 04Jun2018 to feel better. No action was taken regarding bosutinib. At the time of reporting, the subject had not recovered from the event sliding syndrome. The event sliding syndrome was not related to study drug bosutinib. The study drug bosutinib was discontinued on 24May2018. The patient was hospitalized on 07Feb2019 following the dialysis session, in front of the presence of a malaise at the connection, with alteration of the general state and loss of 5 kg in one week, cachexic and 'incuric state' (carelessness). On the vascular plan purulent melting of the 2nd left toe was observed. Realization of a doppler of the lower limbs reassuring, with a transcutaneous partial pressure of oxygen also reassuring. Evidence of staphylococcus aureus was found at the level of the samples. Antibiotic treatment with Augmentin in probabilistic, continued. Amputation was performed on 18Feb2019. Continuation of Hydrea, increased by the patient progressively until 6 tablets, with occurrence of pancytopenia in connection with a toxicity of the drug. Oral mycosis with important aphtosis occurred. Finally, occurrence of a malaise after the session of hemodialysis on 02Mar2019, with death of the patient quickly in the continuations. The patient died on 02Mar2019. The malaise repeated of 26Feb2019 was ongoing at the time of death. The cause of death was reported as alteration of the general status in a patient with fragile general status (given the comorbidities). It was unknown whether an autopsy was done. The action taken for levofloxacin was dose not changed. The investigator assessed malaise at the connection for dialysis session as unrelated to study drug and to concomitant drugs. In response to this event, hydroxyurea (HYDREA) dose was increased.

FU (20Feb2018): New information reported includes product data and event detail (confirm two events of diarrhea were one event which reoccurred after drug reintroduction and bubble skin eruption was not a serious adverse event).

FU (07Mar2018): New information received includes: bosutinib regimen data.

FU (17Apr2018): New information received includes an additional event (bullous eruption on the back of the hands) along with an update about clinical course with outcome and action taken with bosutinib in response to the events.

FU (18May2018): New information received from the Site includes additional medical history, new SAE (blood deglobulisation on fistula bleeding), laboratory data, and additional treatment received. This case was upgraded to serious.

FU (14Jun2018): New information received from the site included: event (new event 'sliding syndrome' added).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

FU (02Aug2018): New information received included new events added (bronchitis with fever, vomiting).

FU (09Aug2018): New information includes reaction data (new event diarrhea with onset date 24May2018, outcome of vomiting updated from not resolved to recovered on 05Jun2018), causality between bosutinib and event vomiting (updated from related to unrelated), lab data, and additional suspect drug levofloxacin (related to diarrhea).

FU (12Sep2018): New information received includes: event causality for levofloxacin was added.

FU (06Dec2018): New information received included: dosage regimen of bosutinib, medical history, and additional events.

FU (13Dec2018): New information received from the investigational site includes: Medical history details, confirmed causality, event status.

FU (05Dec2019): New information received from the clinical team includes: death details and seriousness for event 'alteration of the general status in a patient with fragile general status (given the comorbidities)'.

FU (27Dec2019): News information received includes updated cause of death. Narrative updated.

FU (07Jan2020): New information received from the study coordinator includes: discontinued date of bosutinib updated.

FU (05Feb2021): New information received from the clinical team included: diarrhea grade 2 (onset 20Oct2017) recovered on Jun2018 and another episode of diarrhea grade 2 in the same period of time from 05Dec2017 to Jun2018 (subsumed under one event).

FU (13Dec2021): This is a FU non-interventional study report (Post Authorization Safety Study) for protocol B1871047.
Updated information: cause of death was updated to Alteration of general status. New events: alteration of general status with cachexia and carelessness rated as grade 5 (fatal).

FU (14Dec2021): This is a FU non-interventional study report (Post Authorization Safety Study) for protocol B1871047.
Updated information: event blood deglobulisation on fistula bleeding was corrected to fistula bleeding. Onset date, seriousness, causality assessment unchanged. Event alteration of general status with cachexia and carelessness was corrected to Malaise at the connection for dialysis session. Seriousness criteria hospitalization and medically significant added for this event. Onset date of this event corrected to 07Feb2019. Cause of death corrected. Event bronchitis with fever corrected to bronchitis.

Amendment: This FU report is being submitted to amend previously reported information: The causality as reported for malaise with suspect product Levofloxacin was updated to unrelated in the corresponding field.

FU (27Dec2022): New information received includes: Event data (Recurrence of bullous eruption on the back of the hands changed outcome from Recovered/Resolved to Recovered/Resolved with Sequel)

FU (08Feb2023): New information received includes: events investigator aware date, event grade.

FU (10Feb2023): New information received includes reaction data (recovery date for event bronchitis updated from 25May2018 to 30Jun2018, outcome for event nausea updated from resolving to recovered on 30Apr2018).

FU (23Mar2023): New information received includes For event diarrhea with onset 24May2018 stop date changed to 10Aug2018, for event bronchitis action taken corrected to dose not changed (previously withdrawn).

FU (24Mar2023): New information received includes reaction data (outcome and stop date of malaise added, onset date of inflammatory comedo added), and clinical course details.

FU (29Mar2023): New information received includes: general physical health deterioration updated to fatal and serious for hospitalisation; stop date of diarrhea updated to 08Feb2018; start date for second event of diarrhea (with stop date 10Aug2018) updated to 09Feb2018; action taken for levofloxacin updated to dose not changed.

FU (17Apr2023): New information received includes: cause of death.

Follow-up attempts completed. No further information expected.

FU (25Jul2023): New information received includes: it was confirmed that the event "malaise at the connection for dialysis session" did not led to death.
Follow-up attempts completed. No further information expected.

FU (27Jul2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: dosage regimen of bosutinib.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Comment: Based on the reasonable temporal association and considering diarrhea (both episodes), nausea and vomiting are consistent with the known safety profile of bosutinib and levofloxacin, the Company cannot completely exclude the possible causality between these events and administration of bosutinib and levofloxacin. Conversely, the reported bullous eruption, venous stenosis, comedo and burn of finger on the back of the hands, malaise, bleeding, bronchitis and General physical health deterioration (both episodes, event onset 01-FEB-2018 with fatal outcome) are unrelated to the suspect drugs, bosutinib and levofloxacin but likely attributed to intercurrent medical conditions in this elderly patient with underlying CML, renal disorder with dialysis and type 2 diabetes mellitus is at increased risk of infections.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	19-MAY-2018	Body temperature	fever	
2		Gene mutation identification test	no mutation	
3	03-APR-2018	Gene mutation identification test	39.3 %	
4	03-MAY-2018	Haemoglobin	122 g/l	
5	05-MAY-2018	Haemoglobin	91 g/l	
6	FEB-2019	Investigation	Staphylococcus aureus at level of the samples	
7		Weight	loss	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	11-OCT-2017 / OCT-2017; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	500 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	20-OCT-2017 / OCT-2017; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	26-OCT-2017 / 29-OCT-2017; 4 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	05-DEC-2017 / DEC-2017; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	400 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	28-DEC-2017 / 30-DEC-2017; 3 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	400 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	04-JAN-2018 / JAN-2018; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet;	400 mg, 1x/day; Oral	chronic myeloid leukemia	18-JAN-2018 /

Mfr. Control Number: 2017550776

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #8		(Chronic myeloid leukaemia)	20-JAN-2018; 3 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #9	400 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	24-JAN-2018 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #10	200 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	02-MAR-2018 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #11	200 mg day before dialyses and 300 mg a day other days; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	MAY-2018 / 24-MAY-2018; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #12	rotation; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	03-MAY-2018 / 05-JUN-2018; 1 month 3 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #13	UNK; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	04-JUN-2018 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Bullous eruption (Dermatitis bullous); known before the introduction of bosutinib
2014 to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus);
2008 to 2008	Relevant Med History	Leg amputation (Leg amputation); following an arteriopathy of the lower limbs
Unknown	Relevant Med History	Arteriopathy (Arterial disorder); complicated by a perforating disorder
17-MAY-2015 to 17-MAY-2015	Relevant Med History	Toe amputation (Toe amputation); following Methicillin-resistant Staphylococcus aureus infection
Unknown	Relevant Med History	Methicillin-resistant Staphylococcus aureus infection (Staphylococcal infection);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		DEC	1950	66 Years	Female	38.00 kg	03	OCT	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Fracture of the right hip [Hip fracture]
Icteric cholestasis [Jaundice cholestatic]
anemia [Anaemia]
decrease of bosutinib efficacy [Neoplasm progression]
URINARY INFECTION [Urinary tract infection]
right shoulder pain [Arthralgia]
vitamin D deficiency [Vitamin D deficiency]
malnutrition [Malnutrition]
Hematoma on scar (post hip fracture surgery) [Scar]
Hematoma on scar (post hip fracture surgery) [Haematoma]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

15. DAILY DOSE(S)
#1) 300 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 03-JUN-2016 / Unknown

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) SPECIAFOLDINE (FOLIC ACID) ; Unknown
#2) CONTRAMAL (TRAMADOL HYDROCHLORIDE) ; Unknown
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Unknown
#4) PLAVIX (CLOPIDOGREL BISULFATE) ; Unknown
#5) DOLIPRANE (PARACETAMOL) ; Unknown
#6) UVEDOSE (COLECALCIFEROL) ; Unknown

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	
Unknown	Relevant Med History	Skin dry (Dry skin)

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018010518

24c. DATE RECEIVED BY MANUFACTURER
08-DEC-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

arterial hypertension [Hypertension]
face hematoma [Haematoma]
peri inguinal inflammation of both hands and feet [Inflammation]

Case Description: The initial case was missing the following minimum criteria: no reportable event. Upon receipt of follow-up information on 29Mar2019, this case now contains all required information to be considered valid.

OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.

A 66-year-old female patient received bosutinib (BOSULIF), first regimen since 03Jun2016 at 300 mg daily, second regimen from 03Oct2017 to 14May2019 at 300 mg 1x/day, third regimen from 22May2019 to 27May2019 at 100 mg daily, oral, fourth regimen from 28May2019 to 04Jun2019 at 200 mg daily, oral and fifth regimen since 05Jun2019 at 300 mg daily, oral. The patient's relevant medical history included: "peripheral arteriopathy" (unspecified if ongoing); "skin dryness" (unspecified if ongoing); "left toe necrosis" (unspecified if ongoing); "femoral stent" (unspecified if ongoing); "memory disorders", start date: 17Jun2016 (unknown if ongoing). Concomitant medication(s) included: SPECIAFOLDINE; CONTRAMAL; KARDEGIC; PLAVIX; DOLIPRANE; UVEDOSE; STRESAM. The following information was reported: NEOPLASM PROGRESSION (non-serious) with onset 03Oct2017, outcome "recovered" (04Sep2018), described as "decrease of bosutinib efficacy"; INFLAMMATION (non-serious) with onset 20Mar2018, outcome "recovered" (12Jun2018), described as "peri inguinal inflammation of both hands and feet"; MALNUTRITION (non-serious) with onset 12Jun2018, outcome "not recovered"; HAEMATOMA (non-serious) with onset 06Mar2019, outcome "recovered" (Apr2019), described as "face hematoma"; HIP FRACTURE (hospitalization) with onset Apr2019, outcome "recovering", described as "Fracture of the right hip"; ANAEMIA (non-serious) with onset 02May2019, outcome "recovered" (06May2019), described as "anemia"; HYPERTENSION (non-serious) with onset 02May2019, outcome "not recovered", described as "arterial hypertension"; ARTHRALGIA (non-serious) with onset 07May2019, outcome "not recovered", described as "right shoulder pain"; JAUNDICE CHOLESTATIC (non-serious) with onset 14May2019, outcome "recovering", described as "Icteric cholestasis"; SCAR (non-serious), HAEMATOMA (non-serious) all with onset May2019, outcome "recovering" and all described as "Hematoma on scar (post hip fracture surgery)"; VITAMIN D DEFICIENCY (non-serious) with onset 16May2019, outcome "not recovered"; URINARY TRACT INFECTION (non-serious) with onset 21May2019, outcome "recovered" (Jun2019), described as "URINARY INFECTION". The patient underwent the following laboratory tests and procedures: Ultrasound abdomen: (17May2019) normal.
Clinical course: On an unspecified date in 2017, the subject experienced loss of response to treatment for which no seriousness criterion was reported. In response to this event, bosutinib daily dose was increased up to 300 mg per day on 03Oct2017. On 03Oct2017, the subject experienced decrease of bosutinib efficacy rated grade 1 and assessed as non-serious. Action taken in the result of the event was dose increased. At the time of reporting, the event decrease of bosutinib efficacy had resolved on 04Sep2018. It was also reported that there was no mention of disease progression at the time of loss of efficacy of bosutinib. The investigator considered the event decrease of bosutinib efficacy as related to the study drug and unrelated to concomitant medications.On 06Mar2019, the subject experienced fall grade 1 (subsumed under face hematoma). On 06Mar2019, the subject experienced face hematoma rated grade 1 and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event face hematoma had resolved in Apr2019. The investigator considered the event face hematoma as unrelated to the study drug and concomitant medications. In Apr2019, the subject had a fracture of the right hip following a fall, rated grade 3 and requiring hospitalization. She was operated on 01May2019.On 14May2019, the subject developed icteric cholestasis, rated grade 2 and non-serious. In response to the event, study drug bosutinib was temporarily withdrawn on 14May2019. Bosutinib was resumed on 22May2019 and it was unknown whether the event recurred upon resumption. The investigator considered the event icteric cholestasis as related to the study drug and not related to concomitant medications. As of 21Aug2019, it was reported, the subject experienced urinary infection on 21May2019, considered non-serious and assessed grade 2. Laboratory data included an abdominal ultrasound was performed on 17May2019, and was normal. The event fracture of right hip was resolving; and urinary infection was recovered in Jun2019. The event icteric cholestasis was recovering. The action taken with bosutinib in response to the events was dose not changed.On 07May2019, the subject experienced right shoulder pain rated grade 2 and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event right shoulder pain had not resolved. The investigator considered the event right shoulder pain as unrelated to the study drug and concomitant medications.On 16May2019, the subject experienced vitamin D deficiency rated grade 2 and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event vitamin D deficiency had not resolved. The investigator considered the event vitamin D deficiency as unrelated to the study drug and concomitant medications.On 12Jun2018, the subject experienced malnutrition rated grade 2 and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event malnutrition had not resolved. The investigator considered the event malnutrition as unrelated to the study drug and concomitant medications.In May2019, the subject experienced 'hematoma scar, rated grade 1' further updated to Hematoma on scar (post hip fracture surgery) and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event 'hematoma scar, rated grade 1' was resolving. The investigator considered the event Hematoma on scar (post hip fracture surgery) as unrelated to the study drug and concomitant medications.On 02May2019, the subject experienced anemia rated grade 2 and assessed as non-serious and arterial hypertension rated grade 3 and assessed as non-serious. Action taken in the result of the events was dose not changed. At the tile of reporting, the event anemia had resolved on 06May2019 and the event arterial hypertension had not resolved. The investigator considered the event anemia and arterial hypertension as unrelated to the study drug and concomitant medications.On 20Mar2018, the subject experienced peri inguinal inflammation of both hands and feet rated grade 1

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

and assessed as non-serious. Action taken in the result of the event was dose not changed. At the time of reporting, the event inguinal inflammation of both hands and feet had resolved on 12Jun2018. The investigator considered the event inguinal inflammation of both hands and feet as unrelated to the study drug and concomitant medications.The investigator considered that the event urinary infection was unrelated to bosutinib or to a concomitant drug. The investigator considered this event fracture of the right hip as unrelated to study drug bosutinib and unrelated to concomitant medications. The investigator considered the event icteric cholestasis as related to study drug bosutinib and unrelated to concomitant medications. The last action taken for bosutinib was temporarily withdrawn. Therapeutic measures were taken as a result of hip fracture.

The reporter considered "icteric cholestasis" and "decrease of bosutinib efficacy" related to bosutinib. The reporter considered "fracture of the right hip", "anemia", "urinary infection", "right shoulder pain", "vitamin d deficiency", "malnutrition", "hematoma on scar (post hip fracture surgery)", "arterial hypertension", "face hematoma" and "peri inguinal inflammation of both hands and feet" not related to bosutinib.

Follow-up (17May2019): New information received from the investigator includes start date and dose of bosutinib, medical history and concomitant medications.

Follow-up (24May2019): New information received from the CRO includes: medical history, lab data, dosage regimen of suspect drug, action taken of bosutinib, new events(fracture of the right hip and icteric cholestasis).

Follow-up (21Aug2019): New information received from the physician included: suspect drug data (restart date of bosutinib: 22May2019), action taken (dose not changed), and new event (urinary infection), and causality statement (urinary infection unrelated to bosutinib and concomitant drugs)

Follow-up (28Aug2019): New information received from the CRO includes: onset date and outcome of event Fracture of the right hip updated to Apr2019 and recovering (previously 02May2019 and recovered), onset date and stop date of event peri inguinal inflammation of both hands and feet updated, New adverse events (right shoulder pain, vitamin D deficiency, Malnutrition, 'hematoma scar, rated grade 1', Anemia, arterial hypertension, icteric cholestasis, face hematoma, decrease of bosutinib efficacy, peri inguinal inflammation of both hands and feet).

Follow-up (29Aug2019): New information received from the investigational site via CRO includes update of patient's clinical course (subject presented with fracture of right hip following a fall in Apr2019. Operate on 01May2019).

Follow-up (25Sep2019): new information reported includes additional treatment dates and doses of bosutinib, updated action taken.

Follow-up (20Dec2019): New information received includes event verbatim 'scar opened with inflammatory hematoma' changed to 'hematoma scar, rated grade 1'.

Follow-up (14Nov2023): This is a non-interventional study report (Post Authorization Safety Study) received from investigational site via clinical team for protocol B1871047. After reconciliaion, updated information included : event fall should be deleted as subsumed under face hematoma.

Follow-up (08Dec2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: Event term "Hematoma scar" was updated to "Hematoma on scar (post hip fracture surgery)".

Case Comment: Based upon FU, the event fall is deleted and subsumed under facial hematoma.

The event Hematoma on scar (post hip fracture surgery), fracture of the right hip, musculoskeletal pain, vitamin D deficiency, Malnutrition, inflammation, hematoma and non-fatal neoplasm progression are considered unrelated to bosutinib and deemed an accidental occurrence. Conversely, the Company cannot completely exclude the possible causality between icteric cholestasis, anemia, and bosutinib administration. Urinary tract infection is likely an intercurrent infection in this female subject with underlying malignancy.
The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	17-MAY-2019	Ultrasound abdomen	normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet;	300 mg, 1x/day; Unknown	Unknown	03-OCT-2017 /

Mfr. Control Number: 2018010518

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #2			14-MAY-2019; 589 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	100 mg, daily; Oral	Unknown	22-MAY-2019 / 27-MAY-2019; 6 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Oral	Unknown	28-MAY-2019 / 04-JUN-2019; 8 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Oral	Unknown	05-JUN-2019 / Unknown; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) STRESAM (ETIFOXINE HYDROCHLORIDE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Peripheral arterial disease (Peripheral arterial occlusive disease);
Unknown	Relevant Med History	Digital necrosis (Extremity necrosis);
Unknown	Relevant Med History	Vascular stent insertion (Vascular stent insertion);
17-JUN-2016 to Unknown	Relevant Med History	Memory disturbance (Memory impairment);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		JUL	1956	61 Years	Male	81.00 kg		SEP	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Diarrhea [Diarrhoea]
INFECTIOUS PNEUMOPATHY [Pneumonia]
CONSTIPATION [Constipation]
infectious episode [Infection]
aggravation of renal failure [Renal failure]
macroscopic hematuria [Haematuria]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 08-SEP-2017 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) EXFORGE (AMLODIPINE BESILATE, VALSARTAN) ; SEP-2017 / 23-NOV-2017
#2) AMLOR (AMLODIPINE BESILATE) ; 09-AUG-2017 / SEP-2017
#3) SMECTA [DIOSMECTITE] (DIOSMECTITE) ; 08-SEP-2017 / Ongoing
#4) AMLODIPINE (AMLODIPINE) ; 24-NOV-2017 / Ongoing
#5) TIORFAN (RACECADOTRIL) ; SEP-2017 / SEP-2018
#6) SODIUM BICARBONATE (SODIUM BICARBONATE) ; 20-JUN-2019 / Unknown

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
Unknown to Ongoing	Relevant Med History	Renal insufficiency (Renal failure)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018013652

24c. DATE RECEIVED BY MANUFACTURER
14-SEP-2021

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a report from a Non-Interventional Study source and post authorization safety study for Protocol B1871047, Study alias BOSEVAL. This is a non-interventional study case reporting non-serious events only. A 61-year-old male subject received bosutinib (BOSULIF) oral since 08Sep2017 at 400 mg once per day for chronic myeloid leukemia. Relevant medical history included ongoing HA and ongoing renal insufficiency. The subject received concomitant medications amlodipine besilate, valsartan (EXFORGE), oral from Sep2017 (Batch/Lot number was not reported) to 08Nov2017, at unknown dose daily, oral from 09Nov2017 (Batch/Lot number was not reported) to 23Nov2017, at dose reduction, unknown dose daily for hypertension, amlodipine besilate (AMLOR) taken for hypertension from 09Aug2017 to Sep2017; diosmectite (SMECTA) taken for diarrhoea from 08Sep2017 and ongoing; amlodipine (manufacturer unknown) taken for hypertension from 24Nov2017 and ongoing; racecadotril (TIORFAN) taken for diarrhoea from Sep2017 to Sep2018; sodium bicarbonate (manufacturer unknown) taken for an unspecified indication from 20Jun2019 to an unspecified stop date; enoxaparin sodium (LOVENOX) taken for phlebitis from Aug2019 to 2019. He also received (after the events) pneumococcal vaccine, single for viral prophylaxis in Jul2020. In Sep2017, the subject developed diarrhea, rated grade 1 and non-serious. Diarrhea occurred every other day within 3 to 6 hours after the intake of bosutinib. The investigator reported that the diarrhea occurred for the following two days 3-6 hours after the administration. On 14Nov2017, the subject developed aggravation of renal failure assessed as non-serious and rated grade 1. As a result, no action was taken with bosutinib and amlodipine besilate, valsartan was stopped on 23Nov2017. At the time of the report, aggravation of renal failure had not resolved yet. In Nov2017, the subject experienced constipation assessed as non-serious and rated grade 1. No action was taken with bosutinib in response to constipation. Constipation resolved on 09Jan2018. In Jun2018, the subject experienced diarrhea assessed as non-serious and rated grade 1. No action was taken with bosutinib in response to diarrhea (onset date Jun2018). Diarrhea resolved on 05Sep2018. In Nov2018, the subject experienced an episode of infectious pneumopathy rated grade 2 and non-serious. In Jan2019, the subject presented with an infectious episode assessed as non-serious and rated grade 1. In Dec2019, the subject experienced macroscopic hematuria in Dec2019 reported as non-serious and rated grade 2. The reporter stated: one episode of macroscopic hematuria work-up with pelvic ultrasound: normal and thorax X-ray: discreet dead-end filling on the left side. No action was taken with bosutinib in response to infectious episode. Infectious episode resolved in Jan2019. The action taken with bosutinib in response to the events was dose not changed, but it was advised to take bosutinib in the evening since development of diarrhea. On 23Nov2017, this product amlodipine besilate, valsartan was temporarily stopped in response to aggravation of renal failure. The subject recovered from the event diarrhea (first onset) on 28Nov2017, from the event infectious pneumopathy in Nov2018, from constipation from 09Jan2018, from diarrhea (second onset) on 05Sep2018, from infectious episode on Jan2019, and from macroscopic hematuria on 08Jan2020; while event aggravation of renal failure was not recovered.

According to the investigator, the event diarrhea was related to study drug bosutinib, while the events infectious pneumopathy and macroscopic hematuria were unrelated to study drug and to concomitant drugs. The investigator considered the events constipation and infectious episode as unrelated to bosutinib or to a concomitant medication. The investigator considered the event diarrhea (onset date Jun2018) as related to study drug bosutinib and unrelated to a concomitant medication. The investigator considered the event aggravation of renal failure as unrelated to bosutinib and related to concomitant amlodipine besilate, valsartan.

Follow-up (11Jan2018): New information reported includes: product data, medical history data, concomitant medication data, and clinical details.

Follow-up (22Jan2018): New information received includes: event onset date (updated to Sep2017).

Follow-up (28Dec2018): New information received includes additional event infectious pneumopathy.

Follow-up (16Jul2019): New information received includes: suspect product data (route of administration, indication), concomitant medication data (start date updated), reaction data (new event 'aggravation of renal failure', constipation, diarrhea with onset Jun2018, infectious episode, event outcome, causality).

Follow-up (22Jul2019): New information received from the investigational site includes: concomitant medication data (start date and dose adjustment).

Follow-up (09Jun2020): New information received includes: reaction data (new event "macroscopic hematuria" was added) and laboratory data.

Follow-up (23Mar2021): New information received from CRO: The causality assessment between the event diarrhea (onset date Jun2018) and bosutinib was removed from SAE form.

Follow-up (07Jun2021): New information received from the investigational site via the CRO includes causality assessment of event diarrhea grade 1 onset in Jun2018.

No follow-up attempt initiated. No further information expected.

Follow-up (14Sep2021): New information received from the investigational site includes: EXFORGE changed from suspect product to concomitant medication, and new concomitant medications.

Mfr. Control Number: 2018013652

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

No follow-up attempt initiated. No further information expected.

Case Comment: The Company cannot completely exclude a possible causality between the reported event diarrhea (both episodes) and the study drug bosutinib based on temporal association and the known safety profile of bosutinib. Constipation, infectious pneumopathy and unspecified infection are most likely intercurrent medical conditions, unrelated to bosutinib. Similarly, based on the information provided, the events 'aggravation of renal failure and also hematuria are assessed as unrelated to bosutinib, contributory role of amlodipine besylate and valsartan cannot be excluded.
The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Chest X-ray	discreet dead-end filling on the left side	
2		Ultrasound pelvis	normal	

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) LOVENOX [ENOXAPARIN SODIUM] (ENOXAPARIN SODIUM) ; AUG-2019 / 2019

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		FEB	1947	70 Years	Female	63.00 kg	28	NOV	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

digestive disorders [Functional gastrointestinal disorder]
smelly sweating [Skin odour abnormal]
abdominal pain [Abdominal pain]
Aphtosis [Aphthous ulcer]
Asthenia [Asthenia]
Pruritus at abdomen [Pruritus]
erythema on abdomen [Erythema]
Intermittent diarrhea [Diarrhoea]
Intermittent abdominal pain [Abdominal pain]
Diarrhea [Diarrhoea]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 500 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 28-NOV-2017 / Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History weaned	Chronic alcoholism (Alcoholism)
Unknown	Relevant Med History resolved	Pulmonary tuberculosis (Pulmonary tuberculosis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018036249

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Cold [Nasopharyngitis]
Chest pain during a walk [Chest pain]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. This is a non-interventional clinical study case reporting non-serious events only.

A 70-year-old female subject started to receive bosutinib (BOSULIF) at 500 mg daily by unspecified route on 28Nov2017, and at 500 mg daily by unspecified route on 02Jul2018 and ongoing for chronic myeloid leukemia. Relevant medical history included weaned chronic alcoholism, pulmonary tuberculosis (resolved), myalgia (resolved) and ongoing pleural effusion from 28Feb2018, ongoing chronic myeloid leukemia, ongoing exertional dyspnoea, ongoing asthenia. The subject did not receive any treatment for chronic alcoholism, pulmonary tuberculosis, myalgia and pleural effusion. Myalgia was due to previous treatment with nilotinib, resolved; pleural effusion was due to previous treatment with dasatinib, not resolved. She did not receive concomitant medication. On 28Nov2017, since the initiation of bosutinib, the subject experienced digestive disorders and smelly sweating. The events were both assessed as non-serious and grade 1. Corrective treatment included diosmectite (unspecified trade name) at an unknown daily dose from 28Nov2017 to 28Feb2018 as prophylaxis against nausea. The subject was seen on consultation on 28Feb2018 and was considered as fully recovered from both events. The clinical outcome of the event digestive disorders and smelly sweating was recovered on 28Feb2018. On an unspecified date in Jul2018, the subject experienced abdominal pain and aphtosis both rated grade 1. Abdominal pain and aphtosis resolved on 05Dec2018. On 03Sep2018, at the consultation, the subject was found to have asthenia grade 2, pruritus at abdomen and erythema on abdomen grade 2. The events were rated as non-serious. As of 07Sep2018, the events events asthenia, and pruritus and erythema on abdomen were not yet recovered. Erythema of abdomen was resolved on 05Dec2018 while pruritus at abdomen was not resolved. During the visit on 05Dec2018, the subject was found to have diarrhea grade 2, in intermittent way, cold grade 1 in Dec2018. The events were rated as non-serious. Diarrhea grade 2 and cold grade 1 were resolved on 06Mar2019. In Mar2019, the subject experienced grade 2 intermittent diarrhea and grade2 intermittent abdominal, non-serious. There were several disorders, very episodic, which were associated with diarrhea and abdominal pain. Evolution of intermittent abdominal pain (Mar2019) was favorable under symptomatic treatment and resolved on 26Jun2019. The event intermittent diarrhea was also resolved on 26Jun2019. In Jul2019, the subject experienced chest pain during a walk rated grade 1 and non-serious. Despite the event, the suspect drug bosutinib was pursued unchanged. On 06Aug2019, the subject had a consultation in cardiology department following a chest pain during a walk, an electrocardiogram and a cardiac stress test were performed and were normal. The subject recovered from this event on 06Aug2019. No action was taken with bosutinib in response to all the events.

Investigator Initial Aware Date for events Diarrhea with start date of 05Dec2018 and Cold: 05Dec2018.Investigator Initial Aware Date for events Diarrhea and Abdominal pain with start date of Mar2019 and Cold: 26Jun2019. Investigator Initial Aware Date for events Chest pain, Erythema, Asthenia, Pruritus, Aphthous ulcer and Abdominal pain with start date of Jul2018: 03Sep2019. Investigator Initial Aware Date for events: Functional gastrointestinal disorder and Sweat odor abnormal: 17Jan2018.
The investigator assessed the events diarrhea grade 2, cold grade 1 and chest pain as unrelated to bosutinib. The investigator considered there was a reasonable possibility that other events were related to bosutinib.

Follow-up (30Jan2018): New information received from clinical team includes indication for use bosutinib, medical history provided.

Follow-up (07Mar2018): New information received from the investigator includes: medical history (added previous use with nilotinib and dasatinib), treatment received (diosmectite), and clinical outcome (updated from not recovered to recovered).

Follow-up (07Sep2018): New information received from CRO includes: newly added events (abdominal pain, aphtosis, asthenia, and pruritus and erythema on abdomen), with seriousness criteria, outcome and causality assessment.

Follow-up (01Mar2019): Additional information received through CRO included new events (diarrhea and cold), causality assessment, seriousness criteria, outcome.

Follow-up (26Apr2019): Follow-up attempts completed. No further information expected.

Follow-up (02Jul2019): New information reported includes new events (grade 2 intermittent diarrhea and grade2 intermittent abdominal).

Follow-up (12Jul2019). New information received from the study coordinator included: Outcome of events, treatment.

Follow-up (10Sep2019): New information received from the study coordinator include lab data, and reaction data (outcome of event Intermittent abdominal pain (updated from not recovered to recovered), and added a new event "chest pain").

Follow-up (28Nov2019): New information received from CRO included: recovery date of event intermittent abdominal pain.

Mfr. Control Number: 2018036249

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (19Dec2019): New information received from CRO includes updated event term (from "Pruritus and erythema on abdomen" to "pruritus at abdomen" and "erythema on abdomen"), updated outcome for events erythema on abdomen, diarrhea and cold, intermittent diarrhea.

Follow-up (10May2023): This is a report from a Non-Interventional study source from the investigational site via the CRO. Updated information includes: Patient's initials changed from Unknown to Privacy; Investigator Initial Aware Date.

Follow-up (08Jun2023): This is a non-interventional study follow up report received from the investigational site via the CRO. Updated information included: dosage regimens (dose of first regimen and started date of second regimen) updated, medical history.

Follow-up (14Nov2023): This is a non-interventional study follow up report received from the investigational site via the CRO. Updated information included: event outcome and stop date for "aphtosis".

Case Comment: Based on the information currently available, a possible contributory role of the suspect drug to the reported events cannot be completely excluded based on temporal association.
The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06-AUG-2019	Cardiac stress test	Normal	
2	06-AUG-2019	Electrocardiogram	Normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	500 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	02-JUL-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event	nilotinib (NILOTINIB); Drug Reaction: Myalgia (Myalgia) resolved, due to previous treatment with tyrosine kinase inhibitors (nilotinib (unspecified trade name))
Unknown	Past Drug Event	dasatinib (DASATINIB); Drug Reaction: Pleural effusion (Pleural effusion) ongoing pleural effusion due to previous treatment with tyrosine kinase inhibitors (dasatinib (unspecified trade name))
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);
28-FEB-2018 to Ongoing	Relevant Med History	Pleural effusion (Pleural effusion);
Unknown to Ongoing	Relevant Med History	Exertional dyspnoea (Dyspnoea exertional);
Unknown to Ongoing	Relevant Med History	Asthenia (Asthenia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		NOV	1967	50 Years	Male	100.00 kg		DEC	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional clinical study case reporting non-serious events only. This is a report from a Pfizer Sponsored Non-Interventional Study for Protocol B1871047, Center ID/Subject ID 22|02.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 24-NOV-2017 / 08-JAN-2018

19. THERAPY DURATION
#1) 46 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) COVERSYL /00790703/ (PERINDOPRIL ARGININE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
Unknown to Ongoing	Relevant Med History	Obesity (Obesity)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018038166

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
26-JAN-2018

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2018038166

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 50-years-old male subject of an unspecified ethnicity started to receive bosutinib (BOSULIF) via an unspecified route of administration from 24Nov2017 to 08Jan2018 at 500 mg once daily for chronic myeloid leukaemia. Medical history included ongoing arterial hypertension, ongoing obesity, and urinary lithiasis that resolved on unknown date. Concomitant medication included perindopril arginine (COVERSYL) orally ongoing for arterial hypertension. The subject previously took imatinib mesilate (GLIVEC) which failed due to poor compliance. Consequently, bosutinib was initiated. The subject experienced diarrhea on Dec2017. The event was assessed as non-serious and grade 2. No relevant laboratory tests or complementary examinations were performed. The action taken in response to the event diarrhea for bosutinib was permanently withdrawn on 08Jan2018. The diarrhea was not relieved by "usual anti-diarrhea products (unspecified trade names)". The clinical outcome of the event diarrhea was recovered on Jan2018.

The investigator considered that there was a reasonable possibility that the event diarrhea was related to the study drug bosutinib but as unrelated to concomitant medication perindopril arginine.

Case Comment: Based on the information currently available, there was a reasonable possibility that the event diarrhea was related to bosutinib based on temporal association and known drug safety profile.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History resolved on unknown date	Urinary calculus (Calculus urinary);
Unknown	Past Drug Event poor compliance	GLIVEC (GLIVEC); Drug Reaction: Treatment failure (Treatment failure)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1974	43 Years	Male	70.00 kg	20	SEP	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Thrombocytopenia [Thrombocytopenia]
Epigastralgia [Abdominal pain upper]
Bronchitis [Bronchitis]
Anemia [Anaemia]
Constipation [Constipation]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, 1x/day	#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 24-AUG-2017 / 20-SEP-2017	#1) 28 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018040242

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-JAN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter (Physician) for protocol B1871047.

A 43-year-old male patient received bosutinib (BOSULIF), first regimen from 24Aug2017 to 20Sep2017 at 500 mg 1x/day, oral and second regimen from 19Oct2017 to 05Mar2018 at 400 mg 1x/day for chronic myeloid leukaemia. The patient had no relevant medical history. There were no concomitant medications.
On 20Sep2017, the subject developed thrombocytopenia, rated grade 4. Laboratory tests were performed and revealed platelet count as follows (reference range:150000-400000): 38000/mm3 on 29Aug2017, 43000/mm3 on 05Sep2017, 25000/mm3 on 13Sep2017, and 11000/mm3 on 26Sep2017. The seriousness criterion of the event thrombocytopenia was hospitalization since the subject was hospitalized in the day hospital for the transfusion of 27Sep2017 and 23Feb2018 then hospitalized from 23Feb2018 due to disease progression (blast phase). The subject was transfused with one platelet pack on 23Feb2018 then 8 platelet packs between 26Feb2018 and 08Mar2018, during hospitalization. The action taken in response to the event thrombocytopenia for bosutinib was dose reduced. Following thrombocytopenia, bosutinib dose that was at 500 mg since 24Aug2017 was temporarily withdrawn from 20Sep2017 to 18Oct2017 and then reduced to 400 mg once daily from 19Oct2017.
On 25Feb2018, the subject experienced epigastralgia and bronchitis, which were assessed as non-serious and of the grade 2. As a result of the events, epigastralgia and bronchitis, the dose of bosutinib was not changed. In Feb2018, the event, epigastralgia, had resolved. In Mar2018, the event bronchitis had resolved.
On 02Mar2018, the subject experienced anemia, which was assessed as non-serious and of the grade 2. As a result of the event, anemia, the dose of bosutinib was not changed. On 07Mar2018, the subject experienced constipation, which was assessed as non-serious and of the grade 2. In response to the event constipation, bosutinib dose was not changed.
Thrombocytopenia and anemia both resolved on 08Mar2018 while constipation was resolving.

The investigator considered that there was a reasonable possibility that the event thrombocytopenia was related to the study drug but not to a concomitant drug.
The investigator considered the events epigastralgia, bronchitis, anemia and constipation as not related to the study drug and concomitant medications.

Follow-up (17Feb2018): New information received from the investigational site includes: suspect product details (updated route of administration and added indication CML), and clinical course details.

Follow-up (17Apr2019): New information received from the CRO includes: seriousness criterion for thrombocytopenia (hospitalization), clinical course, event outcome.

Follow-up (18Apr2019): New information received from the Site includes new AEs (epigastralgia, bronchitis, anemia and constipation).

Follow-up (02Jun2020): New information received from the CRO includes: updated action taken

Follow-up (19Jan2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter (Physician) for protocol B1871047. Updated information: additional bosutinib dosage regimen (400 mg daily from 19Oct2017 to 05Mar2018).

Case Comment: By close temporal relationship and absence of factors which may provide an alternative cause, the event thrombocytopenia may be attributed to suspect drug bosutinib, the event is consistent with the known toxicity profile of the suspect product. Conversely, the reported epigastralgia, bronchitis, anemia and constipation, occurred after around 5 months of the last dose of bosutinib, are considered unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	29-AUG-2017	Platelet count	38000 /mm3	400000 150000
2	05-SEP-2017	Platelet count	43000 /mm3	400000 150000
3	13-SEP-2017	Platelet count	25000 /mm3	400000 150000
4	26-SEP-2017	Platelet count	11000 /mm3	400000 150000

14-19. SUSPECT DRUG(S) continued

Mfr. Control Number: 2018040242

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	19-OCT-2017 / 05-MAR-2018; 4 months 15 days

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
PRIVACY	FRANCE		OCT	1969	48 Years	Female	57.00 kg	06	OCT	2017	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Iron deficiency [Iron deficiency]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

(Continued on Additional Information Page)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 05-JUL-2017 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	none ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018042255

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2018042255

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 48-year-old female patient received bosutinib (BOSULIF), since 05Jul2017 (ongoing) at 500 mg 1x/day. The patient had no relevant medical history. There were no concomitant medications.
The following information was reported: IRON DEFICIENCY (non-serious) with onset 06Oct2017, outcome "recovered" (23Nov2017).
Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed.
Additional information: Event rated grade 1.
The reporter considered "iron deficiency" not related to bosutinib.

Follow-up (19Sep2023): This is a follow-up from a non-interventional study report received from the CRO.
Updated information included: patient's initials, reporter information.

Case Comment: Based on the information currently available, there was not a reasonable possibility that the event Iron deficiency was related to bosutinib, but most likely due to underlying condition.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06-OCT-2017	Serum ferritin	0.010 ug/ml	0.150 0.013

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1956	61 Years	Female	105.00 kg			2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

ERYSIPELAS [Erysipelas]
DENTAL DEGRADATION [Tooth disorder]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 300 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 28-OCT-2015 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#2) VALSARTAN (VALSARTAN) ; 09-OCT-2013 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Fibromyalgia (Fibromyalgia)
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018046638

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047.

A 61-year-old female patient received bosutinib (BOSULIF), since 28Oct2015 (ongoing) at 300 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: "Fibromyalgia" (ongoing); "Hypothyroidism" (ongoing); "Hypertension arterial" (ongoing). Concomitant medication(s) included: LEVOTHYROX oral taken for hypothyroidism (ongoing); VALSARTAN oral taken for hypertension, start date: 09Oct2013 (ongoing).
On an unspecified date in 2016, the subject experienced diarrhea rated grade 2 and considered non-serious. In Oct2017, the subject developed erysipelas, rated grade 2 and led to hospitalization. The subject received some unspecified antibiotics as corrective treatment. In 2017, the subject developed dental degradation, rated grade 2 and led to hospitalization. The subject underwent dental care under general anaesthesia as corrective treatment. Despite the events the study drug bosutinib was pursued unchanged. The action taken in response to the events for bosutinib was dose not changed. The subject recovered from the event diarrhea on 24May2016, from erysipelas in Oct2017 and from the event dental degradation on 22Jun2017.

The investigator considered the events erysipelas and dental degradation were unrelated to study drug bosutinib. The investigator considered this event diarrhea as related to bosutinib and unrelated to a concomitant drug.

Follow-up (07May2019): New information reported includes updated dose of bosutinib, new event (diarrhea), outcome, seriousness and assessment.

Follow-up (19Sep2023): This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter (Physician) for protocol B1871047; new information received from the investigator via the CRO. Updated information included: Patient's initials updated, Bosulif dose was updated to 300 mg once daily (previously 500 mg).

Case Comment: In agreement with the study investigator, the reported events of erysipelas and dental degradation are not related to the study drug. The events may possibly represent intercurrent medical conditions. This case will be reassessed upon receipt of follow-up information. Based on the information provided in the case, this individual report would not seem to modify the risk-benefit profile of the subject drug. Conversely, the Company cannot completely exclude the possible causality between the reported diarrhea and the administration of bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		JAN	1951	66 Years	Male	103.00 kg		APR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Iron deficiency [Iron deficiency]
Bone pain [Bone pain]
Cervical pain [Neck pain]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 22-OCT-2016 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ASPEGIC (ACETYLSALICYLATE LYSINE) ; 10-FEB-2016 / Ongoing
#2) COLECALCIFEROL (COLECALCIFEROL) ; 16-MAR-2015 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
24-SEP-2009 to Ongoing	Relevant Med History	Sleep apnea syndrome (Sleep apnoea syndrome)
Unknown to Ongoing	Relevant Med History	Benign prostatic hypertrophy (Benign prostatic hyperplasia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018088565

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
22-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 66-year-old male subject was receiving bosutinib (BOSULIF) ongoing since 22Oct2016 at 500 mg daily orally for chronic myeloid leukemia. The subject had medical history of sleep apnea syndrome ongoing since 24Sep2009, ongoing benign prostatic hypertrophy. Concomitant medications included acetylsalicylate lysine (ASPEGIC) ongoing since 10Feb2016 by oral route for vascular risks and colecalciferol (unspecified trade name) ongoing since 16Mar2015 by oral route for persistent deficiency. On an unspecified date in Apr2017, the subject developed diarrhea, rated grade 1 and non-serious. On 24Apr2018 the subject experienced iron deficiency; on 13Jun2018 the subject experienced bone pain and on an unspecified date in Apr2019 the subject experienced cervical pain. Investigator Initial Aware Date of Iron deficiency: 27Jun2018. Investigator Initial Aware Date of bone pain: 13Jun2018. Investigator Initial Aware Date of Diarrhea: 13Apr2017 (earliest event). Investigator Initial Aware Date of Cervical pain: 12Jun2019. The subject underwent the following laboratory tests and procedures: Haemoglobin (13-18): (unspecified date) Increased; (23Aug2018) 9.6 g/dl; Examination: (2019) negative. The action taken with bosutinib in response to the events was dose not changed. The clinical outcome of diarrhea was recovered on 09Aug2017; iron deficiency was recovered on 30Nov2018; bone pain was recovered on 27Aug2018, and cervical pain was recovered on 11Dec2019.

The reporter considered "diarrhea" related to bosutinib and unrelated to concomitant drugs. The reporter considered "iron deficiency", "bone pain" and "cervical pain" not related to bosutinib or to concomitant drugs.

Follow-up (08Jan2019): New information includes: additional event was reported: on 23Aug2018, the subject developed iron deficiency, rated grade 2 and not serious. On 23Aug2018, hemoglobin was 9.6 g/dl (normal range 13-18). No action was taken with study drug bosutinib. The subject received injections of iron (FERINJECT). Hemoglobin values progressively increased and the event was considered as resolving.

The investigator considered this event as unrelated to study drug and to concomitant medications.

Follow-up (22Feb2019): New information includes: additional event was reported: on 13Jun2018, the subject presented with bone pain which was considered as non-serious and rated as grade 1. Bone pain was described of mechanical origin. No action was taken with the study drug in response to the event. The subject recovered on 27Aug2018.

According to the investigator, the bone pain was not related to study drug or concomitant medication.

Follow-up (12Jul2019): New information received from the CRO includes: additional event was reported: in Apr2019, the subject presented with cervical pain which was considered as non-serious and rated as grade 1. Cervical pain were described as fluctuating, non permanent, associated with pain on the foot, which examination remained negative. No action was taken with the study drug in response to the event. The subject did not recover from the event cervical pain.

According to the investigator, the cervical pain was not related to study drug or concomitant medications.

Follow-up (29May2020): New information received from CRO: On 11Dec2019, the subject recovered from cervical pain.

Follow-up (14Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: reaction data (the event iron deficiency onset date updated to 24Apr2018 (previously reported as 23Aug2018), event outcome updated to recovered with stop date of 30Nov2018) and investigator initial awareness dates added for each event.

Follow-up (22Jun2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the Clinical team for protocol B1871047.
Updated information included: Iron deficiency (23Aug2018) was removed from medical history.

Case Comment: Based on the reasonable temporal association, considering the reported diarrhea is consistent with the known safety profile of bosutinib, and lacking alternative explanations, the Company cannot completely exclude the possible causality between the reported event and bosutinib administration. The company concurs with the investigator that the events iron deficiency, bone pain and cervical pain are unrelated to bosutinib. The events most likely represent intercurrent conditions.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Haemoglobin	Increased g/dl	18 13
2	23-AUG-2018	Haemoglobin	9.6 g/dl	18 13
3	2019	Physical examination Negative	negative	

Mfr. Control Number: 2018088565

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		DEC	1957	59 Years	Male	84.00 kg		AUG	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Nausea [Nausea]
Actinic keratosis [Actinic keratosis]
Eczema [Eczema]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 23-AUG-2017 / Unknown

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ASPEGIC [ACETYLSALICYLIC ACID] (ACETYLSALICYLIC ACID) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
APR-2017 to Ongoing	Relevant Med History	Dyspnea (Dyspnoea)
Unknown	Relevant Med History	Erectile dysfunction (Erectile dysfunction)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018092375

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-FEB-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047, reporting non-serious events only.

A 59-year-old male subject started to receive bosutinib (BOSULIF) oral from 23Aug2017 to an unspecified date at 500 mg, 1x/day, oral from 11Oct2018 to an unspecified date at 200 mg, 1x/day, oral from an unspecified date to an unspecified date at 300 mg, 1x/day, oral from 29Nov2018 to 09Dec2018 at 400 mg, 1x/day for chronic myeloid leukaemia. The subject medical history included dyspnea ongoing since Apr2017. The subject did not receive any concomitant medication. On an unspecified date in Aug2017, the subject developed diarrhea, rated grade 1 and non-serious. The subject also experienced actinic keratosis on 22Nov2017, rated grade 2 and non-serious. The subject received racecadotril (TIORFAN) and loperamide (trade name unspecified) by oral route ongoing since 08Nov2018 for gastrointestinal disorder. On 08Dec2018, the subject was found to have non-serious hepatotoxicity rated grade 3 with aspartate aminotransferase at 231 IU/l (normal range: 0 - 35 IU/l) and alanine aminotransferase at 465 IU/l (normal range: 0 - 35 IU/l) and non-serious thrombocytopenia rate grade 1. As a result of the events, bosutinib was permanently withdrawn on 09Dec2018. The subject was not recovered from the event hepatotoxicity and the final outcome of thrombocytopenia was unknown. The subject was recovering from other events.

The investigator considered event diarrhea, hepatotoxicity and thrombocytopenia were related with study drug bosutinib and event actinic keratosis was unrelated with study drug bosutinib.

Follow-up (13Dec2018): Newinformation received from investigational site includes: dosage and action taken of bosutinib, new events (hepatotoxicity, thrombocytopenia), lab data, seriousness criteria, causality assessment, outcome of the events.

Follow-up (21Feb2019): follow-up attempts completed. No further information expected.

Follow-up (22Feb2019): New information includes Medical history also included: erectile dysfunction, dyslipidemia, migraine and pleural effusion from 27Apr2017 to 06May2017.
Concomitant drug included acetylsalicylic acid (ASPEGIC) by oral route ongoing for cardiovascular risk prevention. On 07Jun2018, the subject experienced eczema, rated grade 2 and reported as non-serious. In response to the event, no action was taken with bosutinib. The event resolved in Jun2018. In 2019, the subject developed nausea, rated grade 1 and reported as non-serious. The subject complained of some grade 1 nausea when taking bosutinib. In response to the event, no action was taken with bosutinib. At reporting time, the event was resolving.

According to the reporter, the event eczema was unrelated to bosutinib and to concomitant drugs.
According to the reporter, the event nausea was related to bosutinib and unrelated to concomitant drugs.

Follow-up (04Mar2019 and 05Mar2019): New information received from the investigator via study coordinator includes: Events hepatotoxicity rated grade 3 and thrombocytopenia rate grade 1 should be deleted as they were reported by error. It was confirmed that hepatotoxicity rated grade 3 and thrombocytopenia rate grade 1 alongside with information reported with these events were reported by error as they concerned another subject: bosutinib dose at 200 1x/day, at 300 mg 1x/day and at 400 mg 1x/day were deleted, laboratory data were deleted. Racecadotril (TIORFAN), loperamide should be deleted (to be confirmed).

Follow-up (07Mar2019). New information includes: it was confirmed that racecadotril (TIORFAN), loperamide and bosutinib dose at 200 1x/day, at 300 mg 1x/day and at 400 mg 1x/day should be deleted.

Follow-up (25May2020): New information received from investigational site includes that patient recovered from nausea on 20Nov2019.

Follow-up (14Feb2023): New information received from CRO stated that the patient recovered from 'diarrhea' on 06Feb2019 and from 'actinic keratosis' resolved on 28Feb2018.

Case Comment: Based on the known drug safety profile and temporal association, the Company concurs with the reporter that there is a reasonable possibility of the causal association between the events, diarrhea and nausea, and the suspect drug, bosutinib. The events eczema and actinic keratosis are most likely intercurrent conditions and assessed as unrelated to bosutinib.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Dyslipidemia (Dyslipidaemia);
Unknown	Relevant Med History	Migraine (Migraine);
27-APR-2017 to 06-MAY-2017	Relevant Med History	Pleural effusion (Pleural effusion);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1950	67 Years	Male	66.00 kg	07	SEP	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

worsening of angina [Angina pectoris]
Hypochondrium pain right [Abdominal pain upper]
worsening of pleural effusion [Pleural effusion]
worsening of pleural effusion [Condition aggravated]
abdominal pain [Abdominal pain]
Diffuse articular and muscular pain [Arthralgia]
Diffuse articular and muscular pain [Myalgia]
mood disorder [Affective disorder]
gait instability [Gait disturbance]
diarrhea [Diarrhoea]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) PLAVIX (CLOPIDOGREL BISULFATE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, 1x/day	#1) Oral
#2) 75 mg, 1x/day	#2) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) coronary insufficiency with multiple stent i
(Continued on Additional Information Page)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 01-SEP-2017 / 08-SEP-2017	#1) 8 days
#2) Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TENORMINE (ATENOLOL) ; Ongoing
#2) AMLODIPINE (AMLODIPINE) ; Ongoing
#3) ROSUVASTATIN (ROSUVASTATIN) ; Ongoing
#4) EZETIMIBE (EZETIMIBE) ; 28-MAR-2017 / Ongoing
#5) CORVASAL [MOLSIDOMINE] (MOLSIDOMINE) Tablet ; Ongoing
#6) FUROSEMIDE (FUROSEMIDE) ; Ongoing
(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Ischemic heart disease (Myocardial ischaemia)
Unknown to Ongoing	Relevant Med History	Raynaud's syndrome (Raynaud's phenomenon)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018129398

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
28-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

skin rash [Rash]
gingivorrhagia [Gingival bleeding]
exertional breathlessness [Dyspnoea]
vertigo [Vertigo]
hepatic cytolysis [Hepatic cytolysis]
skull eruption [Rash]
concentration disorder [Disturbance in attention]
hypersomnia [Hypersomnia]
asthenia [Asthenia]
skin dryness [Dry skin]
lumbalgia [Back pain]
asthenia [Asthenia]
Abdominal bloating [Abdominal distension]
ZONA [Herpes zoster]
exertional breathlessness [Dyspnoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 67-year-old male patient received bosutinib (BOSULIF), first regimen from 01Sep2017 to 08Sep2017 at 300 mg 1x/day, second regimen since 11Sep2017 at 300 mg daily, third regimen since Nov2017 at 200 mg 1x/day (200 mg, 1x/day (some days)), fourth regimen from 29Jan2018 to 26Feb2018 at 100 mg 2x/day and fifth regimen since 20Mar2018 at 100 mg 1x/day, all oral for chronic myeloid leukaemia; clopidogrel bisulfate (PLAVIX), (ongoing) (Batch/Lot number: unknown) at 75 mg 1x/day, oral for coronary artery insufficiency; acetylsalicylate lysine (KARDEGIC), (ongoing) (Batch/Lot number: unknown) at 75 mg 1x/day, oral for coronary artery insufficiency. The patient's relevant medical history included: "Ischemic heart disease" (ongoing); "Raynaud's syndrome" (ongoing); "Pleural effusion" (ongoing). Concomitant medication(s) included: TENORMINE oral taken for myocardial ischaemia (ongoing); AMLODIPINE oral taken for myocardial ischaemia (ongoing); ROSUVASTATIN oral taken for myocardial ischaemia (ongoing); EZETIMIBE oral taken for myocardial ischaemia, start date: 28Mar2017 (ongoing); CORVASAL [MOLSIDOMINE] (ongoing); FUROSEMIDE (ongoing); PANTOPRAZOLE (ongoing); TAHOR; PREGABALINE. On 07Sep2017, the subject developed diffuse articular and muscular pain, mood disorder, gait instability, diarrhea, skin rash, gingivorrhagia, exertional breathlessness and vertigo. In particular the event diffuse articular and muscular pain was described as: articular and muscular pain of right arm, lefty elbow and cruralgia. Gait instability, diarrhea, skin rash and gingivorrhagia were assessed as grade 1. Diffuse articular and muscular pain, breathlessness and vertigo were both assessed as non-serious and grade 1. In response to skin rash, bosutinib was interrupted from 08Sep2017 to 10Sep2017. Bosutinib was resumed on 11Sep2017. In response to the event diffuse articular and muscular pain bosutinib was dose reduced. No action was taken with bosutinib in response to mood disorder, gait instability, diarrhea, gingivorrhagia, breathlessness and vertigo. On 17Nov2017, the subject developed hepatic cytolysis assessed as grade 1. No action was taken with bosutinib in response to hepatic cytolysis. On 29Nov2017, the subject experienced skull eruption and concentration disorder, both assessed as non-serious and grade 1. In Nov2017, the subject decreased himself some days the dose of bosutinib to 200 mg once daily due to diffuse pains, concentration disorder and skull eruption. On 02Jan2018 hepatic cytolysis became grade 2. On 29Jan2018, the subject also experienced asthenia, rated as grade 1. In response to asthenia, dose of bosutinib was modified to 100 mg twice daily from 29Jan2018 to 26Feb2018. The event did not recovered. On 26Feb2018, the subject experienced worsening of pleural effusion (at right hypochondre level) grade 2, abdominal pain rated as grade 1 and hypersomnia, rated as grade 1. In response to the worsening of pleural effusion, bosutinib was temporarily withdrawn from 27Feb2018 (last dose 26Feb2018) to 19Mar2018, and was then resumed on 20Mar2018 at 100 mg once daily. Previous treatment was withdrawn due to pleural effusion. Pleural effusion reoccurred after introduction of bosutinib. No action was taken with bosutinib in response to abdominal pain and hypersomnia. On 19Mar2018, the subject experienced skin dryness which was reported as non-serious. In response to the event, dose of bosutinib was not changed. In Mar2018, the subject experienced lumbalgia which was reported as non-serious. In response to the event, dose of bosutinib was not changed. On 15Jun2018, the subject experienced exertional breathlessness, assessed as non-serious. No action was taken with bosutinib in response to exertional breathlessness. Lab data on 06Feb2018 was at follows: red blood cells at 4.69 x10^12/L (normal range 4.28 - 5.57), hemoglobin at 13.9 g/dL (normal range 13.4 -16.7), hematocrit at 43.6 % (normal range 39.2 -48.6), mean corpuscular volume at 93 um3 (normal range 82.1 -97), mean corpuscular hemoglobin at 29.6 pg (normal range 27.3 -32.8), mean corpuscular hemoglobin concentration at 31.9 g/dL (normal range 32.4 -36.3), leucocytes at 6.6 x10^9/L (normal range 4.1 -10.0), neutrophils at 3.21 x10^9/L (normal range 1.8 -6.1), eosinophils at 0.09 x10^9/L (normal range 0.05 -0.58), basophils at 0.05 x10^9/L (normal range lower than 0.09), lymphocytes at 2.47 x10^9/L (normal range 1.2 -3.6), monocytes at 0.77 x10^9/L (0.23 -0.73), platelets at 143 x10^9/L (normal range 161 -393), AST at 79 IU/L (normal range 0 -34), ALT at 141 IU/L (normal range 0 -40), alkaline phosphatase at 75 IU/L (normal range 45 -129), total bilirubin at 7.3 umol/L (normal range 5 -21), calcium at 2.4 mmol/L (normal range 2.14 -2.5), phosphorus at 1.09 mmol/L (normal range 0.78 -1.65), C-reactive protein at 1.5 mg/L (normal range lower than 5.0), urea at 10.2 mmol/L (normal range 3.2 -8.2), creatinine at 90 umol/L (53 -97), glomerular filtration rate at 74 ml/min, sodium at 141 mmol/L (normal range 135 -145), potassium at 4.6 mmol/L (normal range 3.5 -4.5). Other lab test found AST 37UI/L (N 10-50) and ALT 41 IU/L (N 10-50) on 12May2017; AST 32 IU/L (N 0-34), ALT 34 IU/L (N 0-40), alkaline phosphatase 91 IU/L (N 45-129) and bilirubin total 6.6 umol/l (N 5-21) on 02Nov2017; AST 40 IU/L (N 0-34), ALT 55IU/L (N 0-40), alkaline

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

phosphatase 84 IU/L (N 45-129) and bilirubin total 9.7 umol/l (N 5-21) on 17Nov2017; AST 50 IU/L (N 0-34), ALT 68 IU/L (N 0-40), alkaline phosphatase 85 IU/L (N 45-129) and bilirubin total 8.1 umol/l (N 5-21) on 27Nov2017; AST 81 IU/L (N 0-34), ALT 165 IU/L (N 0-40), alkaline phosphatase 74 IU/L (N 45-129) and bilirubin total 7.2 umol/l (N 5-21) on 02Jan2018; AST 31 IU/, ALT 31IU/L, Gamma GT 26IU/L and alkaline phosphatase 45IU/L, test done on unspecified date and results received on 19Mar2018. According to the investigator, ALT and AST increased should not be reported as additional events as they were already reported under the event hepatic cytolysis. On 13Sep2018, the subject experienced asthenia considered non-serious and was rated grade 2. In response to the event, bosutinib dose at 100 mg daily was not changed. On 21Jan2019, the subject developed abdominal bloating rated grade 1 and assessed as non-serious. No action was taken with bosutinib in response to this event. In May2019, the subject developed zona assessed as non-serious and rated grade 2. No action was taken with bosutinib in response to zona. Corrective treatment consisted in valaciclovir (unspecified trade name) for 8 days. At the time of the report, zona was resolved on 18May2020. On 27Jul2019, the subject experienced worsening of angina, grade 3 for which the patient presented to emergency room on 06Aug2019 for worsening of angina pain. Coronarography was planned but the date was not provided. There were dilatation and stent placement in Aug2019. The subject was then hospitalized from 06Nov2019 to 12Nov2019 for coronary bypass.No action was taken with bosutinib in response to the event worsening of angina.On 19Jan2020, the subject experienced hypochondrium pain right rated non-serious and grade 1. Coronary angiography on 21Feb2020 with complementary angioplasty on 28Feb2020 stenting x2 of the second marginal and of the saphenous vein on its proximal segment, complete revascularization angina pain at the slightest effort always present, in spite of increase of the corvasal, on 21Aug2020, an attack of the microcirculation could explain its pains. Investigator Initial Aware Date (Exertional breathlessness): 15Jun2018. Investigator Initial Aware Date (Abdominal bloating): 24Jan2019. The action taken for clopidogrel bisulfate and acetylsalicylate lysine was unknown. The action taken for bosutinib was Permanently Withdrawn. Therapeutic measures were taken as a result of angina pectoris, herpes zoster. Skin rash resolved on 10Sep2017, gingivorrhagia resolved on 21Sep2017, exertional breathlessness (onset date 07Sep2017) and vertigo and mood disorder resolved on 19Oct2017. Skin rash did not recur when bosutinib was resumed. On 29Jan2018, the subject had fully recovered from skull eruption and concentration disorder. On 21Jan2019 the patient recovered from diffuse articular and muscular pain. On 11Sep2018 the patient recovered from the worsening of pleural effusion. At the time of the report, the subject had not recovered yet from abdominal pain and exertional breathlessness (onset date 15Jun2018), worsening of angina, Asthenia (onset 29Jan2018). The event Herpes zoster recovered on 18May2020. The subject recovered from hepatic cytolysis on 19Mar2018, from abdominal bloating on 24Sep2019 and from asthenia (onset 13Sep2018) on 24Sep2019. The subject recovered from hypochondrium pain right on 21Sep2020. Skin dryness resolved on 15Jun2018. Lumbalgia resolved on 21Jan2019, hypersomnia recovered on 19Mar2018. The event diarrhea and gait instability were resolved on 29Jan2018.

The investigator assessed all the events as non-serious except for worsening of angina (hospitalization).
The investigator assessed all the events (except exertional breathlessness (onset date 15Jun2018), asthenia (onset date 13Sep2018), abdominal bloating, zona, lumbalgia, worsening of angina) were related to bosutinib and unrelated to a concomitant medication.
The investigator assessed that the event gingivorrhagia was related to bosutinib and to concomitant clopidogrel bisulfate and acetylsalicylate lysine.
The investigator considered that there was not a reasonable possibility that the events (asthenia (onset date 13Sep2018), exertional breathlessness (onset date 15Jun2018), abdominal bloating) was related to the study drug or to a concomitant drug.
The investigator assessed the event zona as neither related to bosutinib nor to concomitant medications.
According to the investigator event diffuse articular and muscular pain, and hypochondrium pain right were related to bosutininb and unrelated to concomitant drug.
The investigator assessed the event worsening of angina as unrelated to both bosutinib and concomitant medications.
According to the reporter, the lumbalgia was considered as unrelated to study drug bosutinib but not related to concomitant medications.

Follow-up (06Apr2018): New information received from investigational site is as follows: drug data and lab data.
Follow-up (11Jun2018): New information received from investigational site includes: Reaction data (ALT and AST increased should not be reported as additional events).
Follow-up (26Jun2018): New information received from CRO includes: action taken updated, new events skin dryness and right lumbalgia added.
Follow-up (09Aug2018 and 14Aug2018): New information received includes additional events (exertional breathlessness (onset date 07Sep2017), vertigo, skull eruption, concentration disorder, and exertional breathlessness (onset date 15Jun2018), and causality assessment for the event right lumbalgia.
Follow-up (17Aug2018): New information received included: Dosage regimen of bosutinib updated.
Follow-up (05Oct2018): Follow-up attempts are completed. No further information is expected.
Follow-up (14Nov2018): New information received from the investigational site via the CRO includes: new event (asthenia).
Follow-up (07Dec2018): New information received the investigational site included investigator's assessment for the event exertional breathlessness with onset date 15Jun2018. (previously unknown) and update on outcome still not recovered.
Follow-up (25Jan2019): New information received included concomitant drug details, stop date of Clopidogrel and acetylsalicylate lysine (both ongoing), new event (abdominal meteorism).
Follow-up (29Jan2019): New information received from the investigational site includes: causality for event abdominal meteorism (reported as unrelated).
Follow-up (31May2019): New information received from the investigator via the CRO included medical history updated (Raynaud's syndrome was no more reported as ongoing), added new event zona.
Follow-up (30Aug2019). New information provided by the investigational site via CRO includes: Subject's height was added. Medical history Raynaud's syndrome was updated to ingoing. Event verbatim "upper limb joint pain" was updated to "Diffuse articular and muscular pain". Grading, reporter's seriousness and causality assessment, onset date, and recovery date, description, and action

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

taken with suspect product for event 'Event diffuse articular and muscular pain', provided. Grading, description and recovery date for previously reported event 'worsening of pleural effusion', provided. New event of 'worsening of angina' along with grading, description, onset date, action taken and seriousness assessment, provided.
Follow-up (10Sep2019): New information received from the CRO includes: study drug bosutinib 100 mg daily was administered from 20Mar2019 and ongoing (instead of 20Mar2018 and ongoing as previously reported). The investigator assessed the event worsening of angina as unrelated to both bosutinib and concomitant medications (causality previously missing).
Follow-up attempt completed. No further information expected.
Follow-up (24Jan2020). New information received from CRO includes updated seriousness for the event worsening of angina (from non-serious to serious as per hospitalization), therapeutic measures taken for worsening angina, and new event (hypochondrium pain right). Case upgraded to serious.
Follow-up (19May2020). New information received from the investigational site via the CRO includes: updated the outcome of the event zona (from resolving to resolved on 18May2020). Additionally, updated the last action taken for bosutinib from dose reduced to dose not changed.
Follow-up attempt completed. No further information expected.
Follow-up (26May2020): New information received from the investigational site via the CRO includes: event verbatim "abdominal meteorism" amended to "abdominal bloating" and outcome of abdominal bloating and asthenia (onset 13Sep2018).
Follow-up (05Oct2020): New information received from the investigational site via CRO includes: outcome of event hypochondrium pain right was updated to "recovered on 21Sep2020" (previously not recovered).
Follow-up (12Nov2020): New information received from the study coordinator included: lab data, concomitant medications.
Follow-up (23Mar2021): New information received from the study site includes: additional concomitant drug (pregabalin), outcome of event skin dryness updated to resolved on 15Jun2018, recovery date of asthenia (13Sep2018) was updated to 24Sep2019, event term updated from "right lumbalgia" to "lumbalgia" with outcome of it updated to resolved on 21Jan2019, onset date of worsening of angina occurred updated to 27Jul2019, causality of lumbalgia between bosutinib was updated to not related (previously related). Causality of event zona was previously reported as unrelated and updated in this version.
Follow-up (06Dec2022): This is a follow-up for a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. Updated information included: lab data added (Coronary angiography on 21Feb2020), treatment of angina updated and clinical course details added.

Follow-up (04Oct2023): New information received from the investigator via the CRO. Updated information: Patient's initials updated, suspect drug data, event information (outcome and grade).

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from clinical team following reconciliation between clinical and safety databases.

Updated information includes: the event hepatic cytolysis became grade 2 on 02Jan2018 and outcome updated (from not recovered to resolved on 19Mar2018), updated outcome for diarrhea (from not recovered to recovered on 29Jan2018) and updated recovery date for gait instability (from 19Oct2017 to 29Jan2018).

Follow-up (28Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: In response to hypochondrium pain right, bosutinib was discontinued.
Follow-up attempts are completed. No further information is expected.

Case Comment: The event worsening of angina is assessed as unrelated to bosutinib but attributed to the pre-existing condition of ischemic heart disease. The Company cannot completely exclude the possible causality between the other reported events and the administration of the study drug, bosutinib. Underlying chronic myeloid leukemia, co-morbidities and polypharmacy may provide alternate explanation for the development of these events.
The follow up information does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12-MAY-2017	Alanine aminotransferase	41	50 10
2	02-NOV-2017	Alanine aminotransferase	34 IU/l	40 0
3	17-NOV-2017	Alanine aminotransferase	55 IU/l	40 0
4	27-NOV-2017	Alanine aminotransferase	68 IU/l	40 0
5	02-JAN-2018	Alanine aminotransferase	165 IU/l	40 0
6	06-FEB-2018	Alanine aminotransferase	141 IU/l	40 0

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
7	MAR-2018	Alanine aminotransferase	31	
8	21-FEB-2020	Angiocardiogram not specified results.	performed	
9	12-MAY-2017	Aspartate aminotransferase	37 IU/l	50 10
10	02-NOV-2017	Aspartate aminotransferase	32 IU/l	34 0
11	17-NOV-2017	Aspartate aminotransferase	40 IU/l	34 0
12	27-NOV-2017	Aspartate aminotransferase	50 IU/l	34 0
13	02-JAN-2018	Aspartate aminotransferase	81 IU/l	34 0
14	06-FEB-2018	Aspartate aminotransferase	79 IU/l	34 0
15	MAR-2018	Aspartate aminotransferase	31	
16	06-FEB-2018	Basophil count	0.05 x10 9/l	0.09
17	02-NOV-2017	Blood alkaline phosphatase	91 IU/l	129 45
18	17-NOV-2017	Blood alkaline phosphatase	84 IU/l	129 45
19	27-NOV-2017	Blood alkaline phosphatase	85 IU/l	129 45
20	02-JAN-2018	Blood alkaline phosphatase	74 IU/l	129 45
21	06-FEB-2018	Blood alkaline phosphatase	75 IU/l	129 45
22	MAR-2018	Blood alkaline phosphatase	45	
23	02-NOV-2017	Blood bilirubin	6.6 umol/l	21 5
24	17-NOV-2017	Blood bilirubin	9.7 umol/l	21 5
25	27-NOV-2017	Blood bilirubin	8.1 umol/l	21 5
26	02-JAN-2018	Blood bilirubin	7.2 umol/l	21 5
27	06-FEB-2018	Blood bilirubin	7.3 umol/l	21 5
28	06-FEB-2018	Blood calcium	2.4 mmol/L	2.5 2.14
29	06-FEB-2018	Blood creatinine	90 umol/l	97 53
30	06-FEB-2018	Blood phosphorus	1.09 mmol/L	1.65 0.78
31	06-FEB-2018	Blood potassium	4.6 mmol/L	4.5 3.5

Mfr. Control Number: 2018129398

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
32	06-FEB-2018	Blood sodium	141 mmol/L	145 135
33	06-FEB-2018	Blood urea	10.2 mmol/L	8.2 3.2
34	06-FEB-2018	C-reactive protein	1.5 mg/l	5
35	06-FEB-2018	Eosinophil count	0.09 x10 9/l	0.58 0.05
36	MAR-2018	Gamma-glutamyltransferase	26	
37	06-FEB-2018	Glomerular filtration rate	74 ml/min	
38	06-FEB-2018	Haematocrit	43.6 %	48.6 39.2
39	06-FEB-2018	Haemoglobin	13.9 g/dl	16.7 13.4
40	06-FEB-2018	Lymphocyte count	2.47 x10 9/l	3.6 1.2
41	06-FEB-2018	Mean cell haemoglobin	29.6 pg	32.8 27.3
42	06-FEB-2018	Mean cell haemoglobin concentration	31.9 g/dl	36.3 32.4
43	06-FEB-2018	Mean cell volume	93 um3	97 82.1
44	06-FEB-2018	Monocyte count	0.77 x10 9/l	0.73 0.23
45	06-FEB-2018	Neutrophil count	3.21 x10 9/l	6.1 1.8
46	06-FEB-2018	Platelet count	143 x10 9/l	393 161
47	06-FEB-2018	Red blood cell count	4.69 x10 12/l	5.57 4.28
48	06-FEB-2018	White blood cell count	6.6 x10 9/l	10.0 4.1

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	11-SEP-2017 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, 1x/day (some days); Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	NOV-2017 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	100 mg, 2x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	29-JAN-2018 / 26-FEB-2018; 29 days
#1) Bosulif (BOSUTINIB) Film-coated tablet;	100 mg, 1x/day; Oral	chronic myeloid leukemia	20-MAR-2018 /

Mfr. Control Number: 2018129398

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #5		(Chronic myeloid leukaemia)	Unknown; Unknown
#2) PLAVIX (CLOPIDOGREL BISULFATE) ; Regimen #1	75 mg, 1x/day; Oral	coronary insufficiency with multiple stent insertion (Coronary artery insufficiency)	Ongoing; Unknown
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Regimen #1	75 mg, 1x/day; Oral	coronary insufficiency with multiple stent insertion (Coronary artery insufficiency)	Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) PANTOPRAZOLE (PANTOPRAZOLE) ; Ongoing

#8) TAHOR (ATORVASTATIN CALCIUM) ; Unknown

#9) PREGABALINE (PREGABALINE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Pleural effusion (Pleural effusion);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1945	72 Years	Male	88.00 kg	29	MAR	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

diarrhea [Diarrhoea]
crepitant of two bases pulmonary [Rales]
Lower limb edema [Oedema peripheral]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP)

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 15-MAR-2017 / 28-MAR-2017	#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 25-JAN-2005 / Ongoing
#2) PANTOPRAZOLE (PANTOPRAZOLE) ; 02-OCT-2014 / Ongoing
#3) LANTUS (INSULIN GLARGINE) ; 02-OCT-2017 / Ongoing
#4) DIAMICRON (GLICLAZIDE) ; 02-OCT-2014 / Ongoing
#5) EUCREAS (METFORMIN HYDROCHLORIDE, VILDAGLIPTIN) ; 24

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
Unknown to Ongoing	Relevant Med History	Arterial disorder (Arterial disorder)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018158204

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
26-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

for protocol B1871047.

A 72-year-old male patient received bosutinib (BOSULIF), first regimen from 15Mar2017 to 28Mar2017 at 100 mg 1x/day, second regimen from 29Mar2017 to Apr2017 at 200 mg and third regimen since Apr2017 (ongoing) at 100 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: "Diabetes" (ongoing); "Arterial disease" (ongoing); "Chronic myeloid leukemia" (ongoing); "Sequelae of cerebrovascular accident", start date: 1979 (ongoing). Concomitant medication(s) included: KARDEGIC taken for prophylaxis, start date: 25Jan2005 (ongoing); PANTOPRAZOLE taken for gastrooesophageal reflux disease, start date: 02Oct2014 (ongoing); LANTUS taken for diabetes mellitus, start date: 02Oct2017 (ongoing); DIAMICRON taken for diabetes mellitus, start date: 02Oct2014 (ongoing); EUCREAS taken for diabetes mellitus, start date: 24Feb2017, stop date: Apr2017. On 29Mar2017, the subject experienced diarrhea since the intake of bosutinib at 200 mg. The event was assessed as non-serious and grade 1. As a result, the action taken in response to the event was dose of bosutinib was reduced to 100 mg. Resolution of the event diarrhea ensued on Apr2017. On 08Nov2018 the subject experienced crepitant of two bases pulmonary, grade 1 and lower limb edema, grade 1, both assessed as non-serious. Investigator awareness date for events was the day of consultation. No action was taken with study drug in response to the events. The outcome of event crepitant of two bases pulmonary was resolved on 20Jul2020, the outcome of event lower limb edema was resolved on 20Jul2020.

The investigator considered there was a reasonable possibility that the event diarrhea was related to bosutinib and not related to a concomitant medication.
According to the investigator, the events crepitant of two bases pulmonary, grade 1 and lower limb edema, grade 1 were not related to study drug or to concomitant treatment.

Follow-up (20Apr2018): New information received from the investigational site includes dose regimen, start date, concomitant medication.

Follow-up (29Nov2018): New information received from the investigator via CRO includes: medical history, and new events (crepitant of two bases pulmonary, grade 1 and lower limb edema, grade 1).

Follow-up (08Feb2023): This a follow-up report from the investigator via CRO. Updated information included: patient information (height) and event details (start and stop date of the event diarrhea) updated.

Follow-up (10Feb2023): This a follow-up report from the investigator via CRO. Updated information included: reaction data (outcome for event "crepitant of two bases pulmonary" updated from not resolved to resolved on 20Jul2020).

No follow-up attempt are initiated. No further information expected.

Follow-up (22May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information included: Outcome of event lower limb edema was updated to resolved on 20Jul2020 (previously not recovered), action taken updated to "dose not changed" (previously dose reduced).

Follow-up (26Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information included: bosutinib dosage regimens; new medical history, updated action taken.

Case Comment: Based on the temporal association and known product safety profile, there is a reasonable possibility that the event diarrhea was related to bosutinib.
The Company concurs with the investigator that the events crepitant of two bases, pulmonary and lower limb edema are unrelated to bosutinib. These most likely represent intercurrent conditions.
The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	29-MAR-2017 / APR-2017; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet;	100 mg, 1x/day; Unknown	Chronic myeloid leukemia	APR-2017 / Ongoing;

Mfr. Control Number: 2018158204

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #3		(Chronic myeloid leukaemia)	Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#5) EUCREAS (METFORMIN HYDROCHLORIDE, VILDAGLIPTIN) ; 24-FEB-2017 / APR-2017

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);
1979 to Ongoing	Relevant Med History	Cerebrovascular accident (Cerebrovascular accident);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		MAY	1939	78 Years	Female	63.00 kg	02	JAN	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

bronchitis [Bronchitis]
Staged lumbar discopathy grade 2 [Intervertebral disc disorder]
non-febrile gastroenteritis [Gastroenteritis]
non-febrile rhinopharyngitis [Nasopharyngitis]
Posterior inter-apophyseal arthrosis grade 2 [Spinal osteoarthritis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) CML (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 09-FEB-2017 / 15-FEB-2017	#1) 7 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
JUL-2009 to JUL-2009	Relevant Med History	Thyroidectomy (Thyroidectomy)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018202535

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
17-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 78-year-old female patient received bosutinib (BOSULIF), first regimen from 09Feb2017 to 15Feb2017 at 100 mg daily, second regimen from 16Feb2017 to 22Feb2017 at 200 mg daily, third regimen from 23Feb2017 to 16Mar2017 at 300 mg daily, fourth regimen from 17Mar2017 to 15Feb2018 at 400 mg daily, oral and fifth regimen since 29Jun2018 (ongoing) at 400 mg daily, oral for chronic myeloid leukaemia. The patient's relevant medical history included: "THYROIDECTOMY", start date: Jul2009, stop date: Jul2009. The patient's concomitant medications were not reported.
The following information was reported: BRONCHITIS (non-serious) with onset 02Jan2018, outcome "recovered" (07Jan2018); INTERVERTEBRAL DISC DISORDER (non-serious) with onset 01Dec2018, outcome "not recovered", described as "Staged lumbar discopathy grade 2"; SPINAL OSTEOARTHRITIS (non-serious) with onset 14Dec2018, outcome "not recovered", described as "Posterior inter-apophyseal arthrosis grade 2"; GASTROENTERITIS (non-serious) with onset 13Oct2019, outcome "recovered" (15Oct2019), described as "non-febrile gastroenteritis"; NASOPHARYNGITIS (non-serious) with onset 02Dec2019, outcome "recovered" (07Dec2019), described as "non-febrile rhinopharyngitis". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of intervertebral disc disorder, spinal osteoarthritis included NSAIDs started in Dec2018 + analgesics.

Additional information: On 02Jan2018, the patient experienced bronchitis rated grade 2 and on 01Dec2018 she experienced left sciatic pain, CTCAE grade 1, both considered non serious. On 13Oct2019, the patient developed non-febrile gastroenteritis reported as non-serious and rated grade 1. Non-febrile gastroenteritis resolved on 15Oct2019.
On 02Dec2019, the patient developed non-febrile rhinopharyngitis reported as non-serious and rated grade 1. As of 17Jul2023, it was reported that sciatic pain reported by the patient during the consultation of 01Dec2018 leading to the realization of X-ray for assessment of cruralgia. Diagnostic: Staged lumbar discopathy + Inter-APophyseal posterior osteoarthritis. Treatment with NSAIDs started in Dec2018 + analgesics.

The reporter considered "bronchitis", "staged lumbar discopathy grade 2", "non-febrile gastroenteritis", "non-febrile rhinopharyngitis" and "posterior inter-apophyseal arthrosis grade 2" not related to bosutinib.

Follow-up (23May2018): additional information received from the investigational site was as follows: The subject received the study drug bosutinib via oral route for CML (chronic myeloid leukemia).

Follow-up (01Feb2019): New information received from CRO includes new event (sciatic pain) and additional dates of administration and dose for bosutinib.

Follow-up (03May2019): follow-up attempts completed. No further information expected.

Follow-up (22Jul2019): This is a follow-up report from a Non-Interventional Study source, received from the investigational site via the CRO, additional information was as follows: outcome of event left sciatic pain (updated to not recovered).

No FU attempts possible. No further information expected.

Follow-up (01Oct2019): New information received from investigational site included outcome of event left sciatic pain updated to resolved.

Follow-up (03Dec2019): New information received from the investigator included: Outcome for previously reported event 'left sciatic pain' updated and recovery date provided.

Follow-up (06Jan2020): New information received from CRO included new events non-febrile gastroenteritis and non-febrile rhinopharyngitis

Follow-up (17Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: suspect product data (new dose regimen), reaction data (outcome of event "non-febrile rhinopharyngitis", "left sciatic pain" was updated to "staged lumbar discopathy", new event "posterior inter-apophyser arthrosis", event treatment), lab data.

Case Comment: In concurrence with the investigator the reported bronchitis, sciatic pain, arthrosis gastroenteritis and nasopharyngitis are considered unrelated to bosutinib administration. The events are deemed intercurrent medical conditions.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		X-ray	lumbar discopathy + inter-apophyseal arthrosis	

Mfr. Control Number: 2018202535

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
		Staged lumbar discopathy + Posterior inter-apophyseal arthrosis		

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	16-FEB-2017 / 22-FEB-2017; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	23-FEB-2017 / 16-MAR-2017; 22 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	CML (Chronic myeloid leukaemia)	17-MAR-2017 / 15-FEB-2018; 10 months 30 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	400 mg, daily; Oral	CML (Chronic myeloid leukaemia)	29-JUN-2018 / Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1930	88 Years	Male	88.00 kg	13	MAR	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

The 4th right toe osteoarthritis [Osteoarthritis]
obliterant arteriopathy of lower limbs [Arterial occlusive disease]
ASTHENIA [Asthenia]
POLLAKIURIA [Pollakiuria]
anemia [Anaemia]
Bronchitis [Bronchitis]
Superinfection of the 4th right toe [Localised infection]
trophic disorders [Vascular skin disorder]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 13-MAR-2018 / 19-JUN-2018

19. THERAPY DURATION
#1) 99 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LASILIX (FUROSEMIDE) ; 01-OCT-2013 / Ongoing
#2) TAHOR (ATORVASTATIN CALCIUM) ; 01-OCT-2013 / Ongoing
#3) CLOPIDOGREL (CLOPIDOGREL) ; 01-OCT-2013 / Ongoing
#4) LANTUS (INSULIN GLARGINE) ; 01-OCT-2013 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
11-OCT-2010 to Unknown	Relevant Med History	Decompensation cardiac (Cardiac failure)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018226336

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
20-JAN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Study alias BOSEVAL. An 88-year-old male subject was treated with study drug bosutinib (BOSULIF, Film-coated tablet) from 13Mar2018 to 19Jun2018 at 100 mg daily, and from 20Jun2018 and ongoing at 100 mg alternate day for an unspecified indication. The subject had medical history of ongoing diabetes, cardiac decompensation from 11Oct2010 and unknown if ongoing, ongoing arteritis since 12Jun2012, and ongoing renal failure. Ongoing oral concomitant medications taken since 01Oct2013 included furosemide (LASILIX) for cardiac decompensation, atorvastatin calcium (TAHOR) for cardiac decompensation, clopidogrel for cardiac decompensation, and insulin glargine (LANTUS) for diabetes. On 15Mar2018, the subject experienced asthenia (grade 2) and pollakiuria (grade 1), which were assessed as non-serious. No action was taken with study drug in response to the pollakiuria however study drug dose was reduced at 100 mg alternate day from 20Jun2018 in response to the asthenia. On 19Apr2018, the subject developed bronchitis, rated grade 2 and non-serious. Laboratory data was not provided. Treatment received was not reported. On 17Sep2018, the subject experienced the 4th right toe osteoarthritis requiring hospitalization and assessed grade 3. The reported hospitalization date was from 20Sep2018 to 26Sep2018 for osteoarthritis of the 4th right toe. The subject was put under pristinamycin (PYOSTACINE) since 17Sep2018, then under amoxicillin/clavulanic acid (AUGMENTIN) from 20Sep2018. The subject experienced in Sep2019 superinfection of the 4th right toe reported as non-serious and rated grade 2. The germ was identified: Enterobacter cloacae and staphylococcus aureus. Amoxicillin/clavulanic acid was stopped in profit of sulfamethoxazole/ trimethoprim (BACTRIM) and ofloxacin (OFLOCET) on 26Sep2018 with premature stopping of one from them for intolerance. On 12Nov2018, C-reactive protein (CRP) was 249 mg/l. Hospitalization was performed in Oct2018 for leg angioplasty and interphalangeal amputation of the 4th toe. Hospitalization on 04Dec2018 for right transmetatarsal amputation. In response to the 4th right toe osteoarthritis, bosutinib was temporarily withdrawn. On 20Sep2018, the subject experienced obliterant arteriopathy of lower limbs requiring hospitalization / prolongation of hospitalization and assessed grade 3. No action was taken for bosutinib in response to the event obliterant arteriopathy of lower limbs. The subject developed anemia rated grade 2 on 05Jun2019. This event was reported as non-serious. In response to the event, no action was taken with study drug. The reporter stated: aggravation of pre-existing anemia with multifactorial origin (chronic renal failure, hematological disease). A treatment with recombinant erythropoietin was introduced: epoetin beta (NEORECORMON) 20 MU 1 injection weekly by subcutaneous route. The subject experienced trophic disorders on 04Feb2019. The event was reported as non-serious with grade 3. Action taken in response to the events was dose not changed. The events obliterant arteriopathy of lower limbs and trophic disorders had not resolved. The subject had recovered from the event bronchitis on 25Apr2018, from the 4th right toe osteoarthritis on 04Dec2018, from anemia on 16Dec2019 and from superinfection of the 4th right toe on 16Dec2019. The events asthenia and pollakiuria were recovered on 27Aug2018.

According to the investigator, the events bronchitis, obliterant arteriopathy of lower limbs, the 4th right toe osteoarthritis, superinfection of the 4th right toe, anemia and trophic disorders were unrelated to study drug bosutinib or to a concomitant drug. The reporter stated: complete healing of trophic disorders of the right foot following the semi-recent toe amputations with persistence of trophic disorders of the left foot but in good condition for healing and in relation to his well-balanced diabetes.
The investigator considered that there was a reasonable possibility that the events asthenia and pollakiuria were related to the study drug bosutinib, but not related to concomitant medications.

Follow-up (07Aug2018): New information received from the CRO is as follows: On 13Mar2018, the subject experienced asthenia (grade 2) and pollakiuria (grade 1), which were assessed as non-serious. In a result of the events, the dose of bosutinib (BOSULIF), which was in a situation of maintained complete hematological response, was reduced at 100 mg alternate day from 20Jun2018. At the time of reporting, the events asthenia and pollakiuria were resolving. The investigator considered that there was a reasonable possibility that the events, asthenia and pollakiuria, were related to the study drug, bosutinib, but not related to concomitant medications.

Follow-up (16Nov2018): New information received from the study site includes: No action was taken with study drug in response to the pollakiuria however study drug dose was reduced in response to the asthenia.

Follow-up (19Jun2019): New information received from the investigational site included: dosage regimens and action taken of bosutinib; lab data; new events (obliterant arteriopathy of lower limbs and the 4th right toe Osteoarthritis). Case upgraded to serious.

Follow-up (28Jun2019): New information received from CRO included new event (anemia).

Follow-up (05Jul2019): New information received from the investigational site includes: bosutinib action taken.

Follow-up (05Feb2020): new information received from CRO includes, updated outcome of anemia, new event superinfection of the 4th right toe, reporter's comment.

Follow-up (14May2021): New information received from the CRO includes new event (trophic disorders), onset date, outcome of event, seriousness assessment and causality assessment by reporter.

Follow-up (16Sep2021): New information received from the CRO includes: dose was not changed for bosutinib in response to the event trophic disorders.

Mfr. Control Number: 2018226336

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (20Jan2023): This follow-up is received from the investigational site CRO. This is a follow-up to a non-interventional clinical study case. Updated information: reaction data (onset date, outcome, stop date).

Case Comment: The company concurs with the investigator that the events, bronchitis, pollakiuria, obliterant arteriopathy of lower limbs, the 4th right toe Osteoarthritis, superinfection of the 4th right toe and trophic disorders were unrelated to bosutinib but more likely represented intercurrent condition considering underlying diabetes, cardiac decompensation and renal failure. Conversely, considering a plausible drug-event temporal association, the consistency of this event with the known safety profile of the suspect product, and the achieved complete hematological response, a reasonable possibility that asthenia is related to bosutinib administration cannot be excluded. This case will be updated when new information becomes available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	12-NOV-2018	C-reactive protein	249 mg/l	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, alternate day; Unknown	Unknown	20-JUN-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
12-JUN-2012 to Ongoing	Relevant Med History	Arteritis (Arteritis);
Unknown to Ongoing	Relevant Med History	Renal failure (Renal failure);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		JUN	1947	70 Years	Male	90.00 kg		DEC	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

night diuresis increased [Nocturia]
joint pains [Arthralgia]
constipation [Constipation]
AEROPHAGIA [Aerophagia]
Gastroesophageal reflux [Gastrooesophageal reflux disease]
bloating [Abdominal distension]
tearing [Lacrimation increased]
blepharitis [Blepharitis]
right lower limb varicose vein [Varicose vein]
MYCOSIS [Fungal infection]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosutinib (BOSUTINIB) Unknown

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 27-NOV-2017 / Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) JANUMET (METFORMIN HYDROCHLORIDE, SITAGLIPTIN PHOSP
#2) DIPROSONE [BETAMETHASONE DIPROPIONATE] (BETAMETHASO

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
Unknown to Ongoing	Relevant Med History	Psoriasis (Psoriasis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018227830

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

Jean-christophe Ianotto

FRANCE

24c. DATE RECEIVED BY MANUFACTURER
24-AUG-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

COLD [Nasopharyngitis]

Case Description: USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.

A 70-year-old male patient received bosutinib (BOSUTINIB), first regimen since 27Nov2017 at 400 mg daily, oral, second regimen since 08Jan2018 at 200 mg, third regimen since 09Feb2018 at 300 mg 1x/day and fourth regimen since 09Mar2018 at 400 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: 'diabetes' (ongoing); 'psoriasis' (ongoing). Ongoing concomitant medication included metformin hydrochloride, sitagliptin phosphate monohydrate (JANUMET) oral for diabetes and betamethasone dipropionate (DIPROSONE) transdermal for psoriasis. On 19Feb2018, the patient experienced constipation considered non-serious and rated Grade 2. Treatment with macrogol 3350/potassium chloride/sodium bicarbonate/sodium chloride (MOVICOL) at 1 sachet/day was initiated on 03Apr2018. No action was taken for bosutinib in response to the event constipation. Constipation had not recovered at the report time. In Dec2017, the subject had cold assessed Grade 2. The event cold recovered in Dec2017. In Jan2018, the subject experienced aerophagia assessed Grade 1. The event aerophagia recovered in Jan2018. In Feb2018, the subject experienced joint pains assessed Grade 1 and mycosis assessed Grade 2, gastroesophageal reflux and bloating both assessed Grade 1. Events gastroesophageal reflux and bloating recovered in Apr2018. In Sep2018, the subject experienced tearing and blepharitis both assessed Grade 1. Events tearing and blepharitis recovered in Nov2018. On 12Feb2019, the subject experienced right lower limb varicose vein assessed Grade 1. As of 26Apr2019, the site reported that the final outcome assessment for events right lower limb varicose vein, joint pains and mycosis will be performed at the next consultation. As of 10Oct2019 the site reported the subject experienced night diuresis increased on 17Sep2019, rated Grade 1 and reported as non-serious. The action taken with bosutinib was dose not changed. On 28Jan2020, it was reported that the subject experienced loss of response on 30Dec2019. The event was assessed as non-serious and rated Grade 2. In response to the event, the dose of bosutinib was increased. The events constipation, mycosis, right lower limb varicose vein and night diuresis increased were not recovered. The outcome of the Cold was recovered in Dec2017, Aerophagia was recovered in Jan2018, Gastroesophageal reflux and Bloating were recovered in Apr2018, Tearing and Blepharitis were recovered in Nov2018, Joint pains was recovered on 17Mar2020, loss of response was recovered on 02Jun2020. No action was taken with bosutinib in response to joint pains and mycosis.

The event joint pains was related to bosutinib.

According to the investigator, the events joint pains, night diuresis increased and loss of response were related to the study drug and unrelated to concomitant drug.
The investigator considered that there was not a reasonable possibility that the remaining events were related to bosutinib or to a concomitant drug.

Follow-up (19Mar2019). New information from the investigational site included: additional events (cold, aerophagia, joint pains, mycosis, gastroesophageal reflux, bloating, tearing, blepharitis, lower limb varicose vein); onset date, outcome and causality for the new events.

Follow-up (26Apr2019): New information received includes: Causality (for mycosis) and Clinical data.

Follow-up (10Oct2019): New information received from CRO included new event night diuresis increased.

Follow-up (28Jan2020): New information received from the CRO includes details of loss of response.

Follow-up (14May2020) New information received from CRO included clinical outcome (joint pain updated from not recovered to recovered).

Follow-up (19Jun2020) New information received from CRO was as follows: loss of response recovered.

Follow-up (09Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from CRO for protocol B1871047. Updated information included: onset date of the event 'right lower limb varicose vein'.

Follow-up (28Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from CRO for protocol B1871047. Updated information included: additional therapy regimen of bosutinib, updated onset date of event Constipation (from 03Apr2018 to 19Feb2018), updated outcome of event Right lower limb varicose vein (from not recovered to recovered).

Follow-up (22May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information included: additional therapy regimen of bosutinib.
Update action taken with bosutinib in response to joint pains and mycosis. Reporter's causality assessment for the event joint pains provided (related to bosutinib).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Amendment: This follow-up report is being submitted to amend previously transmitted information. The outcome of the event right lower limb varicose vein was updated for not recovered.

Case Comment: The Company deems there is not a reasonable possibility that the reported events are related to the suspect, bosutinib. Of note, the patient was kept on bosutinib and no dose adjustment was made during the duration of events. The reported night diuresis increased is more likely associated with patient's ongoing medical history of diabetes, patient's advanced age may also have contributed. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #2	200 mg; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	08-JAN-2018 / Unknown; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	300 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	09-FEB-2018 / Unknown; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	400 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	09-MAR-2018 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#1) JANUMET (METFORMIN HYDROCHLORIDE, SITAGLIPTIN PHOSPHATE MONOHYDRATE) ; Ongoing

#2) DIPROSONE [BETAMETHASONE DIPROPIONATE] (BETAMETHASONE DIPROPIONATE) ; Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1950	67 Years	Female	57.00 kg	07	MAR	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Bilateral pleural effusion [Pleural effusion]
Transient ischemic attack [Transient ischaemic attack]
Vertigo [Vertigo]
Vomiting [Vomiting]
Fatigue [Fatigue]
Nausea [Nausea]
folic acid deficiency [Folate deficiency]
Vitamin D deficiency [Vitamin D deficiency]
depression [Depression]
Aggravation of hypertension arterial [Hypertension]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 07-MAR-2018 / Unknown	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#2) LERCAN (LERCANIDIPINE HYDROCHLORIDE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2008 to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus)
2000 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018232685

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
04-DEC-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Joint pain [Arthralgia]
Breathlessness [Dyspnoea]
Headache [Headache]
Hypokalemia [Hypokalaemia]
fibrous pachypleuritis [Pleural thickening]
Hypokalemia [Hypokalaemia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 67 year-old female subject (unknown if pregnant) was included in the above mentioned study and started to receive bosutinib (BOSULIF) via an unspecified route from 07Mar2018 at 400 mg daily and from 29Mar2018 to 05Jul2018 at 300 mg daily for an unspecified indication. Relevant medical history included ongoing type 2 diabetes, ongoing arterial hypertension from 2000 and ongoing hypothyroidism from 2000. Concomitant medications included ongoing levothyroxine sodium (LEVOTHYROX) for hypothyroidism and ongoing lercanidipine hydrochloride (LERCAN) for arterial hypertension. On 07Mar2018, the subject experienced nausea which was considered as non-serious and rated as grade 1. No action was taken with bosutinib in response to the event. Nausea resolved on 21Mar2018. On 21Mar2018, the subject presented with aggravation of arterial hypertension which was considered as non-serious and rated as grade 2. In response to this event, bosutinib dose was reduced and the aggravation arterial hypertension resolved on 29Mar2018. On 21Mar2018, the subject presented with vertigo and vomiting, which were assessed as non-serious and of grade 1. In response to these events, bosutinib dose was reduced. Vertigo resolved on 17Apr2018 and vomiting resolved on 05Apr2018. On 05Apr2018, the subject experienced joint pain which was considered as non-serious and rated as grade 1. In response to the event, no action was taken with bosutinib and the joint pain resolved on 17Apr2018. On 17Apr2018, the subject experienced fatigue and breathlessness which were considered as non-serious and rated as grade 1. No action was taken with bosutinib in response to the events. Fatigue and breathlessness resolved on 29May2018. On 27May2018, the subject experienced headache which was considered as non-serious and rated as grade 1. No action was taken with study drug in response to the event. Headache resolved in Jun2018. On 02Jul2018, the subject experienced bilateral pleural effusion, which led to hospitalization/prolongation of hospitalization. In result to the event, bosutinib was withdrawn on 05Jul2018. On 23Aug2018, the subject had recovered from the event bilateral pleural effusion. On 05Jun2018, the subject was the subject of transient ischemic attack which required hospitalization and was rated as grade 1. No action was taken with study drug in response to the event. Transient ischemic attack resolved in Jun2018. In Jul2018, the subject presented with Vitamin D deficiency which was considered as non-serious and rated as grade 2, and folic acid deficiency which was considered as non-serious and rated as grade 2. The action taken with study drug in response to the event was not applicable. Vitamin D deficiency and folic acid deficiency resolved in Jul2018. On 05Jul2018, the subject experienced depression which was considered as non-serious and rated as grade 2. No action was taken with the study drug in response to the event. Depression resolved in Jul2018. No action was taken with study drug in response to the event. Hypokalemia resolved on 12Jul2018. On 09Jul2018, subject experienced hypokalemia, grade 1, non-serious, with outcome of recovered with sequelae on 10Jul2018. Potassium (N 3.4-4.4) was 3.0 mmol/l on 09Jul2028, 2.9 mmol/l on 11Jul2018 and 4.1 mmol on 12Jul2018. Action taken with study drug in response to hypokalemia was not applicable. On 23Aug2018, the subject experienced fibrous pachypleuritis, grade 1, with outcome of recovered in Aug2018. Action taken with study drug in response to fibrous pachypleuritis was not applicable.
The investigator added the following comment: pleural effusion known since this end of 2017 but aggravation of this bilateral pleural effusion. Right pleural symphysis performed on 25Jul2018: no malignancy. Left pleural symphysis performed on 21Aug2018: no malignancy.
For transient ischemic accident and hypokalemia investigator initial aware date was 05Jul2018. For fatigue and Nausea investigator initial aware date was 16Jul2019. For depression and vitamin d deficiency investigator initial aware date was 10Aug2018. For headaches and breathlessness investigator initial aware date was 17Apr2018. For folic acid deficiency and fibrous pachypleuritis investigator initial aware date was 10Aug2018. For joint pain and fibrous Aggravation of hypertension arterial investigator initial aware date was 17Apr2018.

According to the investigator, fatigue, transient ischemic attack, hypokalemia (11Jul2018), Vitamin D deficiency, folic acid deficiency, depression, headache, hypokalemia (09Jul2018) and fibrous pachypleuritis were not related to study drug or concomitant medication while vertigo, vomiting and bilateral pleural effusion, nausea, aggravation arterial hypertension, joint pain and breathlessness were related to study drug bosutinib but not related to concomitant medication.

Follow-up (11Sep2018): New information received from the CRO included: New event (bilateral pleural effusion), action taken, dosage regimens, outcome of the event, causality assessment and seriousness criteria of new event, investigator comment.

Follow-up attempts completed. No further information expected.

Follow-up (16Jul2019): New information received from the study site includes: new events, updated event term dizziness to vertigo.

Follow-up (24Sep2019): New information received included: event verbatim "Vitamin D and folic acid deficiency" was changed to

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

"folic acid deficiency" rated grade 1 and "Vitamin D deficiency" rated grade 2; Event verbatim "Aggravation of anxiety" was changed to "Aggravation of anxiety and depression".

Follow-ups (22Mar2021 and 23Mar2021): New information received from CRO includes: action taken with bosutinib in response to event joint pain updated as dose not changed (previously dose reduced), and updated the severity grade of event Folic acid deficiency as grade 2 (previously grade 1).

Follow-up (27Dec2021): New information received from the investigational site via CRO included: new events "hypokalemia (09Jul2018)" and "fibrous pachypleuritis" added, medical history details, lab data and clinical course.

Follow-up (14Feb2022): New information received from CRO includes: event hypokalemia (11Jul2018) was deleted.

Follow-up (09Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information included: event verbatim "aggravation of anxiety and depression" updated to "anxiety and depression".

Follow-up (03Aug2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information included: Event description depression and anxiety was updated to depression.

Follow-up (04Dec2023): New information was received from the clinical team. Updated information: The event hypokalemia of 11Jul2018 was confirmed. The subject developed hypokalemia from 11Jul2018 to 12Jul2018 (resolved without sequel). The event was not related to the study drug.

Case Comment: Considering a plausible drug-event temporal association and the consistency of the events with the known safety profile of the suspect product, a reasonable possibility that the reported pleural effusion, vertigo, vomiting, nausea, aggravation arterial hypertension, joint pain and breathlessness are related to bosutinib administration cannot be excluded while other events are assessed as unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	09-JUL-2018	Blood potassium Hypokalemia	3.0 mmol/L	4.4 3.4
2	11-JUL-2018	Blood potassium	2.9 mmol/L	4.4 3.4
3	12-JUL-2018	Blood potassium	4.1 mmol/L	4.4 3.4

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Unknown	29-MAR-2018 / 05-JUL-2018; 99 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2000 to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1954	63 Years	Male	95.00 kg	05	DEC	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Alanine aminotransferase increased [Alanine aminotransferase increased]
Aspartate aminotransferase increased [Aspartate aminotransferase increased]
non-cardiac chest pain [Non-cardiac chest pain]
atheroma [Arteriosclerosis]
ulcerative gastritis [Ulcerative gastritis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, 1x/day	#1) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukaemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 05-DEC-2017 / Unknown	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TAREG (VALSARTAN) ; 2005 / Ongoing
#2) BISOPROLOL (BISOPROLOL) ; 2005 / Ongoing
#3) DUOPLAVIN (ACETYLSALICYLIC ACID, CLOPIDOGREL BISULF
#4) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNESIUM) ; Unknown
#5) CRESTOR (ROSUVASTATIN CALCIUM) ; 2005 / Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Ischemic heart disease (Myocardial ischaemia) treated by medication and stents insertion
Unknown	Relevant Med History	Stent insertion NOS (Stent placement)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018240296

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 63-year-old male patient received bosutinib (BOSULIF), first regimen since 05Dec2017 at 400 mg 1x/day and second regimen (ongoing) at 300 mg 1x/day, all oral for chronic myeloid leukaemia. The patient's relevant medical history included: "Ischemic heart disease" (ongoing), notes: treated by medication and stents insertion; "Stent insertion" (unspecified if ongoing); "Prostatic hypertrophy" (ongoing); "Gastritis" (ongoing); "back pain and lumbar pain" (unspecified if ongoing); "back pain and lumbar pain" (unspecified if ongoing). Concomitant medication(s) included: TAREG oral taken for myocardial ischaemia, start date: 2005 (ongoing); BISOPROLOL oral taken for myocardial ischaemia, start date: 2005 (ongoing); DUOPLAVIN oral taken for myocardial ischaemia, start date: 2005; INEXIUM [ESOMEPRAZOLE MAGNESIUM]; CRESTOR oral taken for myocardial ischaemia, start date: 2005 (ongoing).
The following information was reported: DIARRHOEA (non-serious) with onset 05Dec2017, outcome "recovered" (07Dec2017), described as "Diarrhea"; ALANINE AMINOTRANSFERASE INCREASED (non-serious) with onset 09Mar2018, outcome "recovered" (15Dec2018); ASPARTATE AMINOTRANSFERASE INCREASED (non-serious) with onset 09Mar2018, outcome "recovered" (19Jun2018); ULCERATIVE GASTRITIS (non-serious) with onset Apr2018, outcome "recovered" (09Oct2018); NON-CARDIAC CHEST PAIN (non-serious) with onset Jun2018, outcome "recovered" (Jun2018); ARTERIOSCLEROSIS (non-serious) with onset 10Sep2018, outcome "not recovered", described as "atheroma".
The subject underwent the following laboratory tests and procedures: alanine aminotransferase: (09Mar2017) 220 IU/l; (04Jun2017) 107 IU/l; (05Dec2017) 37 IU/l; (03May2018) 628 IU/l, notes: >10 N; (11Jun2018) 131 IU/l; (19Jun2018) 69 IU/l; (15Dec2018) 49 IU/l; aspartate aminotransferase (normal high range 50): (09Mar2017) 84 IU/l; (04Jun2017) 41 IU/l; (05Dec2017) 29 IU/l; (03May2018) 198 IU/l, notes: 4 N; (11Jun2018) 57 IU/l; (19Jun2018) 41 IU/l; (15Dec2018) 38 IU/l; gamma-glutamyltransferase: (03May2018) 1.5 N.
In response to the event hepatic cytolysis, bosutinib was temporarily withdrawn and resumed at 300 mg daily when hepatic work-up was improved. The last action taken in response to events for bosutinib was dosage not changed. Therapeutic measures were taken as a result of diarrhoea; Treatment included loperamide (IMODIUM) and aluminium hydroxide-magnesium carbonate gel, aluminium magnesium silicate, glucose monohydrate, glycyrrhiza glabra (SMECTA) was initiated on unspecified date.

The reporter considered "diarrhea", "alanine aminotransferase increased" and "aspartate aminotransferase increased" related to bosutinib. The reporter considered "non-cardiac chest pain", "atheroma" and "ulcerative gastritis" not related to bosutinib.

Follow-up (21Jun2018): new information received from CRO includes new event hepatic cytolysis, non-serious and additional lab data.

Follow-up (01Aug2018): New information received from investigator includes: bosutinib rechallenge information.

Follow-up (04Sep2018): follow-up attempts completed. No further information expected.

Follow-up (10Dec2018): follow-up attempts completed. No further information expected.

Follow-up (21Dec2018): New information reported included new non serious events (para-trapezoidal lipoma, ulcerative gastritis, dyspnea, chest pain, back pain/lumbar pain, atheroma, abdominal pain and umbilical hernia).

Follow-up (15Jan2019): New information received upon the specific pharmacovigilance form for hepatic events ("hepatic cytolysis") is as follows;
Additional concomitant medications included esomeprazole magnesium (INEXIUM) and rosuvastatin calcium (CRESTOR).
The subject presented with the following symptom: weight gain manifested by abdominal distension.
Alanine aminotransferase was 220 IU/L (normal range <41 or 50) on 09Mar2017, 107 IU/L (normal range <41 or 50) on 05Jun2017, 37 IU/L on 05Dec2017 (in the beginning of treatment), 628 IU/L on 03May2018 (during the treatment), 131 IU/L on 11Jun2018, 69 IU/L on 19Jun2018 and 49 IU/L on 15Dec2018.
Aspartate aminotransferase was 84 IU/L (normal range <50) on 09Mar2017, 41 IU/L (normal range <50) on 04Jun2017, 29 UI/L on 05Dec2017 (in the beginning of treatment), 198 IU/L on 03May2018 (during the treatment), 57 IU/L on 11Jun2018, 41 IU/L on 19Jun2018 and 38 IU/L on 15Dec2018.

Follow-up (14Feb2019): New information received from the study site includes:
Bosutinib (BOSULIF) was taken at 300 mg once daily from on an unspecified date (ongoing).
The concomitant drugs valsartan (TAREG), rosuvastatin and bisoprolol were started in 2005 (ongoing) via oral route for ischemic heart disease. Acetylsalicylic acid/clopidogrel bisulfate (DUOPLAVIN) was also started in 2005 (ongoing) via oral route for ischemic heart disease.

The para-trapezoidal lipoma was rated as grade 1. No action was taken with study drug in response to this event. The subject had not yet recovered from this event.
The ulcerative gastritis was rated as grade 2. No action was taken with study drug in response to this event. The subject recovered from this event on 09Oct2018.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The chest pain was rated as grade 1. No action was taken with study drug in response to this event. The chest pain resolved in Jun2018.
Exertional dyspnea occurred in Jun2018 and was rated as grade 1. No action was taken with study drug in response to this event. This event resolved in Jun2018.
Back pain and lumbar pain was rated as grade 1. No action was taken with study drug in response to this event. The back pain and lumbar pain resolved on 09Oct2018.
The atheroma was rated as grade 1. No action was taken with study drug in response to this event. This event had not yet resolved.
The umbilical hernia was rated as grade 1. No action was taken with study drug in response to this event. This event had not yet resolved.
The abdominal pain was rated as grade 1. No action was taken with study drug in response to this event. The abdominal pain resolved on 18Dec2018.

According to the investigator, the para-trapezoidal lipoma, ulcerative gastritis, chest pain, exertional dyspnea, back pain and lumbar pain, atheroma, umbilical hernia were not related to study drug or concomitant medication while the abdominal pain was considered as related to study drug but not related to concomitant medication.

Follow-ups (23Nov2021 and 25Jan2022): These are follow-ups of non-interventional study report (Post Authorization Safety Study) for protocol B1871047 (Study alias BOSEVAL), received from CRO.
Updated information included: The subject's height; The event term chest pain was changed for 'non-cardiac chest pain'; The event ulcerative gastritis was confirmed as non-serious, Events abdominal pain and umbilical hernia, dyspnea and para-trapezoidal lipoma were deleted as events as considered not clinically significant by the investigator, Event back pain and lumbar pain (from Sep2018) was removed as event as considered as a medical history by the investigator.

Follow-up (09Mar2023): This is a follow-up report from the investigator via CRO.
Updated information: patient initials updated.

Follow-up (13Apr2023): This is a follow-up report from the investigator via CRO.
Updated information: diarrhea stop date updated to 07Dec2017, outcome for alanine aminotransferase increased updated to resolved on 15Dec2018, outcome for aspartate aminotransferase increased updated to resolved on 19Jun2018 and event grading changed from grade 1 to grade 3.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Event "hepatic cytolysis" should be deleted from this case as it was already reported as "ALT elevation" and "ASAT elevation".Event "Exertional dyspnea" should be deleted as investigator confirmed this case was not clinically relevant.

Follow-up attempts are completed. No further information is expected.

Case Comment: Based on the reasonable temporal association and considering the reported diarrhea, alanine aminotransferase increased, aspartate aminotransferase increased are consistent with the known safety profile of bosutinib, the Company cannot completely exclude the possible causality between the reported events and bosutinib administration. Other events assessed as unrelated to the suspect drug and are best explained as intercurrent or underlying medical conditions. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	09-MAR-2017	Alanine aminotransferase	220 IU/l	
2	04-JUN-2017	Alanine aminotransferase	107 IU/l	
3	05-DEC-2017	Alanine aminotransferase	37 IU/l	
4	03-MAY-2018	Alanine aminotransferase >10 N	628 IU/l	
5	11-JUN-2018	Alanine aminotransferase	131 IU/l	
6	19-JUN-2018	Alanine aminotransferase	69 IU/l	
7	15-DEC-2018	Alanine aminotransferase	49 IU/l	

Mfr. Control Number: 2018240296

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
8	09-MAR-2017	Aspartate aminotransferase	84 IU/l	50
9	04-JUN-2017	Aspartate aminotransferase	41 IU/l	50
10	05-DEC-2017	Aspartate aminotransferase	29 IU/l	50
11	03-MAY-2018	Aspartate aminotransferase 4 N	198 IU/l	50
12	11-JUN-2018	Aspartate aminotransferase	57 IU/l	50
13	19-JUN-2018	Aspartate aminotransferase	41 IU/l	50
14	15-DEC-2018	Aspartate aminotransferase	38 IU/l	50
15	03-MAY-2018	Gamma-glutamyltransferase	1.5 N	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#3) DUOPLAVIN (ACETYLSALICYLIC ACID, CLOPIDOGREL BISULFATE) ; 2005 / Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Prostatic hypertrophy (Benign prostatic hyperplasia);
Unknown to Ongoing	Relevant Med History	Gastritis (Gastritis);
Unknown	Relevant Med History	Back pain (Back pain);
Unknown	Relevant Med History	Lumbar pain (Back pain);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1956	61 Years	Male	117.00 kg	14	FEB	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Intermittent hepatic cytolysis [Hepatic cytolysis]
Bronchitis [Bronchitis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 22-NOV-2017 / 16-FEB-2018

19. THERAPY DURATION
#1) 87 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) DIFFU K (POTASSIUM CHLORIDE) ; 2012 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2002 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
2010 to Ongoing	Relevant Med History	Gastroesophageal reflux (Gastrooesophageal reflux disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018306611

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
17-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047.

A 61-year-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 22Nov2017 at 100 mg daily for an unspecified indication. Concomitant medications included two anti-hypertensive drugs (unspecified) and DIFFU K oral taken for hyperkalaemia, start date: 2012 (ongoing). Medical history included arterial hypertension from 2002 and ongoing, gastroesophageal reflux from 2010 and ongoing, meningitis, appendicectomy in 1985. Before bosutinib therapy, subject had occasional alcohol consumption, less once per month (1 glass daily. Alcohol type: beer). The subject had a test of hepatic function the year before the treatment with bosutinib was started (unknown date in 2016) and results were normal. At the bosutinib therapy beginning, the initial status was assessed as normal. During the treatment status was assessed and found ALAT increased. After the treatment status was assessed as normal. On 14Feb2018, the subject experienced intermittent hepatic cytolysis, CTCAE grade 3. The event was considered as serious. In Mar2018, the subject experienced bronchitis, CTCAE grade1, assessed by reporting physician as non-serious. In the result of the event bronchitis, the dose of bosutinib was not changed. The action taken in response to the event intermittent hepatic cytolysis was withdrawn. Bosutinib was discontinued due to the 1st episode from 16Feb2018 to 02May2018 then resumed on 03May2018. Bosutinib was definitively discontinued on 29May2018 due to 2nd episode.
The subject was found to have: alanine aminotransferase (N <41) 478 IU/l on 14Feb2018, 356 IU/l on 19Feb2018, 289 IU/l on 26Feb2018, 208 IU/l on 05Mar2018, 183 IU/l on 08Mar2018, 130 IU/l on 13Mar2018, 96 IU/l on 20Mar2018, 88 IU/l on 26Mar2018, 65 IU/l on 03Apr2018, 61 IU/l on 09Apr2018, 60 IU/l on 16Apr2018, 43 IU/l on 30Apr2018, 42 IU/l on 02May2018, 129 IU/l on 14May2018, 245 IU/l on 28May2018, 105 IU/l on 11Jun2018, 67 IU/l on 19Jun2018, 54 IU/l on 25Jun2018, 47 IU/l on 02Jul2018, 39 IU/l on 17Jul2018, 29 IU/l on 23Jul2018, 36 IU/l on 30Jul2018; aspartate aminotransferase (N <41) 145 IU/l on 14Feb2018, 71 IU/l on 19Feb2018, 88 IU/l on 26Feb2018, 70 IU/l on 05Mar2018, 71 IU/l on 08Mar2018, 53 IU/l on 13Mar2018, 42 IU/l on 20Mar2018, 40 IU/l on 26Mar2018, 30 IU/l on 03Apr2018, 30 IU/l on 09Apr2018, 39 IU/l on 16Apr2018, 26 IU/l on 30Apr2018, 34 IU/l on 02May2018, 41 IU/l on 14May2018, 88 IU/l on 28May2018, 46 IU/l on 11Jun2018, 32 IU/l on 19Jun2018, 30 IU/l on 25Jun2018, 28 IU/l on 02Jul2018, 26 IU/l on 17Jul2018, 26 IU/l on 23Jul2018, 30 IU/l on 30Jul2018, Alkaline phosphatase (N 40-130) 89 IU/l on 14Feb2018, 79 IU/l on 19Feb2018, 87 IU/l on 26Feb2018, 77 IU/l on 05Mar2018, 75 IU/l on 08Mar2018, 69 IU/l on 13Mar2018, 82 IU/l on 20Mar2018, 75 IU/l on 26Mar2018, 70 IU/l on 03Apr2018, 71 IU/l on 09Apr2018, 73 IU/l on 16Apr2018, 70 IU/l on 30Apr2018, 67 IU/l on 02May2018, 81 IU/l on 14May2018, 82 IU/l on 28May2018, 81 IU/l on 11Jun2018, 76 IU/l on 19Jun2018, 78 IU/l on 25Jun2018, 87 IU/l on 02Jul2018, 65 IU/l on 17Jul2018, 69 IU/l on 23Jul2018, 70 IU/l on 30Jul2018; gamma GT (N 8-61) 72 IU/l on 14Feb2018, 73 IU/l on 19Feb2018, 86 IU/l on 26Feb2018, 81 IU/l on 05Mar2018, 97 IU/l on 08Mar2018, 74 IU/l on 13Mar2018, 78 IU/l on 20Mar2018, 74 IU/l on 26Mar2018, 65 IU/l on 03Apr2018, 67 IU/l on 09Apr2018, 64 IU/l on 16Apr2018, 69 IU/l on 30Apr2018, 86 IU/l on 02May2018, 81 IU/l on 14May2018, 73 IU/l on 28May2018, 80 IU/l on 11Jun2018, 77 IU/l on 19Jun2018, 69 IU/l on 25Jun2018, 69 IU/l on 02Jul2018, 71 IU/l on 17Jul2018, 59 IU/l on 23Jul2018, 57 IU/l on 30Jul2018.
Intermittent hepatic cytolysis was resolved on 30Jul2018 and bronchitis recovered in Mar2018.

The investigator considered the event hepatic cytolysis was related to study drug bosutinib and unrelated to concomitant medications.
The investigator considered the event bronchitis was unrelated to study drug bosutinib and to concomitant medications.

Follow-up (11Sep2018): New information received included second dose regimen of bosutinib.

Follow-up (17Sep2018): New information received included lab test results, seriousness of hepatic cytolysis

Follow-up (28Nov2018): New information includes: subject was taking two anti-hypertension concomitant treatments.

Follow-up (21Jan2019): Follow-up attempts completed. No further information expected.

Follow-up (01Feb2019): New information reported includes that the subject was not treated with potassium chloride (DIFFU K), therefore this concomitant medication was deleted.

Follow-up (06Jan2020): New information received included: the event term was changed from hepatic cytolysis to intermittent hepatic cytolysis; outcome and stop date of event intermittent hepatic cytolysis.

Follow-up (17Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information includes: concomitant medication (DIFFU K).

No follow-up attempt is needed. No further information is expected.

Case Comment: Due to a plausible drug-event temporal association as well as positive de- and re-challenge, the company deems there is a reasonable possibility that the event hepatic cytolysis, significantly reported as grade 3 and requiring the definitive discontinuation of the suspect drug, is related to bosutinib. Conversely, always in agreement with the investigator, the company considers there are no evidence or argument that can justify a causal association with the event bronchitis, often a self-supporting, intercurrent episode of infection in patients affected by malignancies. The company does not attribute bronchitis to bosutinib.
The follow-up information received does not alter the previous company clinical evaluation.

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	14-FEB-2018	Alanine aminotransferase	478 IU/l	41
2	19-FEB-2018	Alanine aminotransferase	356 IU/l	41
3	26-FEB-2018	Alanine aminotransferase	289 IU/l	41
4	05-MAR-2018	Alanine aminotransferase	208 IU/l	41
5	08-MAR-2018	Alanine aminotransferase	183 IU/l	41
6	13-MAR-2018	Alanine aminotransferase	130 IU/l	41
7	20-MAR-2018	Alanine aminotransferase	96 IU/l	41
8	26-MAR-2018	Alanine aminotransferase	88 IU/l	41
9	03-APR-2018	Alanine aminotransferase	65 IU/l	41
10	09-APR-2018	Alanine aminotransferase	61 IU/l	41
11	16-APR-2018	Alanine aminotransferase	60 IU/l	41
12	30-APR-2018	Alanine aminotransferase	43 IU/l	41
13	02-MAY-2018	Alanine aminotransferase	42 IU/l	41
14	14-MAY-2018	Alanine aminotransferase	129 IU/l	41
15	28-MAY-2018	Alanine aminotransferase	245 IU/l	41
16	11-JUN-2018	Alanine aminotransferase	105 IU/l	41
17	19-JUN-2018	Alanine aminotransferase	67 IU/l	41
18	25-JUN-2018	Alanine aminotransferase	54 IU/l	41
19	02-JUL-2018	Alanine aminotransferase	47 IU/l	41
20	17-JUL-2018	Alanine aminotransferase	39 IU/l	41
21	23-JUL-2018	Alanine aminotransferase	29 IU/l	41
22	30-JUL-2018	Alanine aminotransferase	36 IU/l	41
23	14-FEB-2018	Aspartate aminotransferase	145 IU/l	41
24	19-FEB-2018	Aspartate aminotransferase	71 IU/l	41
25	26-FEB-2018	Aspartate aminotransferase	88 IU/l	41
26	05-MAR-2018	Aspartate aminotransferase	70 IU/l	41
27	08-MAR-2018	Aspartate aminotransferase	71 IU/l	41

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
28	13-MAR-2018	Aspartate aminotransferase	53 IU/l	41
29	20-MAR-2018	Aspartate aminotransferase	42 IU/l	41
30	26-MAR-2018	Aspartate aminotransferase	40 IU/l	41
31	03-APR-2018	Aspartate aminotransferase	30 IU/l	41
32	09-APR-2018	Aspartate aminotransferase	30 IU/l	41
33	16-APR-2018	Aspartate aminotransferase	39 IU/l	41
34	30-APR-2018	Aspartate aminotransferase	26 IU/l	41
35	02-MAY-2018	Aspartate aminotransferase	34 IU/l	41
36	14-MAY-2018	Aspartate aminotransferase	41 IU/l	41
37	28-MAY-2018	Aspartate aminotransferase	88 IU/l	41
38	11-JUN-2018	Aspartate aminotransferase	46 IU/l	41
39	19-JUN-2018	Aspartate aminotransferase	32 IU/l	41
40	25-JUN-2018	Aspartate aminotransferase	30 IU/l	41
41	02-JUL-2018	Aspartate aminotransferase	28 IU/l	41
42	17-JUL-2018	Aspartate aminotransferase	26 IU/l	41
43	23-JUL-2018	Aspartate aminotransferase	26 IU/l	41
44	30-JUL-2018	Aspartate aminotransferase	30 IU/l	41
45	14-FEB-2018	Blood alkaline phosphatase	89 IU/l	130 40
46	19-FEB-2018	Blood alkaline phosphatase	79 IU/l	130 40
47	26-FEB-2018	Blood alkaline phosphatase	87 IU/l	130 40
48	05-MAR-2018	Blood alkaline phosphatase	77 IU/l	130 40
49	08-MAR-2018	Blood alkaline phosphatase	75 IU/l	130 40
50	13-MAR-2018	Blood alkaline phosphatase	69 IU/l	130 40
51	20-MAR-2018	Blood alkaline phosphatase	82 IU/l	130 40
52	26-MAR-2018	Blood alkaline phosphatase	75 IU/l	130 40
53	03-APR-2018	Blood alkaline phosphatase	70 IU/l	130 40

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
54	09-APR-2018	Blood alkaline phosphatase	71 IU/l	130 40
55	16-APR-2018	Blood alkaline phosphatase	73 IU/l	130 40
56	30-APR-2018	Blood alkaline phosphatase	70 IU/l	130 40
57	02-MAY-2018	Blood alkaline phosphatase	67 IU/l	130 40
58	14-MAY-2018	Blood alkaline phosphatase	81 IU/l	130 40
59	28-MAY-2018	Blood alkaline phosphatase	82 IU/l	130 40
60	11-JUN-2018	Blood alkaline phosphatase	81 IU/l	130 40
61	19-JUN-2018	Blood alkaline phosphatase	76 IU/l	130 40
62	25-JUN-2018	Blood alkaline phosphatase	78 IU/l	130 40
63	02-JUL-2018	Blood alkaline phosphatase	87 IU/l	130 40
64	17-JUL-2018	Blood alkaline phosphatase	65 IU/l	130 40
65	23-JUL-2018	Blood alkaline phosphatase	69 IU/l	130 40
66	30-JUL-2018	Blood alkaline phosphatase	70 IU/l	130 40
67	14-FEB-2018	Gamma-glutamyltransferase	72 IU/l	61 8
68	19-FEB-2018	Gamma-glutamyltransferase	73 IU/l	61 8
69	26-FEB-2018	Gamma-glutamyltransferase	86 IU/l	61 8
70	05-MAR-2018	Gamma-glutamyltransferase	81 IU/l	61 8
71	08-MAR-2018	Gamma-glutamyltransferase	97 IU/l	61 8
72	13-MAR-2018	Gamma-glutamyltransferase	74 IU/l	61 8
73	20-MAR-2018	Gamma-glutamyltransferase	78 IU/l	61 8
74	26-MAR-2018	Gamma-glutamyltransferase	74 IU/l	61 8
75	03-APR-2018	Gamma-glutamyltransferase	65 IU/l	61 8
76	09-APR-2018	Gamma-glutamyltransferase	67 IU/l	61 8
77	16-APR-2018	Gamma-glutamyltransferase	64 IU/l	61 8
78	30-APR-2018	Gamma-glutamyltransferase	69 IU/l	61 8
79	02-MAY-2018	Gamma-glutamyltransferase	86 IU/l	61 8

Mfr. Control Number: 2018306611

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
80	14-MAY-2018	Gamma-glutamyltransferase	81 IU/l	61 8
81	28-MAY-2018	Gamma-glutamyltransferase	73 IU/l	61 8
82	11-JUN-2018	Gamma-glutamyltransferase	80 IU/l	61 8
83	19-JUN-2018	Gamma-glutamyltransferase	77 IU/l	61 8
84	25-JUN-2018	Gamma-glutamyltransferase	69 IU/l	61 8
85	02-JUL-2018	Gamma-glutamyltransferase	69 IU/l	61 8
86	17-JUL-2018	Gamma-glutamyltransferase	71 IU/l	61 8
87	23-JUL-2018	Gamma-glutamyltransferase	59 IU/l	61 8
88	30-JUL-2018	Gamma-glutamyltransferase	57 IU/l	61 8
89	2016	Liver function test	Normal	
90	2017	Liver function test	Normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	UNK; Unknown	Unknown	03-MAY-2018 / 29-MAY-2018; 27 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Meningitis (Meningitis);
1985 to 1985	Relevant Med History	Appendicectomy (Appendicectomy);
Unknown	Relevant Med History	Alcohol use (Alcohol use); occasional; less once per month (1 glass daily). Alcohol type: beer

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1960	57 Years	Male	80.00 kg	08	SEP	2017

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Arthralgia [Arthralgia]
Flu syndrome [Influenza]
Headache [Headache]
Rhinorrhea grade 1 [Rhinorrhoea]
Asthenia grade 1 [Asthenia]
Dyspnea on exertion grade 1 [Dyspnoea exertional]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 01-SEP-2017 / 07-SEP-2017	#1) 7 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TAHOR (ATORVASTATIN CALCIUM) ; 2012 / Ongoing
#2) ZOLOFT (SERTRALINE HYDROCHLORIDE) ; 2010 / Ongoing
#3) CANDESARTAN (CANDESARTAN) ; 2013 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2012 to Ongoing	Relevant Med History	Hypocholesterolemia (Hypocholesterolaemia)
2013 to Ongoing	Relevant Med History	Hypertension (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018306735

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
18-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 57-year-old male patient received bosutinib (BOSULIF), first regimen from 01Sep2017 to 07Sep2017 at 100 mg daily, second regimen from 08Sep2017 to 21Sep2017 at 200 mg daily, third regimen from 22Sep2017 to 05Oct2017 at 300 mg daily and fourth regimen since 06Oct2017 (ongoing) at 400 mg daily. The patient's relevant medical history included: "Hypocholesterolemia", start date: 2012 (ongoing); "Hypertension", start date: 2013 (ongoing); "Anxiodepressive", start date: 2010 (ongoing); "Diverticulitis", start date: Jul2017, stop date: Aug2017. Concomitant medication(s) included: TAHOR taken for hypercholesterolaemia, start date: 2012 (ongoing); ZOLOFT taken for depression, start date: 2010 (ongoing); CANDESARTAN taken for hypertension, start date: 2013 (ongoing).
The following information was reported: DIARRHOEA (non-serious) with onset 08Sep2017, outcome "recovered" (Oct2019), described as "Diarrhea"; ARTHRALGIA (non-serious) with onset 22Sep2017, outcome "recovered" (05Apr2018); HEADACHE (non-serious) with onset 22Sep2017, outcome "recovered" (21Dec2017); INFLUENZA (non-serious) with onset 12Oct2017, outcome "recovered" (19Oct2017), described as "Flu syndrome"; RHINORRHOEA (non-serious) with onset 26Oct2017, outcome "recovered" (Oct2017), described as "Rhinorrhea grade 1"; DYSPNOEA EXERTIONAL (non-serious) with onset 05Apr2018, outcome "recovered" (04Oct2018), described as "Dyspnea on exertion grade 1"; ASTHENIA (non-serious) with onset 04Oct2018, outcome "recovered" (04Apr2019), described as "Asthenia grade 1". The action taken for bosutinib was dosage not changed.

The reporter considered "diarrhea", "arthralgia", "flu syndrome", "headache", "rhinorrhea grade 1", "asthenia grade 1" and "dyspnea on exertion grade 1" not related to bosutinib.

Additional information: Left wrist arthropathy was a symptom of arthralgia (22Sep2017).

Follow-up (07Dec2018): New information includes: new events rhinorrhea and asthenia.

Follow-up (01Feb2019):No follow-up attempts are needed. No further information is expected.

Follow-up (14Feb2019): New information includes action taken in response to event asthenia was dose not changed.

Follow-up (12Sep2019): New information received from the Site includes updated clinical outcome (from 'not recovered' to 'recovered').

Follow-up (13Sep2019): New information received includes the recovery date of event asthenia.

Follow-up (01Jun2022): This is a Non-Interventional Study follow-up report.
Updated information: updated outcome of event diarrhea (from not recovered to recovered in Oct2019).

Follow-up (14May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: event "left wrist arthropathy" removed and new event "dyspnea on exertion grade 1", outcome of event "headache".

Amendment: This follow-up report is being submitted to amend previously reported information: arthralgia recovered on 05Apr2018

Follow-up (18Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: additional information regarding event arthralgia.

Follow-up attempts are completed. No further information is expected.

Case Comment: The company concurs with the investigator that all the reported events are unrelated to suspect drug bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	Unknown	08-SEP-2017 / 21-SEP-2017;

Mfr. Control Number: 2018306735

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
			14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	Unknown	22-SEP-2017 / 05-OCT-2017; 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	Unknown	06-OCT-2017 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2010 to Ongoing	Relevant Med History	Anxiodepressive syndrome (Mixed anxiety and depressive disorder);
JUL-2017 to AUG-2017	Relevant Med History	Diverticulitis (Diverticulitis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		DEC	1956	61 Years	Male	90.00 kg		MAR	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
alfuzosin tablet blocked in the esophagus [Dysphagia]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL, Center ID/ Subject ID 04|03.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 22-MAR-2018 / Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) KEPPRA (LEVETIRACETAM) ; 2011 / Ongoing
#2) ATORVASTATIN (ATORVASTATIN) ; Ongoing
#3) ATENOLOL (ATENOLOL) ; Ongoing
#4) RAMIPRIL (RAMIPRIL) ; Ongoing
#5) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#6) ALFUZOSINE (ALFUZOSIN HYDROCHLORIDE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2011 to Ongoing	Relevant Med History	Epilepsy (Epilepsy)
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018319859

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
30-JUL-2019

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2018319859

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 61-years-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 22Mar2018 at 100mg daily, from 23Apr2018 to 21May2018 at 200mg daily, from 22May2018 to 17Jun2018 at 300mg daily, from 18Jun2018 to 01Jul2018 at 400mg daily, then from 02Jul2018 at 500mg daily, from 22Mar2019 to 03Apr2019 at the dose of 500 mg once daily, then at 400 mg once daily from 04Apr2019, for an unspecified indication. Medical history included epilepsy from 2011 and ongoing, ongoing arterial hypertension, ongoing ischemic heart disease, ongoing dyslipidaemia. Concomitant medication included levetiracetam (KEPPRA) for epilepsy from 2011, atorvastatin for dyslipidemia, atenolol for ischemic heart disease, ramipril for ischemic heart disease, acetylsalicylate lysine (KARDEGIC) for ischemic heart disease, alfuzosin hydrochloride (ALFUZOSINE) for ischemic heart disease. On 22Apr2018, the subject experienced progressive increase of Bosulif grade 1 (as reported), assessed as non-serious. The subject experienced "alfuzosin tablet blocked in the esophagus" on 28Apr2018, seriousness reported as medical significant. The event was rated grade 1. Patient also had diarrhea with onset date Mar2018. The subject went to emergency room on 29Apr2018. It was reported that Somatuline was discontinued 01Apr2016. The action taken in response to the event for bosutinib was dose reduced. No action was taken with alfuzosin hydrochloride. The outcome of the event alfuzosin tablet blocked in the esophagus was recovered on 29Apr2018. The clinical outcome of the event diarrhea was recovered on 04Apr2019.

According to the reporter the event alfuzosin tablet blocked in the esophagus was unrelated to study drug but related to concomitant drug (unspecified).
According to the reporter the event diarrhea was related to study drug

The event progressive increase of Bosulif was reported as related to bositunib and unrelated to concomitant treatment.

Follow-up (29Aug2018). New information received includes: Study drug data (therapy dates/dosages for bosutinib), Reaction data (progressive increase of Bosulif reported as a non-serious event) and Clinical data.

Follow-up (16Nov2018): follow-up attempts completed. No further information expected.

Follow-up (30Jul2019): New information received from the CRO includes new administration dates for bosutinib, new event diarrhea, updated action taken with bosutinib

No follow-up attempt needed. No further information expected.

Case Comment: There is not a reasonable possibility that the event reported as 'alfuzosin tablet blocked in the esophagus' is related to bosutinib administration. Conversely, considering a plausible drug-event temporal association and the consistency of this event with the known safety profile of the suspect product, a reasonable possibility that diarrhea is related to bosutinib administration cannot be excluded.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	Unknown	23-APR-2018 / 21-MAY-2018; 29 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	Unknown	22-MAY-2018 / 17-JUN-2018; 27 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	Unknown	18-JUN-2018 / 01-JUL-2018; 14 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	500 mg, daily; Unknown	Unknown	02-JUL-2018 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	500 mg, daily; Unknown	Unknown	22-MAR-2019 / 03-APR-2019;

Mfr. Control Number: 2018319859

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
			13 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	400 mg, daily; Unknown	Unknown	04-APR-2019 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Ischemic heart disease (Myocardial ischaemia);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		SEP	1942	75 Years	Female	90.00 kg	08	JUN	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

renal failure [Renal failure]
cardiac failure [Cardiac failure]
sepsis suspicion [Sepsis]
Melena [Melaena]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 200 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 13-APR-2018 / 20-JUN-2018

19. THERAPY DURATION
#1) 69 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ALDACTONE /00006201/ (SPIRONOLACTONE) ; 03-MAY-2018 / 20-JUN-2018
#2) RAMIPRIL (RAMIPRIL) ; Ongoing
#3) DETENSIEL /00802601/ (BISOPROLOL) ; Ongoing
#4) PREVISCAN /00789001/ (FLUINDIONE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Cardiac failure (Cardiac failure)
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018326564

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047, (Study alias BOSEVAL). A 75-year-old female subject started to receive bosutinib (BOSULIF) from 13Apr2018 to 20Jun2018. The most recent dose before the events was 200 mg daily. The subject had a history of ongoing cardiac failure, ongoing diabetes, ongoing hypertension, ongoing renal failure and ongoing hyperuricemia. Relevant concomitant medications included spironolactone (ALDACTONE) from 03May2018 to 20Jun2018 for cardiac failure, ongoing ramipril for hypertension, ongoing bisoprolol (DETENSIEL) for hypertension and ongoing fluindione (PREVISCAN) for atrial fibrillation prophylaxis. On 08Jun2018, the subject presented with melena (grade 2) which was considered as non-serious. On 08Jun2018, the subject presented with malaise without loss of consciousness associated with a vertiginous symptomatology. 24 hours later, episodes of vomiting associated with black stool episodes occurred, possibly related to melena. The subject was on proton pump inhibitors and fluindione (PREVISCAN) (last INR control performed a week before at 1.97). Then progressive resolution of the symptomatology. No action was taken with the study drug in response to the event. The melena resolved on 12Jun2018. The subject uric acid level was at 65 mg/L on 13Jun2018 and at 69 mg/L on 16Aug2018 (normal range 26 - 60). The subject hyperuricemia was ongoing before patient enrollment. The subject developed an oligoanuric acute renal failure associated to a cardiac failure, leading to hospitalization in cardiologic palliative care for a week then to cardiology unit. Hospitalization reason: severe hyperkalemia with secondary metabolic acidosis in the context of an acute renal failure. Overdose of beta blocker drug and antivitamin K drug, severe bradycardia and atrial sinusal block. Infectious markers were high (CRP and procalcitonin) with possible septic component treated by probabilistic antibiotic therapy. During the stay, oliguria during 3 days, anemia, thrombopenia and a suspicion of ingrown toenail on right hallux were noted. Recovery of sinusal ryhthm (with stop of bisoprolol). Resumption of anticoagulant. Biological improvement. Improvement of renal function. There was no transfusion despite the persistence of a melena, and her treatment cardiologic treatment was modified with spironolactone switched to furosemide (unspecified trade name). The subject experienced renal failure and cardiac failure on 20Jun2018. Both events were rated grade 3. Both events (renal failure, cardiac failure) were in fact aggravation of pre-existing conditions which occurred after the start of study drug bosutinib. The investigator initial aware date of the events renal failure and cardiac failure was 10Jul2018, date of the consultation with the subject. Bosutinib was definitively interrupted on 20Jun2018, with no resumption of a specific treatment for now. On 20Jun2018, the subject presented with sepsis suspicion which was reported as non-serious and rated grade 3. No action was taken with bosutinib in response to sepsis suspicion. The action taken in response to the events for bosutinib was permanently withdrawn on 20Jun2018. The outcome of renal failure and cardiac failure was recovered on 03Jul2018. The event sepsis suspicion resolved on 26Jun2018.

The investigator considered the events renal failure, cardiac failure and melena as related to study drug bosutinib and unrelated to concomitant medications. The investigator considered the event sepsis suspicion as unrelated to bosutinib and to concomitant medications.

Follow-up (04Sep2018): New information received from the investigational site includes: the investigator initial aware date of the events renal failure and cardiac failure reported.

Follow-up (07Sep2018): New information received from CRO included additional events (hyperuricemia and sepsis suspicion, both non serious), causality assessment (not related), lab test results.

Follow-up (21Sep2018): New information reported includes it confirmed cardiac failure was a pre-existing condition (before start of bosutinib), but renal failure was not a pre-existing condition (renal failure not considered as medical history), and no mention of aggravation provided.

Follow-up (25Jun2019): New information received from the investigator via study site includes: new event(melena).

Follow-up (19Aug2019): New information received from the clinical team includes: medical history updated, events (renal failure, cardiac failure) confirmed as aggravation of pre-existing conditions.

Follow-up attempts completed. No further information expected.

Follow-up (20Nov2021): This is a Non-Interventional Study follow-up report received from the CRO.
Updated information: The events aggravation of renal failure and aggravation of cardiac failure were corrected to renal failure and cardiac failure respectively; lab data; clinical course details (hospitalization reason).

No follow-up attempts initiated. No further information expected.

Follow-up (20Jan2023): This follow-up is received from the investigational site CRO to a non-interventional clinical study case reporting that the investigator's initial aware date was changed "from 12Jun2018" and "03Jul2018 12Jun2018 coded" and patient's initials were added.

Follow-up (14Nov2023). This follow-up is received from in the context of reconciliation from the clinical team. Updated information: hyperuricemia (13Jun2018) deleted as event and added as medical history. Clinical course updated accordingly.

Case Comment: Cardiac failure is unlisted in the SRSD of the study drug, bosutinib, and unrelated per Company assessment.

Based on the information currently available, the Company deems the reported renal failure, cardiac failure, and melena are unlikely

Mfr. Control Number: 2018326564

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

related to the study drug, bosutinib. Of note, the patient had ongoing medical history of cardiac failure, diabetes and hypertension. Similarly, there is no evidence suggesting the reported sepsis suspicion is related to bosutinib.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to RAs, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	13-JUN-2018	Blood uric acid	65 mg/l	60 26
2	16-AUG-2018	Blood uric acid	69 mg/l	60 26
3		C-reactive protein	high	
4	JUN-2018	International normalised ratio	1.97	
5		Procalcitonin	high	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension (Hypertension);
Unknown to Ongoing	Relevant Med History	Renal failure (Renal failure);
Unknown to Ongoing	Relevant Med History	Hyperuricemia (Hyperuricaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1960	58 Years	Male	104.00 kg		MAY	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

OPERATED ANAL FISSURE [Anal fissure]
diarrhea [Diarrhoea]
hemorrhoidal flare-up [Haemorrhoids]
erysipelas [Erysipelas]
CHRONIC ASTHENIA [Asthenia]
cutaneous xerosis [Dry skin]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 22-APR-2018 / 01-MAY-2018	#1) 10 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	NONE ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018369619

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 58-year-old male patient received bosutinib (BOSULIF), first regimen from 22Apr2018 to 01May2018 at 100 mg daily, second regimen from 02May2018 to 11May2018 at 200 mg daily, third regimen since 11May2018 at 300 mg daily and fourth regimen (ongoing). There was no relevant medical history. Concomitant medications were not reported. On unknown date in May2018 the subject experienced diarrhea and on 20Jun2018 hemorrhoidal flare-up. Diarrhea was rated grade 1 and hemorrhoidal flare-up was rated grade 2. In response to the event diarrhea bosutinib was stoppage. In Aug2018 the subject experienced anal fissure rated grade 2 and requiring hospitalization. On 31Aug2018 he had surgery. On 15Apr2019, the subject experienced erysipelas and assessed grade 2. The subject received antibiotics orally from 15Apr2019 to 22Apr2019 for erysipelas. In 2019, the subject experienced chronic asthenia considered non-serious and rated grade 1. In Nov2019, the subject experienced cutaneous xerosis rated grade 1 and considered non-serious. Action taken with study drug in response to "operated anal fissure" was temporarily withdrawn, with rechallenge : negative. Study drug was ongoing at the report time. The last action taken for bosutinib in response to the events was dose not changed. The patient received paracetamol orally on 31Aug2018 as antalgic drug. The outcome of the event diarrhea was recovered on 01Oct2018, while hemorrhoidal was recovered on 24Jun2018. The event operated anal fissure resolved on 31Aug2018. Erysipelas resolved on 22Apr2019. Chronic asthenia and cutaneous xerosis were not resolved at the time of report.

The reported considered events diarrhea and hemorrhoidal as related to bosutinib. The reporter considered the event operated anal fissure, erysipelas and chronic asthenia as unrelated to bosutinib and concomitant medications (as reported). The investigator considered that the event cutaneous xerosis was unrelated to bosutinib or to a concomitant drug. The event erysipelas was not serious.

Follow-up (15Feb2019): New information received includes: bosutinib regimen data, reaction data (added operated anal fissure), and therapeutic measures.

Follow-up (22Jul2019): New information reported includes additional events (erysipelas and chronic asthenia) along with an updated clinical course.

No follow-up attempts possible. No further information expected.

Follow-up (06Jan2020): New information received from the investigational site via the CRO includes: reaction data (seriousness of event erysipelas, new non-serious event cutaneous xerosis, details of event chronic asthenia).

Follow-up (23Jan2020): New additional information received from the CRO included that erysipelas was not serious.

Follow-up (10May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047. Updated information included: start and stop dates of the events (diarrhea and hemorrhoidal crisis) and clinical course.

Follow-up (23Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site. Updated information includes: action taken in response to "operated anal fissure" and suspect drug details.

Case Comment: The Company cannot completely exclude the possible causality between the reported events, diarrhea and hemorrhoidal flare-up, and the administration of the suspect, bosutinib, based on the reasonable temporal association. Diarrhea is a known adverse reaction for bosutinib. Anal fissure, cutaneous xerosis, and erysipelas are deemed unrelated to bosutinib. The reported chronic asthenia is attributed to the patient's underlying disease, unlikely related to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Unknown	Unknown	02-MAY-2018 / 11-MAY-2018; 10 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	Unknown	11-MAY-2018 / Unknown;

Mfr. Control Number: 2018369619

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
			Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	UNK; Unknown	Unknown	Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		DEC	1977	40 Years	Female	59.00 kg		JAN	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Hepatic cytolysis [Hepatic cytolysis]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporters (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 04-DEC-2017 / 17-JAN-2018

19. THERAPY DURATION
#1) 1 month 14 days

20. DID REACTION ABATE AFTER STOPPING DRUG?
☒ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☒ NO ☐ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)
From/To Dates | Type of History / Notes | Description
Unknown

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018382510

24c. DATE RECEIVED BY MANUFACTURER
03-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 40-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 04Dec2017 to 17Jan2018 at 400 mg. The patient's relevant medical history and concomitant medications were not reported.
In Jan2018, the subject experienced hepatic cytolysis, grade 3 and diarrhea grade 2, both assessed as non-serious.
Bosutinib was temporarily withdrawn on unspecified date in response to the events. Hepatic cytolysis resolved on 19Feb2019 and diarrhea resolved on 23Feb2018. The events did not recur at the readministration of the product bosutinib.

The investigator considered the events hepatic cytolysis and diarrhea were related to study drug bosutinib and unrelated to any concomitant medications.

Follow-up (28Nov2018): Follow-up attempts completed. No further information expected.

Follow-up (30Aug2019): new information includes recovery dates of the events.

Amendment: This follow-up report is being submitted to amend previously reported information: action taken for bosutinib updated to temporarily withdrawn, the events did not recur at the readministration of the product.

Follow-up (03Oct2023): This is a non-interventional study follow-up report received from the clinical team in response to query; for Protocol B1871047 (Study alias BOSEVAL). Updated information included after query reply: Bosulif dosing and dates of therapy provided.

Case Comment: Considering the plausible drug-event temporal association, the consistency of the event with the known safety profile of the Pfizer study drug, there is a reasonable possibility that the reported hepatic cytolysis and diarrhea are related to bosutinib administration.

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1948	70 Years	Female	64.00 kg	21	SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

dyspnea [Dyspnoea]
Anorexia [Decreased appetite]
Dysgeusia [Dysgeusia]
vesicular eruption [Rash vesicular]
Oral mycosis [Fungal infection]
skin dryness [Dry skin]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) BACTRIM (SULFAMETHOXAZOLE, TRIMETHOPRIM)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) UNK	#1) Unknown
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Unknown
#2) PROPHYLAXIS (Prophylaxis)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) Unknown / 12-OCT-2018	#1) Unknown
#2) 05-SEP-2018 / Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) PENTACARINAT (PENTAMIDINE ISETHIONATE) ; 25-OCT-2018 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
APR-2018 to MAY-2018	Relevant Med History	Dyspnea (Dyspnoea) with diagnosis of pneumocystosis type pneumopathy on 16Aug2018
16-AUG-2018 to Unknown	Relevant Med History	Pneumocystosis (Pneumocystis jirovecii pneumonia) dyspnea during a travel in Peru in Apr-May2018

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018398804

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
13-MAY-2020

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a report from Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. This is a post-authorization safety study.

A 70-year-old female subject started to receive bosutinib (BOSULIF, film-coated tablet) via an unspecified route of administration, from an unspecified date to 12Oct2018, at unknown dose and frequency, for unspecified indication. Co-suspect medication included sulfamethoxazole / trimethoprim (BACTRIM) since 05Sep2018 by oral route as prophylaxis. Relevant medical history included dyspnea during a travel in Peru in Apr-May2018 with diagnosis of pneumocystosis type pneumopathy on 16Aug2018, arterial hypertension, thyroid nodule, chronic gastritis, asthma and osteoporosis. The subject experienced anorexia grade 1 and dysgeusia grade 1, on 24Sep2018. On 21Sep2018, the subject experienced dyspnea rated grade 2 and requiring hospitalization, and vesicular eruption rated grade 2 occurred on 25Sep2018 and were assessed as non-serious. The investigator commented that the subject presented with dyspnea and cough leading to hospitalization in pneumology unit. Vesicular eruption involved the palm of hands and the sole of the foot. The subject experienced oral mycosis on 25Sep2018. Sulfamethoxazole / trimethoprim was permanently withdrawn in response to vesicular eruption. Sulfamethoxazole / trimethoprim was switched to atovaquone (WELVONE). Then, due to multiple functional signs, it was decided during multidisciplinary due diligence meeting to stop bosutinib on 12Oct2018 and to carry out a therapeutic window of two to three months. On 25Oct2018, corticosteroid therapy and atovaquone were stopped and pentamidine (PENTACARINAT) was introduced. The subject experienced skin dryness grade 1 on 26Oct2018. During pneumonology consultation on unspecified date, symptomatology was improving but images on CT scan still found friction in left lung basis. During the whole consultation, there was a persistent cough. The subject was apyretic and her pulmonary auscultation was subnormal (few frictions on the left basis). On the cutaneous level, cutaneous symptomatology had disappeared, the skin remained dry only. The subject recovered from the events on 26Oct2018 except skin dryness that resolved on 27Nov2018. The reporter considered skin dryness was non-serious. In response to anorexia, dysgeusia, and dyspnea, bosutinib was withdrawn on 12Oct2019. The event anorexia was considered as related to study drug bosutinib and unrelated to concomitant medications. Dysgeusia was considered as related to bosutinib and unrelated to concomitant medications. The event dyspnea was considered as related to study drug bosutinib. Skin dryness resolved on 27Nov2018 and relatedness assessment was not applicable as it occurred after bosutinib discontinuation on 12Oct2018. The event vesicular eruption resolved on 26Oct2018 and was considered as unrelated to bosutinib, sulfamethoxazole / trimethoprim related, and related to concomitant medication atovaquone. There was also appearance of abdominal/lower back pain in the context of chronic cough in a possible context of osteoporosis under corticosteroid therapy. It had been previously decided to do a 2 to 3-month-therapeutic rest period. Therefore, no hematological therapy was resumed upon the consultation. A further blood hematological evaluation (blood count and BCR-ABL, the latter 3 months from the previous one) was planned in end-Nov2018 and a further consultation was scheduled on 12Dec2018. A consultation in infectiology was scheduled and the potentially infectious symptomatology will be discussed. The event oral mycosis was rated grade 1 and was considered as unrelated to study drug bosutinib and unrelated to concomitant medications. No action was taken in response to oral mycosis. The last action taken in response to the events for all suspect products was permanently withdrawn.

The investigator considered that the event skin dryness was unrelated to the study drug or to a concomitant drug. The event vesicular eruption resolved on 26Oct2018 and was considered as unrelated to bosutinib, sulfamethoxazole / trimethoprim related, and related to concomitant medication atovaquone (WELLVONE). The event oral mycosis was rated grade 1 and was considered as unrelated to study drug bosutinib and unrelated to concomitant medications.

Follow-up (15Nov2018): New information received from the investigational site included: medical history; lab data; stop date of bosutinib; events outcome.
Follow-up attempts are completed. No further information is expected.

Follow-up (24Apr2019): New information reported from the clinical team includes clinical course with new events (anorexia with ageusia, oral mycosis, dysgeusia and dry skin).

Follow-up (24May21019): New information received from CRO included start date of events (anorexia with dysgeusia, oral mycosis), outcome of the events(anorexia with dysgeusia, oral mycosis).

Follow-up (29May2019): New information received from the investigational site via the CRO included the event verbatim "Dry skin" changed to "skin dryness", seriousness and causal assessment provided (non-serious and unrelated), event skin dryness outcome updated to recovered.

Follow-up (27Aug2019 and 28Aug2019): New information includes recovery date of skin dryness, updated outcome of the other events, ageusia changed to dysgeusia, onset date of dyspnea, clarification on causality assessment, updated recovery date of dyspnea. The event dysgeusia (26Sep2018) was no longer reported. The onset date of the event vesicular and erythematous eruption was corrected from 24Sep2018 to 25Sep2018, clear causal relationship was provided.

Follow-up (29Aug2019): New information received from the CRO includes: the action taken with bosutinib in response to the event dyspnea (21Sep2018) was updated to withdrawal.

Follow-up (01Oct2019): New information received includes: clinical course (consultation report on 26Oct2018), additional lab data, confirmation of event (the cough (reported as occurring with dyspnea and also causing hospitalization) was not to be reported as

Mfr. Control Number: 2018398804

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

adverse event and was due to medical history of pneumocystosis, and unrelated to pentamidine).

Follow-up (17Oct2019): New information received from the investigational site includes: pentamidine was not considered as a concomitant suspect drug.

Follow-up (13May2020): New information received from CRO included: event term "vesicular and erythematous eruption" updated to "vesicular eruption".

Case Comment: The company concurs with the investigator that the event vesicular eruption was unrelated to bosutinib. Event is likely attributed to sulfamethoxazole / trimethoprim administration based on temporal association and positive dechallenge. Considering a plausible drug event temporal association and the consistency of these events with the known safety profile of the suspect product, a reasonable possibility that dyspnea, anorexia and dysgeusia are related to bosutinib administration cannot be excluded. Oral mycosis and dry skin are deemed unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	26-OCT-2018	Auscultation	subnormal	
2	26-OCT-2018	Auscultation	subnormal, a few frictions on the left basis	
3	26-OCT-2018	Body temperature	apyrexia	
4	26-OCT-2018	Computerised tomogram	friction in left lung basis	
5	26-OCT-2018	Physical examination	persisting cough, dry skin	
		persisting cough, cutaneous symptoms disappeared, skin only dry, appearance of abdominal/lower back pain		

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#3) WELLVONE (ATOVAQUONE) ; Regimen #1	UNK; Unknown	Unknown	Unknown / 25-OCT-2018; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Arterial hypertension (Hypertension);
Unknown	Relevant Med History	Thyroid nodule (Thyroid mass);
Unknown	Relevant Med History	Chronic gastritis (Chronic gastritis);
Unknown	Relevant Med History	Asthma (Asthma);
Unknown	Relevant Med History	Osteoporosis (Osteoporosis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUL	1961	57 Years	Female	118.00 kg		SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Weight loss [Weight decreased]
Cough without fever [Cough]
Nausea [Nausea]
Asthenia [Asthenia]
EPIGASTRALGIA [Abdominal pain upper]
Memory disorders [Memory impairment]
interphalangeal proximal digital arthritis [Arthritis]
bowel obstruction [Intestinal obstruction]
conjunctivitis [Conjunctivitis]
Recurrent aphthosis [Aphthous ulcer]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 200 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 25-SEP-2018 / 07-DEC-2020

19. THERAPY DURATION
#1) 2 years 2 months 13 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TRAMADOL (TRAMADOL) ; 27-JUN-2017 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1990 to 1990	Relevant Med History	Hemorrhoids (Haemorrhoids)
1999 to 1999	Relevant Med History FRACTURE L1L2	Lumbar vertebral fracture (Lumbar vertebral fracture)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018422480

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Rhinitis [Rhinitis]
Vertigo [Vertigo]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 57-year-old female patient received bosutinib (BOSULIF), first regimen from 25Sep2018 to 07Dec2020 at 200 mg daily and second regimen since 08Dec2020 (ongoing) at 300 mg daily. The patient's relevant medical history included: "Hemorrhoid cure", start date: 1990, stop date: 1990; "FRACTURE L1L2", start date: 1999, stop date: 1999, notes: FRACTURE L1L2; "HYSTERECTOMY ENDOMETRIOSIS", start date: 2004, stop date: 2004; "HYSTERECTOMY ENDOMETRIOSIS", start date: 2004, stop date: 2004; "CHRONIC DIVERTICULOSIS" (unspecified if ongoing), notes: CHRONIC; "surgery of right shoulder" (unspecified if ongoing), notes: surgery of right shoulder; "cholecystectomy" (unspecified if ongoing); "Colic diverticulosis" (unspecified if ongoing); "Non-steroidal anti-inflammatory drug sensitivity" (unspecified if ongoing), notes: Non-steroidal anti-inflammatory drug sensitivity; "CML" (ongoing).
Concomitant medication(s) included: TRAMADOL oral taken for analgesic therapy, start date: 27Jun2017 (ongoing).
The following information was reported: ABDOMINAL PAIN UPPER (non-serious) with onset Sep2018, outcome "not recovered", described as "EPIGASTRALGIA"; NAUSEA (non-serious) with onset Sep2018, outcome "recovered" (Jun2019); WEIGHT DECREASED (non-serious) with onset Sep2018, outcome "not recovered", described as "Weight loss"; COUGH (non-serious) with onset Nov2018, outcome "not recovered", described as "Cough without fever"; MEMORY IMPAIRMENT (non-serious) with onset Dec2018, outcome "recovered" (24Jun2019), described as "Memory disorders"; ARTHRITIS (non-serious) with onset Dec2018, outcome "not recovered", described as "interphalangeal proximal digital arthritis"; VERTIGO (non-serious) with onset 18Dec2018, outcome "not recovered"; INTESTINAL OBSTRUCTION (non-serious) with onset 2019, outcome "recovered" (05Nov2019), described as "bowel obstruction"; CONJUNCTIVITIS (non-serious) with onset 2019, outcome "recovered" (2020); ASTHENIA (non-serious) with onset 05Nov2019, outcome "not recovered"; APHTHOUS ULCER (non-serious) with onset 07Apr2020, outcome "not recovered", described as "Recurrent aphthosis"; RHINITIS (non-serious) with onset 2020, outcome "recovered" (08Dec2020). Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of cough, nausea, intestinal obstruction.
In Sep2018, the subject developed weight loss, rated grade 1 and considered as non-serious. In the medical report dated 18Dec2018, the subject's weight was 111 kg (loss of 7 kg). No action was taken with bosutinib in response to the event. The event had not resolved. In Sep2018, the subject developed nausea, rated grade 2 and considered as non-serious. The event epigastralgia, grade 2, occurred in Sep2018. In Nov2018, the subject developed cough without fever, rated grade 2 and considered as non-serious. According to the medical report of 18Dec2018, there was nausea with cough without fever for a month. Antibiotic therapy was initiated on 15Nov2018. A chest X-ray performed in Nov2018 disclosed bronchial syndrome. On 18Dec2018 the subject experienced vertigo, non-serious. On 18Dec2018, the subject experienced memory disorders, non-serious (Grade 1) and on an unknown date is Dec2018 the subject experienced interphalangeal proximal digital arthritis, non-serious (Grade 1). The last consultation on 05Nov2019 stated that the subject experienced bowel obstruction (treated) and conjunctivitis since the last consultation. The event bowel obstruction occurred on unspecified date in 2019 was rated grade 2 and assessed as non-serious and the event conjunctivitis occurred on unspecified date in 2019 was rated grade 1 and assessed as non-serious. Clinical examination on 05Nov2019 revealed performance status at 0 and soft abdomen. On 05Nov2019, the subject developed asthenia, rated grade 2 and considered as not serious. In the medical report of 05Nov2019, asthenia was described. The event did not resolve. In the medical report of 07Apr2020, huge fatigue was still described. On 07Apr2020, the subject was found to have recurrent aphthosis assessed as non-serious (rated grade 1). The subject experienced rhinitis on an unspecified date in 2020. In the report of 08Dec2020, the event rhinitis was rated grade 2. PCR COVID was negative from the last consultation. Action taken as a result of the events was dose not changed. On 05Nov2019, the subject recovered from the event bowel obstruction. The clinical outcome of rhinitis was recovered on 08Dec2020, memory disorders was recovered on Mar2019, nausea was resolved in Jun2019, conjunctivitis was recovered on an unspecified date in 2020, cough without fever was recovered on 28Mar2022 and the subject had not recovered from the remaining events. On 27Sep2023, the investigator via the CRO reported Investigator Initial Aware Date (Memory disorders): 18Mar2019. Event Memory disorders updated: onset date Dec2018 (previously 18Dec2018) and stop date 24Jun2019 (previously Mar2019). On 28Sep2023, Relevant medical history lumbar pain was removed. The outcome of the event Cough without fever was not recovered

The investigator considered the events weight loss, nausea, epigastralgia, cough without fever and asthenia as related to bosutinib and unrelated to concomitant medications. According to the reporter, the events memory disorders, interphalangeal proximal digital arthritis, bowel obstruction, conjunctivitis, recurrent aphthosis and vertigo unrelated to study drug and to concomitant medications; event rhinitis was not related to study drug and concomitant drug.

Follow-up (20Dec2018): New information received included subject's age updated, bosutinib dose and start date provided, medical history and lab data updated, added new events weight loss, nausea with epigastralgia and cough.

Follow-up (28Feb2019): New information received from the investigational site included: medical history data (cholecystectomy, colic diverticulosis and non-steroidal anti-inflammatory drug sensitivity) and event data (verbatim term updated to epigastralgia (previously nausea with epigastralgia).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (29Mar2019): New information reported includes new event (memory disorders) added.

Follow-up (22May2019): New information reported includes new event (interdigital and fingers arthritis) added.

Follow-up (07Nov2019): New information reported included lab data, new events (bowel obstruction and conjunctivitis).

Follow-up (05Jun2020): New information reported includes new event asthenia.

Follow-up (11Aug2020); New information reported from CRO includes additional event aphtous ulcer.

Follow-up (11Feb2021): New information received included: Reaction data (added new rhinitis) and Lab data.

Follow-up (23Feb2021): New received from the investigational site included: updated event term and onset date of recurrent aphthosis; event epigastralgia updated to nausea; outcome of nausea; onset date and outcome of memory disorders; onset date of interdigital and fingers arthritis.

Follow-up (15Mar2021): New information received from CRO included: updated outcome of the event conjunctivitis (from unknown to recovered).

Follow-up (25Oct2021, 03Dec2021): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047 received from CRO.
Updated information: event vertigo outcome, new event epigastralgia.

Follow-up (23May2023): This is a non-interventional study follow-up report from the investigational site via the CRO.
Updated information included: outcome for event Cough without fever updated to recovered on 28Mar2022.

Follow-up attempts are completed. No further information is expected.

Follow-up (12Jul2023): This is a non-interventional study follow-up report from the investigational site via the CRO.
Updated information included clinical details.

Follow-up (24Jul2023): This is a non-interventional study follow-up report from the investigational site via the CRO.
Updated information included: additional dosage of boseval coded.

Follow-up (24Jul2023): This is a follow-up report from the investigator via CRO. Updated information included: details of event rhinitis (rated grade 2, unrelated to concomitant drug).

Follow-up (28Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information included: updated dosage regimens.

Follow-up (27Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information includes: relevant medical history data (neuropathy of the 4 limbs and algodystrophy were removed and going CML added), reaction data (event term "Interdigital and fingers arthritis" on 18Dec2018 was changed to "interphalangeal proximal digital arthritis" from Dec2018, grade 1; grade for event recurrent aphthosis provided as Grade 1; outcome of event epigastralgia was changed from resolved on 05Nov2019 to not resolved); and product data.

Follow-up (27Sep2023 and 28Sep2023): new information received from the investigator via the CRO. On 27Sep2023, the investigator via the CRO reported Investigator Initial Aware Date (Memory disorders): 18Mar2019. Event Memory disorders updated: onset date Dec2018 (previously 18Dec2018) and stop date 24Jun2019 (previously Mar2019). Relevant medical history lumbar pain was removed. The outcome of the event Cough without fever was changed to not recovered.

Follow-up attempts are completed. No further information is expected.

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from clinical team following reconciliation between clinical and safety databases. Updated information: event pruritus was deleted.

Case Comment: Based on available information, the reported events pruritus, memory impairment and arthritis are assessed as unrelated to bosutinib. Based on a temporal relationship and the known drug safety profile, the reported events weight loss, cough, nausea, epigastralgia and asthenia are considered related to bosutinib. The events bowel obstruction, rhinitis, vertigo, arthritis, aphtous ulcer, memory impairment and conjunctivitis are assessed as unrelated to bosutinib. The subject's significant medical history/risk factors for bowel obstruction included hysterectomy endometriosis, chronic diverticulosis and colic diverticulosis.

Mfr. Control Number: 2018422480

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	NOV-2018	Chest X-ray	bronchial syndrome	
2	05-NOV-2019	Eastern Cooperative Oncology Group performance status	0	
3	05-NOV-2019	Physical examination	soft abdomen	
4		SARS-CoV-2 test Negative	negative	
5	18-DEC-2018	Weight loss of 7 kg	111 kg	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	Unknown	08-DEC-2020 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2004 to 2004	Relevant Med History	Hysterectomy (Hysterectomy);
2004 to 2004	Relevant Med History	Endometriosis (Endometriosis);
Unknown	Relevant Med History CHRONIC	Diverticulosis (Diverticulum);
Unknown	Relevant Med History surgery of right shoulder	Shoulder operation (Shoulder operation);
Unknown	Relevant Med History	Cholecystectomy (Cholecystectomy);
Unknown	Relevant Med History	Diverticulum intestinal (Diverticulum intestinal);
Unknown	Relevant Med History Non-steroidal anti-inflammatory drug sensitivity	Drug hypersensitivity (Drug hypersensitivity);
Unknown to Ongoing	Relevant Med History	CML (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1934	84 Years	Female	60.00 kg			2016

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Multi organ failure [Multiple organ dysfunction syndrome]
Pneumopathy [Lung disorder]
Constipation [Constipation]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP)

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 30-OCT-2018
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) DUROGESIC (FENTANYL)
(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, 1x/day	#1) Unknown
#2)	#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 24-JUL-2016 / 30-JUL-2016	#1) 826 days
#2) Unknown	#2) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☒ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LASILIX [FUROSEMIDE] (FUROSEMIDE) ; 2016 / Ongoing
#2) NEBIVOLOL (NEBIVOLOL) ; 2016 / Ongoing
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 12-APR-2013 / Ongoing
#4) ALLOPURINOL (ALLOPURINOL) ; 18-JUN-2018 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia)
Unknown to Ongoing	Relevant Med History	Osteitis (Osteitis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018441517

24c. DATE RECEIVED BY MANUFACTURER
04-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

for protocol B1871047.

An 84-year-old female subject received bosutinib (BOSULIF), first regimen from 24Jul2016 to 30Jul2016 at 100 mg 1x/day and second regimen since 31Jul2016 to 28Oct2018 at 200 mg 1x/day; fentanyl (DUROGESIC), (Batch/Lot number: unknown). The patient's relevant medical history included: "Hypercholesterolemia" (ongoing); "Osteitis" (ongoing); "Gout" (ongoing); "Arterial disease" (ongoing). Concomitant medications included furosemide (LASILIX) taken for diuretics from 2016 and ongoing, nebivolol taken for hypertension arterial from 2016 and ongoing, acetylsalicylate lysine (KARDEGIC) taken for blood thinning agent from 12Apr2013 and ongoing, allopurinol taken for gout from 18Jun2018 and ongoing. The subject experienced dyspnea, which was updated to an event of "pneumopathy", and the onset date was Jun2018. The site described alteration of the general state, arterial hypertension, acute respiratory distress, acute hepatocellular insufficiency, hypoglycemia, anemia, hyperkalemia, lactic acidosis, alteration of renal function, colitis (e. Coli infection), edema of the lower limbs, constipation, crisis of anxiety. The seriousness of pneumopathy was hospitalization and event grade CTCAE was grade 4. It was also reported the subject experienced a non-serious event of constipation grade 2. In response to this event, macrogol 3350, sodium bicarbonate, potassium chloride, sodium chloride (MOVICOL) was introduced. Bosutinib was ongoing at the event pneumopathy onset in Jun2018 and it was permanently withdrawn in response to the events on 28Oct2018. No action was taken with fentanyl in response to the event constipation. On 30Oct2018, the subject experienced multi organ failure/multivisceral failure, which led to death on the same day. De-challenge of bosulif was considered negative. Investigator was aware of death on 22Jan2019, when family was called following subject absence for planned visit. It was unknown if an autopsy was performed. "arterial hypertension, acute respiratory distress, acute hepatocellular insufficiency, hypoglycemia, anemia, hyperkalemia, lactic acidosis, alteration of renal function, colitis (e. Coli infection), edema of the lower limbs, constipation, crisis of anxiety" all these symptoms were related to the adverse event "Multi organ Failure". The outcome of constipation and pneumopathy was not resolved at the time of death.

According to the investigator, the event pneumopathy was related to study drug bosutinib but not related to concomitant drugs, while multi organ failure was not related to study drug or to concomitant treatment. Constipation was unrelated to study drug bosutinib and related to concomitant drug fentanyl (DUROGESIC).

Follow-up (23Jan2019): New information received from the study coordinator includes: outcome of the event, date and cause of the patient death.

Follow-up (25Jan2019 and 29Jan2019). New information includes: multi organ failure added as fatal event, dyspnea was confirmed to be non-fatal (outcome changed to not recovered), action taken updated to permanently withdrawn.

Follow-up (31May2022): New information was received from a non-interventional study from the investigational site via the CRO reporting information updating the event to pneumopathy, an additional non-serious event of constipation, and information regarding the subject's clinical course.

No follow-up attempt initiated. No further information expected.

Follow-up (13Jun2022): This is a non-interventional study follow up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: event "Multi organ Failure" details.

Follow-up (06Jul2023): This is a follow-up report received from the CRO updating pneumopathy onset date update, reporting de-challenge information, and grade of constipation.

Follow-up (31Jul2023): This follow-up is received from the investigator via the CRO. Updated information: medical history (all ongoing), suspect product data (dose regimens).

Follow-up (02Oct2023): This is a non-interventional follow-up study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information includes: bosulif stop date and confirmation that it was ongoing at the time of the event "Lung disorder".

Follow-up (04Oct2023): New information received from CRO reporting information regarding action taken,

Case Comment: Lung disorder is unlisted in the SRSD of Bosutinib and related per Company assessment.

The Company cannot completely exclude the possible causality between the reported Lung disorder and administration of the suspect drug, bosutinib, based on the reasonable temporal association. Based on the limited information provided, the Company concurs with the investigator that the event multi organ failure with fatal outcome and constipation are unrelated to bosutinib. Case will be re-evaluated when additional information becomes available.

The impacts of this report on the benefit/risk profile of the product are evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees and Investigators, as

Mfr. Control Number: 2018441517

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

appropriate.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Unknown	Unknown	31-JUL-2016 / 28-OCT-2018; 2 years 2 months 28 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Gout (Gout);
Unknown to Ongoing	Relevant Med History	Arterial disorder (Arterial disorder);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		SEP	1970	48 Years	Female	78.00 kg	14	SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Hepatic cytolysis [Hepatic cytolysis]
Diarrhea [Diarrhoea]
Diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, 1x/day	#1) Oral

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 13-SEP-2018 / 14-SEP-2018	#1) 2 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CRESTOR (ROSUVASTATIN CALCIUM) ; MAY-2013 / Ongoing
#2) ASPIRINE (ACETYLSALICYLIC ACID) ; 2006 / Unknown
#3) CYSTIPHANE (ARGININE, CYSTEINE, PYRIDOXINE HYDROCHLO

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2006 to 2006	Relevant Med History	Pulmonary embolism (Pulmonary embolism)
2006 to 2006	Relevant Med History	Deep venous thrombosis NOS (Deep vein thrombosis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018471361

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
07-DEC-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 48-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), first regimen from 13Sep2018 to 14Sep2018 at 200 mg 1x/day, second regimen from 17Sep2018 to 23Sep2018 at 200 mg 1x/day, third regimen from 24Sep2018 to 27Sep2018 at 300 mg 1x/day and fourth regimen (ongoing) at 200 mg 1x/day, all oral. The patient's relevant medical history included: "Pulmonary embolism", start date: 2006, stop date: 2006; "Deep venous thrombosis", start date: 2006, stop date: 2006; "Respiratory syndrome", start date: 2001 (ongoing); "Migraine", start date: 1995 (ongoing). Concomitant medication(s) included: CRESTOR oral taken for dyslipidaemia, start date: May2013 (ongoing); ASPIRINE oral taken for thrombosis prophylaxis, start date: 2006; CYSTIPHANE oral taken for alopecia, start date: 12Sep2018.
The following information was reported: DIARRHOEA (non-serious) with onset 14Sep2018, outcome "recovered" (16Sep2018), DIARRHOEA (non-serious) with onset 27Sep2018, outcome "recovered" (15Oct2018) and all described as "Diarrhea"; HEPATIC CYTOLYSIS (non-serious) with onset 09Oct2018, outcome "recovered" (30Apr2019). Clinical course: Events diarrhea were Grade 2. Bositunib was temporarily withdrawn in response to diarrhea of 14Sep2018 and dose decreased in response to the diarrhea of 27Sep2018. Alanine aminotransferase (ALT) was measured at 95 IU/L on 16Oct2018, assessed as grade 1 (normal range - 33), at 124 IU/L, on 30Oct2018, assessed as grade 2, at 221 IU/L on 13Nov2018, assessed as grade 3, at 70 IU/L on 27Nov2018, assessed as grade 1. The patient experienced hepatic cytolysis on 09Oct2018, rated grade 3 and reported as non-serious. Acknowledgement of the adverse event by doctor (dr) on 08Nov2018. The action taken for bosutinib was dosage reduced (bosutinib was temporarily withdrawn at first, and dose decreased at last).

According to the investigators, events were related to bosutinib and unrelated to concomitant drugs.

Follow-up (09Jan2019): New information received from CRO includes new event (hepatic cytolysis), outcome, seriousness and assessment.

Follow-up (01Apr2019): follow-up attempts completed. No further information expected.

Follow-up (12Feb2021): New information received from CRO includes: event outcome, action taken, suspect product data (new dose regimen).

Follow-up (09MAY2022): New information received from investigational site via CRO included: hepatic cytolysis onset date updated to 09Oct2018.

Follow-up (24Apr2023): This is a Non-Interventional study follow-up report for protocol B1871047. Updated information included: patient details (patient's initials); suspect drug details (fourth dosage regimen's start and stop date from 16Oct2018 to 31Mar2019 were deleted and updated as ongoing); and clinical course.

Follow-up attempts are completed. No further information is expected.

Amendment: This follow-up report is being submitted to amend previously reported information: narrative was updated to reflect correct lead sentence.

Amendment: This follow-up report is being submitted to amend previously reported information: event "hepatic cytolysis" was reported as non-serious (previously medically significant was ticked), action taken for bosutinib was updated to dose reduced (previously temporarily withdrawn).

Follow-up (23Nov2023): This is a non-interventional study follow-up report received from the investigator via CRO for protocol B1871047. Updated information: clarification on action taken.

Follow-up (07Dec2023) This is a non-interventional study follow-up report received from the investigator via CRO for protocol B1871047.
Additional information: clarification on action taken.

Case Comment: Based on the available information, a causal relationship cannot be excluded between the suspect study drug bosutinib and the reported event hepatic cytolysis. Drug causality for suspect drug in the onset of the reported episodes of diarrhea cannot be excluded. The events are not related to concomitant medications.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-OCT-2018	Alanine aminotransferase	95 IU/l	33
2	30-OCT-2018	Alanine aminotransferase	124 IU/l	33

Mfr. Control Number: 2018471361

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
3	13-NOV-2018	Alanine aminotransferase	221 IU/l	33
4	27-NOV-2018	Alanine aminotransferase	70 IU/l	33

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, 1x/day; Oral	Unknown	17-SEP-2018 / 23-SEP-2018; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, 1x/day; Oral	Unknown	24-SEP-2018 / 27-SEP-2018; 4 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, 1x/day; Oral	Unknown	Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#3) CYSTIPHANE (ARGININE, CYSTEINE, PYRIDOXINE HYDROCHLORIDE, ZINC) ; 12-SEP-2018 / Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2001 to Ongoing	Relevant Med History	Respiratory abnormality, unspecified (Respiratory disorder);
1995 to Ongoing	Relevant Med History	Migraine (Migraine);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1963	55 Years	Female	Unk	06	OCT	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
lung pain [Pulmonary pain]
diarrhea [Diarrhoea]
vomiting [Vomiting]
headache [Headache]
Rhinorrhea [Rhinorrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 300 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 06-OCT-2018 / 19-OCT-2018

19. THERAPY DURATION
#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ERYTHROMYCIN (ERYTHROMYCIN) ; SEP-2018 / 22-OCT-2018
#2) SPRYCEL (DASATINIB MONOHYDRATE) ; 06-NOV-2018 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Von Willebrand's disease (Von Willebrand's disease)
Unknown to Ongoing	Relevant Med History	Hashimoto's thyroiditis (Autoimmune thyroiditis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018475286

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
29-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 55-year-old female subject received bosutinib (BOSULIF), first regimen from 06Oct2018 to 19Oct2018 at 300 mg 1x/day and second regimen from 22Oct2018 to 27Oct2018 at 100 mg 1x/day for chronic myeloid leukaemia. The subject's relevant medical history included: "Willebrand's disease" (ongoing); "Hashimoto's thyroiditis" (ongoing); "Left eye blindness" (ongoing); "Right sciatalgia" (ongoing); "Hysterectomy" (unspecified if ongoing); "Appendicectomy" (unspecified if ongoing); "Interstitial pneumopathy" (ongoing); "Cough" (ongoing); "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: ERYTHROMYCIN taken for lung disorder, start date: Sep2018, stop date: 22Oct2018; SPRYCEL oral taken for chronic myeloid leukaemia, start date: 06Nov2018 (ongoing).
The subject experienced grade 3 diarrhea, grade 3 vomiting and grade 2 headache, all from the beginning of bosutinib intake on 06Oct2018. Subject discontinued bosutinib on 19Oct20218. Raison discontinuation: treatment was discontinued from 20Oct2018 to 21Oct2018 due to onset of major digestive disorders de associating diarrhea, vomiting grade 3, and headache grade 2. Bosutinib resumed at 100 mg a day on 22Oct2018 and spontaneously discontinued by the subject due to recurrence of digestive disorders grade 3. Diarrhea and vomiting of grade 3 and headache, grade 2 continued. Bosutinib was permanently withdrawn on 27Oct2018. On 31Oct2018, the subject experienced rhinorrhea which was rated grade 1 and reported as non-serious. In Oct2018, the subject experienced lung pain which was assessed as medically significant and was rated grade 2. The reporter stated that the subject went to the emergency room only for consultation. The subject was not hospitalized for the event. Lab test included X-ray on an unspecified date was normal. Cardiological examination on 31Oct2018 showed rhinorrhea. Consultation of otorhinolaryngology on 02Jan2019 showed a normalization. Last action taken for bosutinib was dosage permanently withdrawn on 27Oct2018. The outcome of events diarrhea, vomiting and headache was recovered on 27Oct2018, of event lung pain was recovered in Jan2019, of event rhinorrhea was resolved in Dec2018.

According to the investigator events diarrhea, vomiting and headache were related to study drug and unrelated to concomitant treatments.
The investigator considered there was not a reasonable possibility that the events lung pain and rhinorrhea were related to the study drug.

Follow-up (11Dec2018): New information includes medical history, concomitant medications, and stop date of bosutinib (updated to 27Oct2018).

Follow-up (23May2019): New information reported includes updated dosage regimen for bosutinib, additional events lung pain following cough (serious) and rhinorrhea, laboratory data.

Follow-up (12Jul2019): New information received included: start date of bosutinib; seriousness of event lung pain following cough (deleted hospitalization); removed grade 3 diarrhea, grade 3 vomiting and grade 2 headache to medical history.

Follow-up (11Sep2019). New information received from CRO includes: additional non-serious event (cough), verbatim of pulmonary pain updated (from "lung pain following cough" to "lung pain"), outcome and causality of the new event.

Follow-up (07Oct2020): New information received from CRO includes: event outcome (updated to recovered on 14Dec2018 for event "lung pain").

Follow-up (05Feb2021): New information received from the investigational site via clinical team included: started date of bosutinib, events "diarrhea, vomiting and headache" added (not medical history), action taken updated to permanently withdrawn.

Follow-up (23Apr2021): New information received from the study coordinator includes: dose regimen of bosutinib updated, onset date of events (diarrhea, vomiting and headache) updated, and clinical course updated.

Follow-up (28Jul2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047. Updated information included: stop date of the events (Rhinorrhea and lung pain), event cough deleted.

Follow-up (23Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information included: relevant medical history, concomitant medications, stop date for bosutinib.

Follow-up (29Jun2023): This is a follow-up report to notify that the case AER 2021129710 and AER 2018475286 are duplicates. All subsequent follow-up information will be reported under manufacturer report number AER 2018475286 .

Case Comment: In concurrence with the reporting investigator, the Company considers the reported rhinorrhea occurred 6 days after the last dose of bosutinib is unrelated to bosutinib. Similarly, the reported lung pain is unrelated to bosutinib administration, as well. Based on the temporal relationship and known safety profile of bosutinib, the reasonable possibility of an association between

Mfr. Control Number: 2018475286

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

diarrhea, vomiting, headache and suspect product cannot be ruled out. This case will be re-assessed should additional information become available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	31-OCT-2018	Cardiovascular examination	rhinorrhea	
2	02-JAN-2019	Ear, nose and throat examination	normalization	
3		X-ray	normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	100 mg, 1x/day; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	22-OCT-2018 / 27-OCT-2018; 6 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Blindness, one eye (Blindness unilateral);
Unknown to Ongoing	Relevant Med History	Sciatica (Sciatica);
Unknown	Relevant Med History	Hysterectomy (Hysterectomy);
Unknown	Relevant Med History	Appendicectomy (Appendicectomy);
Unknown to Ongoing	Relevant Med History	Interstitial pneumonitis (Interstitial lung disease);
Unknown to Ongoing	Relevant Med History	Cough (Cough);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1939	79 Years	Male	Unk	27	AUG	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

dry mouth syndrome [Dry mouth]
Constipation [Constipation]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. This is a non-interventional clinical study case reporting non-serious event only.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☒ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, daily	#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 05-FEB-2018 / 26-MAY-2019	#1) 476 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) XARELTO (RIVAROXABAN) ; Ongoing
#2) HYTACAND (CANDESARTAN CILEXETIL, HYDROCHLOROTHIAZIDE) ; Ongoing
#3) ATORVASTATIN (ATORVASTATIN) ; Ongoing
#4) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#5) DIFFU K (POTASSIUM CHLORIDE) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History treated	Arterial hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History treated with COLCHIMAX and COLCHICINE	Gout attack (Gout)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2018477291

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
24-JAN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a post-authorization safety study.
A 79-year-old male subject of an unspecified ethnicity started to receive bosutinib (BOSULIF) at 200 mg daily by oral route on 05Feb2018 to 26May2019 and then at 150 mg daily since 27May2019 and ongoing for chronic myeloid leukemia.
Ongoing relevant medical history included arterial hypertension (treated), gout crisis (treated), and arthrosis (not treated). Past medical history included renal affection (not treated), neuralgia (not treated), inguinal hernia (not treated), herniated disc (not treated), angioedema (not treated), parotid lipoma (not treated), and prostatectomy. The subject previously received nilotinib and experienced arterial disease treated with unspecified product and ongoing at report time, thrombotic accident treated with unspecified product and resolved at report time, and stroke not medically treated and resolved at report time. The subject previously received imatinib and experienced hepatic cytolysis not medically treated and ongoing at report time. The subject previously received dasatinib and experienced pulmonary embolism and pleural effusion not medically treated and both resolved at report time. Past drug history included colchicine /papaver somniferum powder /tiemonium methylsulphate (COLCHIMAX) and colchicine, both from Mar2018 to Mar2018 at unknown daily dose for gout crisis.
Concomitant medication(s) included: XARELTO oral taken for thrombosis prophylaxis (ongoing); HYTACAND oral taken for hypertension (ongoing); ATORVASTATIN oral taken for hypertension (ongoing); KARDEGIC oral taken for prophylaxis (ongoing); DIFFU K taken for prophylaxis (ongoing).
On 27Aug2018, the subject experienced constipation which was assessed as non-serious and grade 1. Corrective measures for constipation consisted in initiation of bicarbonate sodium / potassium tartrate acid (EDUCTYL) from 27Aug2018 to 09Dec2018 at unknown daily dose, laxative (unspecified trade name) from 27Aug2018 to 09Dec2018 at unknown daily dose, and daily enema with unspecified product from an unknown date in 2018 to an unknown date in 2018. No action was taken with bosutinib. No laboratory tests were provided. On 27May2019, the subject experienced dry mouth syndrome assessed as non-serious and rated grade 2. As a result, bosutinib dose was reduced on 27May2019 to 150 mg daily. At the time of the report, the subject had not resolved yet from dry mouth syndrome. The event constipation resolved on 09Dec2018.
The investigator considered there was not a reasonable possibility that the event constipation was related to bosutinib or to a concomitant medication. The investigator considered there was a reasonable possibility that the event dry mouth syndrome was related to bosutinib and not related to a concomitant medication.

Follow-up (03Jan2019): Follow-up attempts are completed. No further information is expected.

Follow-up (14Jun2019): New information received from the investigator via the CRO included bosutinib route of administration, indication and dosage regimen updated, added new event dry mouth syndrome, and action taken updated.

Follow-up (18Jun2019): New information received from the investigator via the clinical team includes medical history, concomitant medications, past drug events, reaction data (start date of event constipation updated to 27Aug2018, outcome of constipation updated to resolved on 09Dec2018, treatment for event constipation).

Follow-up (20Jan2023): This follow-up is received from the investigational site CRO. This is a follow-up to a non-interventional clinical study case. Updated information: new reporter.

Follow-up (24Jan2023): New information received from CRO is as follows: concomitant information (Hytacand, atorvastatin, Kardegic and Xarelto).

Case Comment: The company concurs with the investigator that event dry mouth syndrome was possibly related to bosutinib. Conversely, the event constipation was unrelated to bosutinib, event most likely represented an intercurrent condition. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	150 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	27-MAY-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History not treated	Arthrosis (Osteoarthritis);
Unknown	Relevant Med History Past medical history (not treated)	Renal disorder NOS (Renal disorder);

Mfr. Control Number: 2018477291

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History Past medical history (not treated)	Neuralgia (Neuralgia);
Unknown	Relevant Med History Past medical history (not treated)	Inguinal hernia (Inguinal hernia);
Unknown	Relevant Med History Past medical history (not treated)	Herniated disc (Intervertebral disc protrusion);
Unknown	Relevant Med History Past medical history (not treated)	Angioedema (Angioedema);
Unknown	Relevant Med History Past medical history (not treated)	Parotid lipomatosis (Parotid lipomatosis);
Unknown	Relevant Med History Past medical history	Prostatectomy (Prostatectomy);
Unknown	Past Drug Event arterial disease treated with unspecified product and ongoing at report time	nilotinib (NILOTINIB); Drug Reaction: Arterial disorder NOS (Arterial disorder)
Unknown	Past Drug Event thrombotic accident treated with unspecified product and resolved at report time	nilotinib (NILOTINIB); Drug Reaction: Thrombotic stroke (Thrombotic stroke)
Unknown	Past Drug Event stroke not medically treated and resolved at report time	nilotinib (NILOTINIB); Drug Reaction: Stroke (Cerebrovascular accident)
Unknown	Past Drug Event hepatic cytolysis not medically treated and ongoing at report time	imatinib (IMATINIB); Drug Reaction: Hepatic cytolysis (Hepatic cytolysis)
Unknown	Past Drug Event pulmonary embolism not medically treated and resolved at report time	dasatinib (DASATINIB); Drug Reaction: Pulmonary embolism (Pulmonary embolism)
Unknown	Past Drug Event pleural effusion not medically treated and resolved at report time	dasatinib (DASATINIB); Drug Reaction: Pleural effusion (Pleural effusion)
MAR-2018 to MAR-2018	Past Drug Event unknown daily dose	COLCHIMAX (COLCHIMAX [COLCHICINE;PAPAVER SOMNIFERUM POWDER;TIEMONIUM METHYLSULPHA); Drug Indication: Gout attack (Gout)
MAR-2018 to MAR-2018	Past Drug Event unknown daily dose	COLCHICINE (COLCHICINE); Drug Indication: Gout attack (Gout)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		AUG	1975	43 Years	Female	110.00 kg		OCT	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

hepatic cytolysis [Hepatic cytolysis]
slight cholestasis [Cholestasis]
fibromatous uterus [Uterine leiomyoma]
Digestive disorder [Gastrointestinal disorder]
Dizziness [Dizziness]
asthenia [Asthenia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 200 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 11-OCT-2018 / Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

#1) DIOSMECTITE (DIOSMECTITE) ; 11-OCT-2018 / Ongoing
#2) METOPIMAZINE (METOPIMAZINE) ; 11-OCT-2018 / Ongoing
#3) ACETYLSALICYLATE LYSINE (ACETYLSALICYLATE LYSINE)
#4) LACOSAMIDE (LACOSAMIDE) ; 05-JUL-2018 / Ongoing
#5) KEPPRA [LEVETIRACETAM] (LEVETIRACETAM) ; 29-JUN-2006 / Ongoing
#6) ASPEGIC (ACETYLSALICYLATE LYSINE) ; JUN-2018 / Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
15-JUN-2018 to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia)
Unknown	Past Drug Event	

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019011377

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
22-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.

A 43-year-old, female subject (unknown if pregnant) was recruited in the above mentioned study and received bosutinib (BOSULIF), via an unspecified route of administration, at dose of 200 mg daily from 11Oct2018, then increased at dose of 300 mg daily from an unknown date and increased to 400 mg daily from 20Nov2018 to 09Dec2018 for chronic myeloid leukemia (as second line therapy). Relevant medical history included chronic myeloid leukemia ongoing from 15Jun2018, metabolic disease, hypertension arterial ongoing from 21Jun2018, epilepsy ongoing from 1995, thrombotic accident in Jul2018, gastrooesophageal reflux ongoing. She had no family history of hepatic disease. Concomitant medications included diosmectite ongoing from 11Oct2018 for diarrhoea, metopimazine ongoing from 11Oct2018 for nausea and vomiting, acetylsalicylate lysine ongoing from 05Jul2018 for thromboembolic risk, lacosamide ongoing from 05Jul2018 for epilepsy, levetiracetam (KEPPRA) ongoing from 29Jun2006 for epilepsy, acetylsalicylate lysine (ASPEGIC) ongoing from Jun2018 for thrombotic accident, candesartan ongoing from 04Oct2018 for hypertension arterial, lansoprazole ongoing from unknown date for gastrooesophageal reflux. Past drug history for chronic myeloid leukemia included imatinib mesilate (GLIVEC) with hematologic toxicity and cutaneous toxicity.

The following information was reported: GASTROINTESTINAL DISORDER (non-serious) with onset Oct2018, outcome "recovered" (02Jan2019), described as "Digestive disorder"; HEPATIC CYTOLYSIS (hospitalization) with onset 08Dec2018, outcome "recovered" (04Feb2019); CHOLESTASIS (hospitalization) with onset 08Dec2018, outcome "recovering", described as "slight cholestasis"; UTERINE LEIOMYOMA (hospitalization) with onset 31Dec2018, outcome "recovered" (30Oct2019), described as "fibromatous uterus"; DIZZINESS (non-serious) with onset 2019, outcome "recovered" (08Apr2019); ASTHENIA (non-serious) with onset 2019, outcome "recovered" (08Apr2019).The subject experienced digestive disorder, CTCAE grade 2 in Oct2018, assessed as non-serious and fibromatous uterus, CTCAE grade 1 on 31Dec2018, assessed as serious (without seriousness criteria). On 08Dec2018, the subject developed hepatic cytolysis measured at 15 times higher than the normal value (hepatic toxicity grade 4) and slight cholestasis. The subject was hospitalized on an unknown date for the events (hepatic cytolysis and slight cholestasis). The event fibromatous uterus was serious due to the patient hospitalization. The event recovery date was 30Oct2019 which was the hysterectomy date. However, at the patient's end of study date on 08Apr2019, the adverse event was still ongoing. The subject underwent lab tests which included: ASAT was at 231 IU/l on 08Dec2018 and 461 IU/l on 22Dec2018 (normal range below 35 IU/l); ALAT was at 465 IU/l on 08Dec2018 and 846 IU/l on 22Dec2018 (normal range below 35 IU/l); GGT was at 36 IU/l on 08Dec2018 and 88 IU/l on 22Dec2018 (normal range below 38 IU/l); Bilirubin total was at 11.8 umol/l on 08Dec2018 and 17.3 umol/l on 22Dec2018 (normal range below 21 umol/); Conjugated bilirubin was at 2.4 umol/on 08Dec2018 and 4.1 umol/on 22Dec2018 (normal range below 3.4 umol/); ALT was 560 IU/l on 02Jan2019 (normal range 0 to 33 IU/l); and an abdominal scan at hospital on an unknown date with unknown results. The action taken as a result of the event hepatic cytolysis and cholestasis with bosutinib was permanently withdrawn. The outcome of cholestasis was recovering; digestive disorder was recovered on 02Jan2019 and hepatic cytolysis recovered on 04Feb2019, and for fibromatous uterus was not recovered. In 2019, the subject experienced dizziness and asthenia both was assessed grade 2 and considered as non-serious. The site reported that at examination (2019), dizziness and asthenia grade 2 were noted. No change was made in response to events dizziness and asthenia. The subject was considered recovered from the events dizziness and asthenia on 08Apr2019.
The subject had been hospitalized from 29Oct2019 to 05Nov2019 for a total hysterectomy with bilateral annexectomy for a fibromatous uterus. The event fibromatous uterus was assessed by the investigator as serious (without seriousness criteria). At the time of the report, the subject had not recovered yet from fibromatous uterus.

According to the investigator, the events hepatic cytolysis, cholestasis, digestive disorder, asthenia were related to bosutinib and unrelated to concomitant medications. According to the investigator, the event fibromatous uterus was not related to study drug or to concomitant treatment. The investigator considered that dizziness was unrelated to study drug or to a concomitant drug.

Follow-up (20Feb2019): New information reported includes further lab. results, further medical history, new event (slight cholestasis) and clinical course.

Follow-up (22Feb2019). New information reported includes new events (digestive disorder, fibroma).

Follow-up (12Apr2019): New information reported includes clinical course with new events (dizziness and asthenia).

Follow-up (27Aug2020 and 28Aug2020): New information received from the CRO includes clinical course details: seriousness assessment for the event fibroma and clinical course details.

Follow-up (08Sep2020): New information received from the investigational site includes confirmation that only fibromatous uterus lead to conduct the hysterectomy instead of fibromatous uterus with ovarian cyst (previously reported).

Follow-up (22Sep2020): New information received from the clinical research associate (CRA) includes confirmation that the Investigator did not consider fibromatous uterus with ovarian cyst as event. The ovarian cyst was not considered as an event, only fibroma was reported as event.

Follow-up (29Nov2021): This is a follow up report from a Non-Interventional Study source for Protocol B1871047.

Updated information included: seriousness criteria of event fibroma updated.

Mfr. Control Number: 2019011377

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (25Jan2022): This is a non-interventional follow-up study report (Post Authorization Safety Study) for protocol B1871047.
Updated information included: verbatim of the event "fibroma" changed to "fibromatous uterus".

Follow-up (17Nov2022): This is a follow-up for a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.
Updated information included: medical history, concomitant medication (KEPPRA, ASPEGIC, candesartan, lansoprazole added), causality assessment for event Asthenia updated from unrelated to related to study drug Bosutinib.

Follow-up (14Feb2023): This is a non-interventional study follow-up report received from study site for protocol B1871047 updating the outcome of hepatic cytolysis to resolved on 04Feb2019.

Follow-up (22Jun2023): This is a non-interventional study follow-up report received from the clinical team. Updated information included: Stop Date and Outcome for the "Event fibromatous uterus" updated.

Case Comment: The SAEs, hepatic cytolysis and cholestasis, are unlisted in the RSI of the suspect drug bosutinib and related per company assessment.

The follow-up information received does not alter the previous company evaluation.
Based on the information currently available, a possible contributory role of bosutinib to the reported hepatic cytolysis, along with cholestasis, cannot be completely excluded based on temporal association and considering the known hepatoxic properties of the suspect drug, bosutinib. Further information regarding baseline liver function, pre-existing malignancy status and details surrounding the event are needed for better assessment. Similarly, the Company cannot completely exclude a possible causal relationship between the reported digestive disorder and bosutinib administration. Conversely, the reported fibromatous uterus, dizziness, asthenia are unlikely related to bosutinib.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identifies as part of this review, as well as any appropriate action in response, will be promptly notifies to Regulatory Authorities, Ethics Committees and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Abdomen scan	unknown results	
2	08-DEC-2018	Alanine aminotransferase	465 IU/l	35
3	22-DEC-2018	Alanine aminotransferase	846 IU/l	35
4	02-JAN-2019	Alanine aminotransferase	560 IU/l	33 0
5	08-DEC-2018	Aspartate aminotransferase	231 IU/l	35
6	22-DEC-2018	Aspartate aminotransferase	461 IU/l	35
7	02-JAN-2019	Aspartate aminotransferase	326 IU/l	32 0
8	08-DEC-2018	Blood bilirubin	11.8 umol/l	21
9	22-DEC-2018	Blood bilirubin	17.3 umol/l	21
10	08-DEC-2018	Gamma-glutamyltransferase	36 IU/l	38
11	22-DEC-2018	Gamma-glutamyltransferase	88 IU/l	38
12	08-DEC-2018	Hyperbilirubinaemia	2.4 umol/l	3.4
13	22-DEC-2018	Hyperbilirubinaemia	4.1 umol/l	3.4

Mfr. Control Number: 2019011377

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
14	08-DEC-2018	Investigation (hepatic toxicity grade 4)	15 times higher than the normal value	
15	2019	Investigation	dizziness and asthenia grade 2 were noted.	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	20-NOV-2018 / 09-DEC-2018; 20 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#3) ACETYLSALICYLATE LYSINE (ACETYLSALICYLATE LYSINE) ; 05-JUL-2018 / Ongoing

#7) CANDESARTAN (CANDESARTAN) ; 04-OCT-2018 / Ongoing

#8) LANSOPRAZOLE (LANSOPRAZOLE) ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event	GLIVEC (GLIVEC); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Hematotoxicity (Haematotoxicity)
Unknown	Past Drug Event	GLIVEC (GLIVEC); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Skin toxicity (Skin toxicity)
Unknown	Relevant Med History	Metabolic disorder (Metabolic disorder);
21-JUN-2018 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension);
1995 to Ongoing	Relevant Med History	Epilepsy (Epilepsy);
JUL-2018 to JUL-2018	Relevant Med History	Thrombotic stroke (Thrombotic stroke);
Unknown to Ongoing	Relevant Med History	Gastrooesophageal reflux (Gastrooesophageal reflux disease);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
UNKNOWN	FRANCE		NOV	1951	67 Years	Male	103.00 kg	22	NOV	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

hemoptysis [Haemoptysis]
asthenia [Asthenia]
Diabetes imbalance [Diabetes mellitus inadequate control]

Case Description: EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE (BOSEVAL)

This is a report from a Non-Interventional Study report from the observational study Boseval, for Protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 14-DEC-2017 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) METFORMIN (METFORMIN) ; 2002 / Ongoing
#2) BISOPROLOL (BISOPROLOL) ; Ongoing
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#4) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Coronaropathy (Coronary artery disease)
2002 to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019011393

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-MAR-2021

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional clinical study case reporting non-serious events only.

A 67-year-old male subject started taking bosutinib (BOSULIF film-coated tablets) from 14Dec2017 at 500 mg daily for unknown indication.
Medical history includes ongoing coronarophaty, diabetes ongoing from 2002, ongoing arterial hypertension and ongoing hypercholesterolemia. Concomitant medications include metformin ongoing from 2002 for diabetes, ongoing bisoprolol for arterial hypertension, ongoing acetylsalicylate lysine (KARDEGIC) for arterial hypertension and ongoing atorvastatin sodium (TAHOR) for arterial hypertension.
On 22Nov2018, the subject experienced diabetes imbalance. On 29Nov2018 the subject experienced hemoptysis and on 20Dec2018 asthenia. Diabetes imbalance was assessed as non-serious and rated grade 2. Hemoptysis was rated grade 2 and assessed as non-serious. Hemoptysis led to perform fiberscopy and biopsy. No etiology was found. Asthenia was rated grade 1 and assessed as non-serious. No action was taken with bosutinib in response to the events. The diabetes imbalance recovered on 20Dec2018, the haemoptysis not recovered, the outcome of the asthenia was not recovered.

The event diabetes imbalance was considered by investigator as not related to the suspect drug. The investigator considered there was not a reasonable possibility that the events hemoptysis and asthenia were related to bosutinib or to a concomitant medication.

Follow-up (27Feb2019): Follow-up attempts are completed. No further information is expected.

Follow-up (26Feb2019): Additional information received included: updated investigator initial awareness date, confirmation that hypercholesterolemia and concomitant TAHOR were both ongoing, outcome of event asthenia (not resolved).

Follow-up attempts completed. No further information expected.

Follow-up (16Jul2019): New information received includes additional event diabetes imbalance.

Follow-up attempts completed. No further information expected.

Follow-up(23Mar2021): New information received from investigational site via CRO included outcome not recovered for hemoptysis, outcome recovered on 20Dec2018 for diabetes imbalance

Case Comment: In concurrence with the reporting investigator, the Company considers there is not a reasonable possibility that the reported hemoptysis and asthenia, are related to the study drug, bosuitinib. More information on the subject's underlying malignancy, clinical course are required for the Company to make a better assessment. The reported event diabetes imbalance is more likely associated the subject's pre-existing medical condition of diabetes and not related to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Biopsy	no etiology found	
2		Endoscopy	no etiology found	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
Unknown to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1995	23 Years	Female	58.00 kg		NOV	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Abdominal pain [Abdominal pain]
Nausea [Nausea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, 1x/day	#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 14-NOV-2018 / 20-NOV-2018	#1) 7 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
MAY-2009 to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia)
2009 to 2009	Relevant Med History	Splenomegaly (Splenomegaly)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
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66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019014826

24c. DATE RECEIVED BY MANUFACTURER
15-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 23-year-old female subject started to receive bosutinib (BOSULIF) film-coated tablet, via an unspecified route of administration, from 14Nov2018 to 20Nov2018 at 200 mg once per day, from 21Nov2018 to 27Nov2018 at 300 mg once per day, and from 28Nov2018 to 13Feb2019 at 400 mg once per day, for chronic myeloid leukemia. Medical history included chronic myeloid leukemia from May2009 and ongoing, and splenomegaly from 2009 to 2009. The subject's concomitant medications were not reported. The subject previously took nilotinib hydrochloride (TASIGNA, 300 mg) for the treatment of his CML (chronic myeloid leukemia) up to 12Nov2018. Nilotinib hydrochloride was stopped on 12Nov2018 for intolerance (grade 2 hair loss, grade 2 oedemas, and grade 1 asthenia - resolved). The subject experienced abdominal pain and nausea in Nov2018, both rated grade 2. The action taken in response to the event abdominal pain for bosutinib was dose reduced to new dosage of 300mg from 14Feb2019. The outcome of the event abdominal pain was resolving. The clinical outcome of the event nausea was recovered on 13Feb2019.

According to the investigator, the events were related to the study drug bosutinib but not related to concomitant medication.

Follow-up(11Feb2021): New information received from investigational site via CRO included: suspect product data (stop date and dosing for bosutinib), action taken (updated from dose not changed to dose reduced), and clinical outcome (nausea recovered)

Follow-up (10May2022): This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: severity grade of events abdominal pain and nausea added.

Follow-up (24Apr2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the CRO for protocol B1871047.

Updated information included: Patient initials.

Follow-up (15Sep2023): This is a follow-up report from the investigator via CRO updating the event of abdominal pain to resolving.

Case Comment: Based on the known drug safety profile, the causal association between the events, abdominal pain and nausea, and the suspect drug, bosutinib, cannot be excluded. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	21-NOV-2018 / 27-NOV-2018; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, 1x/day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	28-NOV-2018 / 13-FEB-2019; 2 months 17 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to 12-NOV-2018	Past Drug Event	TASIGNA (TASIGNA); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Hair loss (Alopecia)
Unknown to 12-NOV-2018	Past Drug Event	TASIGNA (TASIGNA); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Oedema (Oedema)
Unknown to 12-NOV-2018	Past Drug Event	TASIGNA (TASIGNA); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia), Drug Reaction: Asthenia (Asthenia)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1949	69 Years	Male	68.00 kg		SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Intermittent diarrhea [Diarrhoea]
Cephalgia [Headache]
hepatic work-up disorder [Liver function test abnormal]
NAUSEA [Nausea]
skin dryness [Dry skin]
Intermittent iron deficiency anemia [Iron deficiency anaemia]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) TARDYFERON (FERROUS SULFATE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, daily	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) CML (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 20-SEP-2018 / SEP-2019	#1) Unknown
#2) Ongoing	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) PREVISCAN [FLUINDIONE] (FLUINDIONE) ; Unknown
#2) SIMVASTATINE (SIMVASTATIN) ; Unknown
#3) NEBILOX (NEBIVOLOL HYDROCHLORIDE) ; Unknown
#4) AMLOR (AMLODIPINE BESILATE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2002 to Unknown	Relevant Med History for a rhythmic atrial disease	Pacemaker insertion (cardiac) (Cardiac pacemaker insertion)
2002 to 2018	Relevant Med History	Arrhythmia atrial (Arrhythmia supraventricular)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019025141

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
04-OCT-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL.
This is a non-interventional clinical study case reporting non-serious events only. This is a post-authorization safety study.

A 69-year-old male subject started to receive bosutinib (BOSULIF) orally at 400 mg daily from 20Sep2018 to an unspecified date in Sep2019, and from Oct2019 at 400 mg daily for chronic myeloid leukaemia (CML). Additional suspect included ferrous sulfate (TARDYFERON), at an unknown dose and frequency via an unspecified route of administration, from an unknown date and ongoing for an unknown indication. Relevant medical history included pacemaker in 2002 for a rhythmic atrial disease, cardiac arrhythmia by atrial fribrillation (CA / AF) occurred from 2002 to 2018, percutaneous mitral valvuloplasty in 1995 and in 2015 for rheumatic mitral constriction associated with triscuspid insufficiency, double stroke in 2014, and several episodes of nephritic colic. Concomitant medications from unspecified date as cardiac prevention included fluindione (PREVISCAN), simvastatin, nebivolol hydrochloride (NEBILOX), amlodipine (AMLOR).
In Sep2018, the subject experienced intermittent diarrhea rated grade 2 and assessed as non-serious. Action taken was reported as dose decreased for study drug. The subject was given loperamide hydrochloride (IMODIUM) for intermittent diarrhea.
In Oct2018, the subject experienced intermittent iron deficiency anemia, non-serious and rated grade 2. The physician had noticed iron deficiency anemia in this patient on 18Oct2018. Action taken with bosutinib for this event was dose not changed. The subject experienced cephalgia on an unspecified date in 2019 rated as grade 1. The reporter stated it was a discontinuous but annoying cephalgia. No action was taken for bosutinib in response to event cephalgia. The subject developed skin dryness on 20Mar2019, reported as non-serious and rated grade 1. In response to the event, no action was taken with bosutinib. In Sep2019 the subject experienced hepatic work-up disorder, grade 2, seriousness was not reported. In Oct2019, the subject experienced nausea, non-serious and rated grade 1. Action taken with bosutinib for this event was dose not changed. As a result of the event hepatic work-up disorder, bosutinib was temporarily withdrawn. The last action taken with bosutinib was dose reduced. The outcome of event Intermittent diarrhea was resolved on an unspecified date in Oct2021, hepatic work-up disorder was resolved on 15Mar2021, cephalgia recovered in Mar2019, nausea resolved on 16Oct2019, skin dryness resolved on 05Feb2020 and intermittent iron deficiency anemia resolved on 01Jun2021.

The investigator considered 'intermittent diarrhea' as related to study drug and to concomitant treatment ferrous sulfate (TARDYFERON). No action was taken with ferrous sulfate.
The investigator considered the events 'headache', 'hepatic work-up disorder' and 'nausea' as related to study drug and unrelated to concomitant drugs. The investigator considered the event 'skin dryness' and 'intermittent iron deficiency anemia' were unrelated to bosutinib and to concomitant drug.

Follow-up (21Jan2019): New information received from the investigational site via the clinical team included: indication and route of administration of Bosutinib, relevant medical history, concomitant medication, action taken details.

Follow-up (06Nov2019): New information received from CRO includes: reaction data (added event headache), and clinical course details.

Follow-up (07Nov2019): New information received from the investigational site via CRO includes: patient's weight, new event (hepatic work-up disorder), updated action taken (from dose reduced to dose not changed).

Follow-up (13Jan2020): New information received from the investigational site via CRO includes: medical history and reaction data (outcome of the event hepatic work-up disorder was updated from unknown to resolved).

Follow-up (09Apr2020): new information received from CRO includes: reaction data (CTCAE grade, recovery date, causality, new episode of diarrhea) and action taken.

Follow-up (10Apr2020): New information received from the investigational site via the clinical team and the CRO included dosage regimen of bosutinib, action taken of bosutinib in response to the events, outcome of event headache, reporter causality between the event headache and bosutinib(related).

Follow-up (16Nov2020): New information received from the CRO includes additional suspect (TARDYFERON), previously reported event headache was corrected to cephalgia with recovery date updated, previously reported first event of diarrhea was updated to intermittent diarrhea with updated onset (from 2018 to Sep2018) and updated outcome (from recovered to not recovered), updated outcome of hepatic work-up disorder (from recovered to not recovered), and new events (skin dryness, iron deficiency, nausea).

Follow-up (26Nov2020): New information received from the CRO stated that diarrhea with onset date Oct2019 was deleted as 'intermittent diarrhea' was present from 2018 and ongoing.

Follow-up (26Jan2022): This is non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047 received from the investigational site via CRO.
Updated information: updated outcome of events intermittent diarrhea, intermittent iron deficiency and hepatic work-up disorder, updated action taken with bosutinib.

Mfr. Control Number: 2019025141

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (21Feb2022): A clarification was provided to the query sent.
Updated information: outcome of the event iron deficiency of Oct2018 (resolved).

Follow-up (04Oct2023): This is a report from a Non-Interventional Study source from the investigational site via the CRO. Updated information included: Event term updated from "intermittent iron deficiency" to "Intermittent iron deficiency anemia", event "Iron deficiency" was removed.

Case Comment: Based on the information currently available, known drug safety profile and temporal association, the Company considered that the reported events episodes of diarrhea, headache, nausea and hepatic work up disorder are related to the Pfizer suspect drug bosutinib. Conversely, the reported intermittent iron deficiency anemia and skin dryness are deemed unrelated to bosutinib. The follow up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	SEP-2019	Liver function test	disorder	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, daily; Oral	CML (Chronic myeloid leukaemia)	OCT-2019 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2002 to 2018	Relevant Med History	Arrhythmia cardiac (NOS) (Arrhythmia);
2002 to 2018	Relevant Med History	Atrial fibrillation (Atrial fibrillation);
1995 to 1995	Relevant Med History	Valvuloplasty cardiac (Valvuloplasty cardiac);
2015 to 2015	Relevant Med History	Valvuloplasty cardiac (Valvuloplasty cardiac);
Unknown	Relevant Med History	Mitral stenosis rheumatic (Mitral valve stenosis);
Unknown	Relevant Med History	Tricuspid insufficiency (Tricuspid valve incompetence);
2014 to 2014	Relevant Med History	Stroke (Cerebrovascular accident);
Unknown	Relevant Med History several episodes of nephritic colic	Colic renal (Renal colic);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1948	70 Years	Male	95.00 kg			2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Heart failure [Cardiac failure]
Pleural effusion [Pleural effusion]
Scalp scab [Scab]
Pruritus [Pruritus]
dyspnea [Dyspnoea]
Constipation [Constipation]
Urging mictions [Micturition urgency]
cramps [Muscle spasms]
thrombocytosis due to MPLW515 mutation [Thrombocytosis] **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) SKENAN (MORPHINE SULFATE) **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, daily
#2) UNK

16. ROUTE(S) OF ADMINISTRATION
#1) Oral
#2) Unknown

17. INDICATION(S) FOR USE
#1) Unknown
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 10-APR-2018 / 01-MAY-2018
#2) Unknown

19. THERAPY DURATION
#1) 22 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) EZETROL (EZETIMIBE) ; 16-APR-2013 / Ongoing
#2) PANTOPRAZOLE (PANTOPRAZOLE) ; 2018 / Ongoing
#3) INCRUSE (UMECLIDINIUM BROMIDE) ; DEC-2017 / Ongoing
#4) BISOPROLOL (BISOPROLOL) ; 2008 / Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Pleural effusion (Pleural effusion)
Unknown	Relevant Med History	Thrombotic stroke (Thrombotic stroke)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019063548

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-MAY-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Missed one dose of bosutinib [Product dose omission issue]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.

A 70-year-old male subject received bosutinib, orally, at 100 mg daily from 10Apr2018 to 01May2018 then 200 mg daily from 02May2018 to 31May2018; 100 mg daily from 01Jun2019 to 23Oct2019; 200 mg daily from 06Nov2019 to 12Nov2019 and 300 mg daily from 13Nov2019 and ongoing, and morphine sulfate (SKENAN), via an unspecified route of administration, from an unspecified date and at unknown dose, both for an unspecified indication. Medical history included pleural effusion, thrombotic accident, obliterative arteriopathy of lower limbs and ischemic stroke. Concomitant medications included ezetimibe (EZETROL) from 16Apr2013 and ongoing for cholesterol high, pantoprazole from 2018 and ongoing for gastric protector, umeclidinium bromide (INCRUSE) from Dec2017 and ongoing for chronic obstructive pulmonary disease and bisoprolol from 2008 for arterial hypertension. It was reported that on an unknown date in 2018, the subject missed one dose of bosutinib. On 26Jun2018 the subject experienced constipation, grade 2, assessed as non-serious. No action was taken with study drug in response to the event. Event was not recovered. On 20Dec2018 the subject experienced urging miction, grade 2, assessed as non-serious. No action was taken with study drug in response to the event. Event was recovering. On 08Jan2019 the subject experienced scalp scab, grade 1, and pruritus, grade 1, both assessed as non-serious. Action taken was reported as no change. The events were resolved on 15Oct2019. In Apr2019, the subject experienced heart failure which was rated as grade 3 and considered as medically significant. He went to emergencies. Event resolved on 12Apr2019. No action was taken with bosutinib in response to this event. On 21May2019, the subject experienced pleural effusion assessed as serious due to hospitalization and rated grade 3. The patient presented only with one episode of pleural effusion. The event required talc pleurodesis. Pleural effusion resolved on 08Jul2019. Bosutinib dose was reduced in response to this event. On 05Nov2019, the subject experienced loss of response rated grade 2, which assessed as non-serious. Action taken was reported as dose increased. On 07Jan2020, the event loss of response resolved. In Feb2020, the subject experienced dyspnea rated grade 2 and considered non-serious. In response to the event, bosutinib dose was reduced. The event was not resolved. On 07Jul2020, the subject experienced cramps rated grade 1 and considered non-serious. Action taken was reported as not applicable. The event was resolved on 20Oct2020. On 07Jul2020, the subject experienced "thrombocytosis due to MPLW515 mutation" rated grade 2 and considered non-serious. No action was taken in response to the event. The event had not resolved.

The investigator considered there was a reasonable possibility that the events heart failure, pleural effusion, scalp scab, pruritus, dyspnea and cramps were related to bosutinib. According to the investigator, the events cramps and pleural effusion were unrelated to concomitant drug.

The investigator considered there was not a reasonable possibility that the events constipation, urging miction, "thrombocytosis due to MPLW515 mutation" and missed one dose of bosutinib were related to bosutinib. The investigator considered the event constipation related to concomitant treatment morphine sulfate (SKENAN), while the other events were assessed as not related to concomitant treatment.

Follow-up (20Mar2019): New information reported includes new events constipation, urging miction, scalp scab and pruritus, action taken with bosutinib, clinical outcome and additional suspect drug morphine sulfate (SKENAN).

Follow-up (27Jun2019): New information reported includes pleural effusion and action taken with bosutinib.

Follow-up (21Oct2019): New information reported includes the subject fully recovered from pleural effusion on 08Jul2019 and from scalp scab and pruritus on 15Oct2019.

Follow-up (12Nov2019): New information reported includes loss of response rated grade 2 and assessed as non-serious and action taken with bosutinib.

Follow-up (23Jan2020): New information reported includes the event loss of response resolved on 07Jan2020.

Follow-up (02Mar2020): New information reported includes bosutinib dosing regimens.

Follow-up (17Aug2020): New information reported includes new event dyspnea, cramps and thrombocytosis.

Follow-up (04Jan2021): New information reported includes the event verbatim "thrombocytosis" was changed to "thrombocytosis due to MPLW515 mutation" considered non serious (no other change).

Follow-up (13Jan2021 and 18Jan2021): New information reported includes new event heart failure considered as medically significant, date of heart failure resolved and confirmation that the event pleural effusion required hospitalization.

Follow-ups (20Jan2021 and 26Jan2021): New information received from a Non-Interventional Study source, received via the

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

investigational site via the CRO includes: reaction data (event cramps resolved on 20Oct2020), confirmation of only one episode of pleural effusion.

Follow-up (04Mar2021): New information reported includes event detail for pleural effusion.

Follow-up (09Feb2023): This is a follow-up report from the investigator via CRO. Updated information includes: Investigator's causality assessment for the event "missed one dose of bosutinib".

Follow-up (24Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.
Updated information: causality assessment of the event cramps (the event cramps was related to the study drug BOSULIF and unrelated to concomitant drug).

Follow-up (01Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: hospitalization criterion removed for Pleural effusion

Follow-up (10Mar2023): The new This is a follow up report combining information from duplicate reports #2019063548 and #PV202300040828. The current and all subsequent follow-up information will be reported under manufacturer report number #2019063548. information reported from contactable reporter(s) (Physician and Other HCP) included investigator initial awareness date updated to 26Jun2018 (from 08Jan2019).

Follow-up (23May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047. Updated information included: pleural effusion (grade, seriousness (H) and causality vs concomitant).

Case Comment: Cardiac failure is unlisted in the RSI of the SRSD of bosutinib and unrelated per company assessment.

Based on the clinical information currently provided the company deems there is not a reasonable possibility that cardiac failure is related to suspect drug bosutinib, the underlying malignancy together with the medical history of pleural effusion, thrombotic/ischemic stroke, peripheral obliterative arteriopathy, cholesterol high, chronic obstructive pulmonary disease and arterial hypertension, are considered the most likely causes. Similarly, constipation, micturition, and thrombocytosis, are evaluated as unrelated to bosutinib, in agreement with the reporter, and particularly considering also patient's gender and age for micturition urgency, SKENAN co-administration for constipation and underlying disease for thrombocytosis. Conversely, due to the known drug safety profile, pleural effusion with consequent dyspnea, muscle spasm, and pruritus with scab are assessed as related to bosutinib. This case will be reassessed should additional information become available. The follow-up information received does not alter the previous company clinical evaluation.

The impacts of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees and Investigators, as appropriate.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	Unknown	02-MAY-2018 / 31-MAY-2018; 395 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	100 mg, daily; Oral	Unknown	01-JUN-2019 / 23-OCT-2019; 145 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Oral	Unknown	06-NOV-2019 / 12-NOV-2019; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet;	300 mg, daily; Oral	Unknown	13-NOV-2019 /

Mfr. Control Number: 2019063548

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #5			Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Peripheral obliterative arteriopathy (Peripheral arterial occlusive disease);
Unknown	Relevant Med History	Ischemic stroke (Ischaemic stroke);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		AUG	1950	68 Years	Male	114.00 kg		DEC	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
RIGHT WRIST PAIN [Arthralgia]
Allergy to surimi [Food allergy]
psoriatic lesions [Psoriasis]
arthralgia intermittent [Arthralgia]
exertional dyspnea [Dyspnoea exertional]
asthenia [Asthenia]
constipation [Constipation]
insomnia [Insomnia]
alternation of constipation and diarrhea [Gastrointestinal motility

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) CML (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 15-DEC-2018 / 22-DEC-2018

19. THERAPY DURATION
#1) 8 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) NAPROXENE [NAPROXEN] (NAPROXENE [NAPROXEN]) ; 15-JAN-2019 / 20-JAN-2019
#2) ASPEGIC (ACETYLSALICYLATE LYSINE) ; 10-JAN-2019 / Ongoing
#3) SOLUPRED [METHYLPREDNISOLONE] (METHYLPREDNISOLONE)

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2000 to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
2000 to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019075107

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
07-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

disorder]
Asthenia Grade 2 [Asthenia]
Eczematiforme skin eruption grade 1 [Eczema]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 68-year-old male subject started to receive bosutinib (BOSULIF) film-coated tablet, oral from 15Dec2018 to 22Dec2018 at 100 mg daily, oral from 23Dec2018 to 29Dec2018 at 200 mg daily, oral from 30Dec2018 to 29Jun2019 at 300 mg daily, via an unspecified route of administration from 30Jun2019 to 26Feb2020 at 400 mg daily, via an unspecified route of administration from 27Feb2020 at 300 mg daily, and via an unspecified route of administration from 15Jul2020 and ongoing at 200 mg daily; for chronic myeloid leukaemia (CML). Medical history included arterial hypertension (HTA) from 2000 and ongoing, hypercholesterolemia from 2000 and ongoing, sleep apnea from 2012 and ongoing, arthrose knee left from 1990 and ongoing and low back pain grade 2 (non-serious) from Nov2018 and ongoing. Concomitant medication(s) included: NAPROXENE [NAPROXEN] oral taken for arthralgia, start date: 15Jan2019, stop date: 20Jan2019; ASPEGIC oral taken for arthralgia, start date: 10Jan2019 (ongoing); and methylprednisolone (SOLUPRED] oral taken from 28Mar2019, stop date: 30Mar2019. The subject experienced eczematiform skin eruption rated Grade 1 (non-serious) from Dec2018. On 10Jan2019, the subject experienced Insomnia, grade 1, Psoriatic lesions, grade 1, asthenia, grade 2, constipation, grade 1, arthralgia intermittent, grade 1 and exertional dyspnea, grade 1. For the event arthralgia, he was treated with naproxen oral from 15Jan2019 and ongoing, and acetylsalicylic acid (ASPEGIC) oral from 10Jan2019 and ongoing. On 28Mar2019 the subject experienced allergy surimi, grade 2, serious (medically significant) due to emergency visit. He received methylprednisolone (SOLUPRED) oral, from 28Mar2019 to 30Mar2019 for allergy surimi. On 16May2019, the subject experienced alternation of constipation and diarrhea considered non-serious and rated grade 1. No action was taken with study drug in response to the event. The subject developed asthenia in Dec2019, considered as not serious. In response to these events, bosutinib dose was reduced to 300 mg daily as of 27Feb2020 (and ongoing). The subject experienced right wrist pain from Jan2020, serious (medically significant), action taken was dose not changed. The last action taken for bosutinib was dose reduced due to the event eczematiform skin eruption. On 30Mar2019, the subject recovered from allergy surimi. On 16May2019, the subject recovered from the events exertional dyspnea, insomnia, psoriatic lesions, constipation and asthenia (onset 10Jan2019). Event arthralgia intermittent recovered in Jul2020, right wrist pain recovered on 27Feb2020. Event alternation of constipation and diarrhea was resolved on 21Nov2019; asthenia (onset Dec2019) and eczematiform skin eruption was resolved on 30Apr2020.

The reporter considered there was a reasonable possibility that the events psoriatic lesions, arthralgia intermittent, exertional dyspnea, eczematiform skin eruption, asthenia (Dec2019 and 10Jan2019) were associated with study drug, and considered there was not a reasonable possibility that the events were associated with concomitant drug.
The investigator considered there was not a reasonable possibility that the events insomnia, constipation, allergy surimi, alternation of constipation and diarrhea, right wrist pain were related to study drug or to concomitant treatment.

Follow-up (25Feb2019): New information received included bosutinib indication (chronic myeloid leukaemia) and route of administration (oral).

Follow-up (25Jun2019): New information received from the investigator via CRO included added new events allergy surimi and low back pain.

Follow-up (22Jul2019): New information received from the CRO and investigator via CRO included outcome of the event low back pain and recovery date of event allergy surimi.

Follow-up (13Sep2019): New information received from CRO: outcome of events arthralgia, exertional dyspnea, insomnia, psoriatic lesions, constipation and asthenia (updated to resolved on 16May2019).

Follow-up (23Jan2020): New information received from the CRO includes details on bosutinib dosage, new events (alternation of constipation and diarrhea, joint pain), outcome, seriousness and assessment.

Follow-up (13Mar2020): New information received from the CRO includes bosutinib data (dose reduced), new events (asthenia and skin problems in Jun2019), causality assessment.

Follow-ups (04Aug2020): New information received from the CRO includes medical history (low back pain) was updated, concomitant medications considered treatment for the event arthralgia, new bosutinib dose, details for the event joint pain/ increased joint pain, and last action taken.

Follow-up (22Sep2020): follow-up attempts completed. No further information expected.

Follow-up (02Nov2021 and 03Nov2021): New information received from investigational site via CRO included: dosage regimen, event

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

verbatim, recovered date, event onset date, new events (eczematiform skin eruption), updated event (from joint pain to right wrist pain), case upgraded to serious, causality assessment.

Follow-up (15Sep2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047. Updated information: new reporter (other HCP) added, start date of event Wrist pain updated from 23Feb2020 to Jan2020, stop date updated from 23Feb2022 to 27Feb2020; outcome of event Alternation between constipation and diarrhea, asthenia (DEC2019) and Eczematiforme skin eruption updated from not recovered to recovered and recovered date added, grade of event Eczematiforme skin eruption reported.

Follow-up (15May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047. Concomitant medications and causality assessment for asthenia (Dec2019 and 10Jan2019) .

Amendment: This follow-up report is being submitted to amend previously reported information: event skin problem was deleted as it has been updated to Eczematiforme skin eruption with onset in Dec2018.

Follow-up (07Sep2023): This is a follow-up report received from the CRO.
Updated information included: new concomitant drug Solupred.

Case Comment: In agreement with investigator, a causal relationship between the events "psoriatic lesions, intermittent arthralgia, asthenia (both episodes), exertional dyspnea, eczematiform skin eruption" and study drug cannot be excluded based on temporal association; but not associated with concomitant drug. There was not a reasonable possibility that the events "insomnia, constipation, allergy surimi, alternation of constipation and diarrhea, right wrist pain" were associated with study drug, but most likely due to underlying or intercurrent conditions or concomitant intake of other medications.
The follow up information does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	CML (Chronic myeloid leukaemia)	23-DEC-2018 / 29-DEC-2018; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	CML (Chronic myeloid leukaemia)	30-DEC-2018 / 29-JUN-2019; 182 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	30-JUN-2019 / 26-FEB-2020; 242 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	27-FEB-2020 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	200 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	15-JUL-2020 / Ongoing; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#3) SOLUPRED [METHYLPREDNISOLONE] (METHYLPREDNISOLONE) ; 28-MAR-2019 / 30-MAR-2019

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2012 to Ongoing	Relevant Med History	Sleep apnea (Sleep apnoea syndrome);
1990 to Ongoing	Relevant Med History	Arthrosis (Osteoarthritis);

Mfr. Control Number: 2019075107

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
NOV-2018 to Ongoing	Relevant Med History Low. Grade 2 (non-serious)	Low back pain (Back pain);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1951	67 Years	Female	75.00 kg	06	JUL	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Pleural effusions [Pleural effusion]
pericardial effusion [Pericardial effusion]
Dyspnea [Dyspnoea]
chronic asthenia [Asthenia]
infectious pneumonia [Pneumonia]
Aggravation of chronic renal failure [Chronic kidney disease]
FEBRILE SYNDROME [Pyrexia]
Thoracic pain [Chest pain]
asthenia [Asthenia]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) TRIATEC [RAMIPRIL] (RAMIPRIL)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Oral
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukaemia (Chronic myeloid leukaemia)
#2) Nephroprotective therapy (Nephroprotective therapy)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 06-JUL-2018 / 20-JUL-2018	#1) 15 days
#2) 07-JUL-2020 / 11-JUL-2020	#2) 5 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ANAFRANIL (CLOMIPRAMINE HYDROCHLORIDE) ; 2008 / Ongoing
#2) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; 1991 / Ongoing
#3) IMOVANE (ZOPICLONE) ; 1991 / Ongoing
#4) TEMESTA [LORAZEPAM] (LORAZEPAM) ; 1991 / Ongoing
#5) ORELOX (CEFPODOXIME PROXETIL) ; 28-SEP-2018 / 03-OCT-2018
#6) ARANESP (DARBEPOETIN ALFA) ; 02-AUG-2019 / Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
2008 to Ongoing	Relevant Med History	Depression (Depression)
1991 to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019075123

24c. DATE RECEIVED BY MANUFACTURER
07-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.
NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

diarrhea [Diarrhoea]
intestinal meteorism [Flatulence]
blood pressure increased [Blood pressure increased]
subconjunctival hemorrhage of the left eye [Conjunctival haemorrhage]
rhinopharyngitis [Nasopharyngitis]
exertional dyspnea [Dyspnoea exertional]
urinary infection grade 2 [Urinary tract infection]
Anemia [Anaemia]
Hypovitaminosis D [Vitamin D deficiency]
Gastroenteritis [Gastroenteritis]
Vertigo [Vertigo]
Sweat [Hyperhidrosis]
Diarrhea [Diarrhoea]
Epigastric pain [Abdominal pain upper]
asthenia [Asthenia]
bloating [Abdominal distension]
digestive disorders [Functional gastrointestinal disorder]
abdominal spasms [Abdominal rigidity]
anxiety [Anxiety]
anorexia [Decreased appetite]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 67-year-old female subject received bosutinib (BOSULIF) orally from 06Jul2018 to 20Jul2018 at 100 mg daily, from 21Jul2018 to 04Aug2018 at 200 mg daily, from 05Aug2018 to 02Aug2019 at 300 mg daily, from 01Dec2019 to 15Dec2019 at 100 mg daily, from 16Dec2019 at 200 mg once daily and from unspecified date and ongoing at 300 mg daily, for chronic myeloid leukaemia. Concomitant suspect drug included ramipril (TRIATEC) orally from 07Jul2020 to 11Jul2020 as nephroprotective therapy. Medical history included depression ongoing from 2008, hypothyroidism ongoing from 1991, insomnia ongoing from 1991, cervical spondylosis ongoing from 2016, breast cancer ongoing from 2011 and chronic renal failure in 2010 and unknown if ongoing. Concomitant medications included clomipramine hydrochloride (ANAFRANIL) oral ongoing from 2008 for depression, levothyroxine sodium (LEVOTHYROX) oral ongoing from 1991 for hypothyroidism, zopiclone (IMOVANE) oral ongoing from 1991 for insomnia, lorazepam (TEMESTA) oral ongoing from 1991 for insomnia, cefpodoxime proxetil (ORELOX) oral from 28Sep2018 to 03Oct2018 for nasopharyngitis, darbepoetin alfa (ARANESP) ongoing from 02Aug2019, and ongoing vitamin D. The subject experienced asthenia grade 1 on 06Jul2018 with result of resolved on 17Jan2019, intestinal meteorism grade 1 in Jul2018 with result of resolved in Aug2018, blood pressure increased grade 1 on 22Aug2018 with result of resolved on the same day, rhinopharyngitis grade 2 on 28Sep2018 with result of resolved on 03Oct2018, exertional dyspnea grade 1 on 18Oct2018 with result of resolved on 17Jan2019, diarrhea grade 1 on 21Aug2018 and with result of resolved on the same day, subconjunctival hemorrhage of the left eye grade 1 on 22Aug2018 with result of resolved in Aug2018, all assessed as non-serious. Returning from a trip, the subject suffered from febrile syndrome grade 2, dyspnea and chest pain, she was hospitalized from 20Jul2019 to 26Jul2019 in pulmonology, where a chest CT scan showed bilateral pleural effusion of low abundance. C-reactive protein was at 240 mg/ml. She had a favorable evolution and was discharged home on 26Jul2019. The action taken for bosutinib in response to febrile syndrome was dose not changed. The event resolved on 26Jul2019. The subject experienced pericardial effusion on 20Jul2019, requiring hospitalization from 31Jul2019 to 02Aug2019, and rated grade 2 resolved in Nov2019. The event pleural effusion from 19Jul2019 with dyspnea was rated grade 2. The respiratory distress was considered as symptom of pleural effusion. In response to event pericardial effusion, bosutinib was temporaraily withdrawn and the event did not reappear with the reintroduction of the product. Since 2019, the subject developed chronic asthenia rated grade 3. Bosutinib was withdrawn in response to chronic asthenia. The event required hospitalization from 31Jul2019 to 02Aug2019. The event chronic asthenia resolved on 19Aug2019. During this 2nd hospitalization, a transthoracic echocardiography performed on 01Aug2019 showed a pericardial effusion of small abundance. It was reported that pneumological explorations do not permit to decide on the imputability of these events to bosutinib. In front of inflammatory signs and febricula, an empiric antibiotic therapy was initiated with piperacillin sodium/tazobactam sodium (TAZOCILLINE) and allowed an improvement on the general status and a resolution of fever. Currently, the subject was better on the respiratory level. She remained asthenic. On auscultation, there was no clinical sign of pleural effusion. The suspension of bosutinib was maintained for now. On 09Aug2019, the subject experienced infectious pneumonia rated grade 3 and requiring the subject's hospitalization. Bosutinib dose was not changed in response to infectious pneumonia. The outcome of the event infectious pneumonia was resolved on 21Aug2019. It was reported that the subject was hospitalized from 31Jul2019 to 02Aug2019 then from 09Aug2019 to 19Aug2019. The subject experienced non-serious event urinary infection grade 2 in Jan2019 and resolved in Jan2019. On 19Jul2019, the subject developed thoracic pain, rated grade 1 and considered as not serious. No action was taken with bosutinib in response to this event. The event resolved in 26Jul2019. In Jul2019, the subject developed anemia and hypovitaminosis D, both rated grade 2 and considered as not serious. No action was taken with bosutinib in response to the events. The events resolved in Aug2019. In Jul2019, the subject developed gastroenteritis, rated grade 1 and considered as not serious. No action was taken with bosutinib in response to this event. The event resolved on 20Jul2019. In

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Jul2019, the subject developed diarrhea, rated grade 1 and considered as not serious. No action was taken with bosutinib in response to this event. The event resolved in Aug2019. In Jul2019, the subject experienced bloating, rated grade 1. No action was taken. The event was resolved in Aug2019. On 31Jul2019, the subject experienced anxiety, rated grade 2, non-serious resolved in Aug2019. In Aug2019, the subject experienced anorexia, rated grade 2, non-serious, resolved in Nov2019. (Reporter comment: alteration of general condition was marked by weight loss of 10kg and anorexia) On 08Aug2019, the subject developed vertigo, sweats, and epigastric pain, both rated grade 1 and considered as not serious. No action was taken with bosutinib in response to the events. The events resolved on 08Aug2019. On 18Sep2018, the subject developed aggravation of chronic renal failure, rated grade 3 and considered as serious and seriousness criteria was hospitalization and medically significant. Per clinical team chronic renal failure was present from 2010 (medical history) but was never explored, and recently managed at the pre-end stage during the 2nd hospitalization of the subject from 31Jul2019 to 02Aug2019. The date of 18Sep2018 was the date the event transitioned to grade 2, it was not a serious adverse event. No action was taken with bosutinib in response to this event. The event was not resolved. In Dec2019 the subject suffered again from asthenia grade 1, assessed as non-serious. Bosutinib was interrupted from 03Aug2019 to 30Nov2019 for pneumopathy. The action taken for bosutinib was withdrawn on 03Aug2019. Asthenia was resolved in 05Mar2020. The subject was treated with ramiprilum (TRIATEC) as a chronic renal failure neuroprotective treatment. After a week of treatment, the subject experienced angioneurotic edema which required a hospitalization in resuscitation unit for 24 hours. As a result of this event ramipril was permanently withdrawn. The subject was admitted in emergency then intensive care unit on 11Jul2020 for oedema of left part of tongue following administration of ramipril. The outcome was favourable leading to discharge on 11Jul2020. On 03Jul2020, the subject experienced abdominal spasms, non-serious, resolved in Jul2020. No action taken with bosutinib. In Dec2019, the subject experienced digestive disorders grade 1, non-serious, resolved in Mar2020. No action taken. Hospitalization from 31Jul2019 to 02Aug2019 and 09Aug2019 to 19Aug2019 was a comment referring to hospitalization for persistent asthenia due to chronic renal failure with anemia. 1st hospitalization from 20 to 26Jul2019 was for febrile syndrome, 2nd hospitalization from 31Jul to 02Aug2019 was for pleural effusions and Chronic asthenia as a consequence of chronic failure known for more than 10 years, that was not being treated and worsened during the study. 3rd hospitalization from 09Aug2019 to 19Aug2019 was for dyspnoea and infectious pneumonitis. Awareness date of the event pericardial effusion in Jul2019. Low abundance pericardial effusion without hemodynamic repercussions notified in the hospitalization report. Last action taken in response to the event for bosutinib was dose not changed, for ramipril was permanently withdrawn on 11Jul2020.

The investigator considered there was a reasonable possibility that pleural effusion with dyspnea, pericardial effusion, asthenia grade 1, intestinal meteorism, diarrhea grade 1, bloating, digestive disorders was associated with a study drug bosutinib, but not associated with a concomitant drug.
The investigator considered there was not a reasonable possibility that blood pressure increased grade 1, rhinopharyngitis grade 2, exertional dyspnea grade 1, subconjunctival hemorrhage of the left eye grade 1, urinary infection grade 2, thoracic pain, anemia grade 2, hypovitaminosis D grade 2, aggravation of chronic renal failure grade 3, gastroenteritis grade 1, vertigo grade 1, sweats grade 1, diarrhea grade 1 and epigastric pain grade 1, anxiety were associated with a study drug or concomitant drug.
The investigator considered that the events febrile syndrome, chronic asthenia, and infectious pneumonia were related to bosutinib.
The investigator considered the event febrile syndrome, chronic asthenia was not related to a concomitant drug.
The investigator considered the event angioneurotic edema as unrelated to suspect drug bosutinib and related to concomitant drug ramipril.
The investigator considered the event abdominal spasms not related to bosutinib but related to concomitant drug TRIATEC.
The investigator considered the event anorexia unrelated to bosutinib.

Follow-up (25Feb2019): New information received included bosutinib route of administration and indication.

Follow-up (25Jun2019): New information received from the investigator via the CRO includes: new event urinary infection.

Follow-up (02Aug2019): New information received from the Investigator includes: additional serious events (respiratory distress and pleural effusion), seriousness criterion (hospitalization), start date and stop date of the new events.

Follow-up (09Aug2019): New information received from the investigator via the CRO includes: an additional event pleural effusion (onset date 07Aug2019).

Follow-up (04Sep2019): New information received from the investigational site reporting information regarding the clinical course of the event and action taken with bosutinib.

Follow-up (05Sep2019): New information received from the investigational site via the CRO includes: new adverse events (febrile syndrome, chronic asthenia and infectious pneumonia).

Follow-up (13Sep2019): New information received from the investigational site via the CRO includes: stop date of bosutinib (03Aug2019), concomitant drug details, reaction data (grade of febrile syndrome updated to grade 2 and outcome updated to resolved on 26Jul2019, onset date of the event chronic asthenia updated from 31Jul2019 to 2019, action taken with bosutinib in response to the event infectious pneumopathy was updated to dose not changed, previously reported event "pleural effusion" with onset on 31Jul2019 was updated to event term "pleural effusion with dyspnea" with onset in Jul2019, deleted event "pleural effusion" with onset on 07Aug2019, outcome of event asthenia (onset on 06Jul2018) updated to resolved on 17Jan2019, onset date of the event urinary tract infection updated from Jan2019 to 2019, added additional events " thoracic pain, anemia, hypovitaminosis D, renal failure, gastroenteritis, vertigo, sweats, diarrhea, and epigastric pain).

Follow-ups (19Sep2019): New information reported includes that respiratory distress was replaced by febrile syndrome and pleural

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

effusion, asthenia was present on 21Aug2019, the patient was hospitalized from 20Jul2019 to 26Jul2019 for febrile syndrome with C-reactive protein at 240 mg/ml, investigator's causality assessment for the event febrile syndrome, start date of chronic asthenia (31Jul2019).

Follow-up (01Oct2019): New information received from the CRO included action taken for febrile syndrome provided as dose not changed, outcome of event infectious pneumonia updated as recovered and recovery date provided, causality between events febrile syndrome, chronic asthenia, infectious pneumonia with bosutinib provided as unrelated, added new events respiratory distress and chronic renal failure.

Follow-up (03Dec2019): New information received from clinical team includes deleted event respiratory distress as it was a symptom of the event pleural effusion and updated causality for pleural effusion (from unrelated to related).

Follow-up (06Dec2019): New information received from clinical team stated that the event 'chronic renal failure' was a non-serious adverse event.

Follow-up (11Dec2019): New information received from clinical team includes: medical history data (chronic renal failure in 2010), reaction data (chronic renal failure removed as event) and confirmation with clinical rationale that the event renal failure (onset 18Sep2018) was a non-serious event (grade 2).

Follow-up (06Jan2020): New information received from the investigational site via the CRO includes: event pneumonia updated (outcome resolving), event description updated (pleural effusion and dyspnea separated), event renal failure updated to aggravation of chronic renal failure (seriousness, causality remained the same, recovery date updated to Oct2018), and causality data for events febrile syndrome, chronic asthenia, and infectious pneumonia (updated to related).

Follow-up (23Jan2020): New information reported from the site includes: event verbatim "pleural effusion" updated to "pleural effusions" with start date 09Aug2019 (to be clarified).

Follow-up (13Mar2020): New information reported from the site includes: updated hospitalization dates for events asthenia and pleural effusion (09Aug2019-19Aug2019), new lab data chest CT scan (performed in Jul2019) and trans thoracic echocardiography (performed in Aug2019), new event asthenia with grade 1 on 02Dec2019 non-serious, outcome not recovered.

Follow-up (31Jul2020): New information received from CRO includes updated start date of medical history breast cancer from 2011 to 2001, additional medical history of cervical spondylosis, additional bosutinib dosage, additional concomitant Triatec, updated start date of concomitant drug anafranil from 2008 to 2000, new event angioneurotic edema and clinical course details.

Follow-up (21Jan2021): New information received from CRO includes: updated dose regimens of bosutinib, new event (pericardial effusion on 20Jul2019), and updated outcome of event pleural effusion and infectious pneumonia (resolved on 21Aug2019).

Follow-up (04Apr2022 and 05Apr2022): This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL, received from the investigator via the CRO.
Updated information includes: updated outcome of events (exertional dyspnea, aggravation of chronic renal failure and asthenia), updated onset date of events (chronic asthenia and asthenia), new events (bloating, abdominal spasms, digestive disorders, anxiety and alteration of general condition), updated action taken of bosutinib (dose not changed), and clinical course.

Follow-up (02Jun2022): This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL, received from the investigator via the CRO.

Updated information: Event digestive disorders onset date was Dec2019 and stop dated was Mar2020.

Follow-up (15Sep2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter (Other HCP) for protocol B1871047.

Updated information includes: updated dosing regimens, stop date for exertional dyspnoea .'

Follow-up (15May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information includes: medical history (start date for breast cancer updated), concomitant drug details (start date updated for ANAFRANIL) and event details (hospitalization dates for Pericardial effusion).

Amendment: This follow-up report is being submitted to amend previously reported information: Thoracic pain (on 19Jul2019) recovered in Jul2019 (previously captured as 26Jul2019). Chronic asthenia (in 2019) recovery date corrected to 02Aug2019 (previously captured as 19Aug2019). Pleural effusions start date was corrected to 09Aug2019 (previously captured as 19Jul2019).

Follow-up (06Sep2023, 07Sep2023 and 07Sep2023): This is a non-interventional study follow up report from the investigational site via the CRO and the clinical team in response to query.
Updated information includes: date of lab Transthoracic echocardiography updated, event "aletration of general condition" updated to "anorexia" rated grade 2 (from Aug2019 to Nov2019 unrelated to bosutinib), onset date of event abdominal spasms grade 2 updated

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

to 03Jul2020, onset date of event urinary infection grade 2 updated to Jan2019, onset date of event Pleural effusions updated to 19Jul2019 and recovery date updated to Nov2019, recovery date of event chronic asthenia updated to 19Aug2019, recovery date of event thoracic pain updated to 26Jul2019, recovery date of event asthenia in Dec2019 updated to 05Mar2020, anxiety on 31Jul2019 rated grade 2, event "aggravation of chronic renal Failure" on 18Sep2018 rated grade 3, hospitalization details, clinical course.

Follow-up (07Sep2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the investigational site CRO for protocol B1871047. Updated information included: event Chronic renal failure worsened seriousness upgraded to hospitalization and medically significant.

Case Comment: Based on the limited information provided and known safety profile of the suspect drug, in agreement with the reporter, the Company cannot completely exclude the possible causality between the reported dyspnea, asthenia, intestinal meteorism, diarrhea, pleural effusion (both episodes), pericardial effusion, pneumonia, pyrexia, asthenia grade 1 and the administration of the suspect drug, bosutinib. Similarly, considering lacking of the alternative explanations, the Company cannot completely rule out the possible causality between the reported blood pressure increased, rhinopharyngitis, exertional dyspnea, subconjunctival hemorrhage of the left eye, urinary tract infection, thoracic pain, anemia, hypovitaminosis D, gastroenteritis, vertigo, sweats, diarrhea, epigastric pain, renal failure, bloating, digestive disorders and bosutinib administration. The event angioneurotic edema is serious and unexpected relative to the suspect drug, bosutinib. The reported abdominal spasms, anxiety and alteration of general condition are unrelated to suspect drug bosutinib. This case will be updated when new information becomes available.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to RAs, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	22-AUG-2018	Blood pressure measurement	increased (grade 1)	
2	20-JUL-2019	Body temperature	fever	
3	JUL-2019	C-reactive protein	240 mg/ml	
4	JUL-2019	Computerised tomogram	bilateral pleural effusion of low abundance	
5	01-AUG-2019	Echocardiogram	pericardial effusion of small abundance	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	21-JUL-2018 / 04-AUG-2018; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	05-AUG-2018 / 02-AUG-2019; 11 months 29 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	100 mg, daily; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	01-DEC-2019 / 15-DEC-2019; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	200 mg, 1x/day; Oral	Chronic myeloid leukaemia (Chronic myeloid leukaemia)	16-DEC-2019 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet;	300 mg, daily; Oral	Chronic myeloid leukaemia	Ongoing;

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #6		(Chronic myeloid leukaemia)	Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) VITAMIN D [VITAMIN D NOS] (VITAMIN D NOS) ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1991 to Ongoing	Relevant Med History	Insomnia (Insomnia);
2011 to Ongoing	Relevant Med History	Breast cancer (Breast cancer);
2010 to Unknown	Relevant Med History	Chronic renal failure (Chronic kidney disease);
2016 to Ongoing	Relevant Med History	Cervical spondylosis (Spinal osteoarthritis);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1953	66 Years	Female	70.00 kg	06	FEB	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Digestive infectious syndrome [Gastrointestinal infection]
Epigastralgia [Abdominal pain upper]
Fever sensation [Pyrexia]
vertigo [Vertigo]
abdominal meteorism [Flatulence]
skin eruption [Rash]
shortness of breath [Dyspnoea]
Epigastralgia [Abdominal pain upper]
sensation of cold [Feeling cold]
polyphagia [Hyperphagia]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) MEDIATENSYL [URAPIDIL] (URAPIDIL)

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 400 mg, daily
#2) 120 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Oral
#2) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 16-JAN-2019 / 07-FEB-2019
#2) Unknown

19. THERAPY DURATION
#1) 23 days
#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) PANTOPRAZOLE (PANTOPRAZOLE) ; Ongoing
#2) BISOPROLOL (BISOPROLOL) ; Ongoing
#3) EXFORGE (AMLODIPINE BESILATE, VALSARTAN) ; Ongoing
#4) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; 2010 / Ongoing
#5) PRAVASTATIN (PRAVASTATIN) ; Ongoing
#6) VITAMINE B12 (CYANOCOBALAMIN) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019075415

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Skin rash [Rash]
Sternum pain [Bone pain]
dorsal pain [Back pain]
Cough [Cough]
Anxiety [Anxiety]
Asthenia [Asthenia]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 66-year-old female patient received bosutinib (BOSULIF), first regimen from 16Jan2019 to 07Feb2019 at 400 mg daily, oral, second regimen since 08Feb2019 at 300 mg daily, oral, third regimen from 11Feb2019 to 15Jul2019 at 300 mg daily, oral and fourth regimen since 23Jul2019 at 200 mg daily for chronic myeloid leukaemia; urapidil (MEDIATENSYL [URAPIDIL]), (Batch/Lot number: unknown) at 120 mg daily, oral. The patient's relevant medical history included: "arterial hypertension" (ongoing); "hypothyroidism" (ongoing); "hypercholesterolemia" (ongoing); "fibromyalgia" (ongoing); "pericardial effusion" (unspecified if ongoing), notes: cardiomegaly was a symptom of pericardial effusion. Concomitant medication(s) included: PANTOPRAZOLE oral (ongoing); BISOPROLOL oral (ongoing); EXFORGE oral (ongoing); LEVOTHYROX oral, start date: 2010 (ongoing); PRAVASTATIN oral (ongoing); VITAMINE B12 oral (ongoing). The patient experienced digestive infectious syndrome (grade 3) on 06Feb2019 with seriousness criterion hospitalization. The patient underwent lab tests and procedures on 06Feb2019 which included C-reactive protein: 51.8 mg/l (normal high: 5), and white blood cell count: 13.8 x10 9/l (normal range: 3.8-11). The action taken in response to the event for bosutinib was dose reduced. Corrective treatments included: amoxicillin/ clavulanic acid (AUGMENTIN) 3 g daily from 06Feb2019 to 10Feb2019 and metronidazole benzoate (FLAGYL) 1.5 g daily from 06Feb2019 to 08Feb2019. The outcome of the event digestive infectious syndrome was resolved on 11Feb2019. On 28Feb2019, the patient experienced fever sensation, sternum pain, epigastralgia and dorsal pain, and in Feb2019 vertigo, all assessed as non-serious (grade 1). As a result of these events, action taken regarding bosutinib was reported as dose not changed. On 09Apr2019, the patient developed abdominal meteorism which was assessed as non-serious and grade 1. No action was taken with bosutinib in response to abdominal meteorism. On 09Apr2019, the patient experienced sensation of cold considered non-serious and rated grade 1. No action was taken for bosutinib in response to the event. The event recovered on 23Apr2019. On 09Apr2019, the patient experienced polyphagia considered non-serious and rated grade 1. No action was taken for bosutinib in response to the event. The event recovered on 23Apr2019. On 23Apr2019, abdominal meteorism, epigastralgia (28Feb2019) resolved. Fever sensation resolved on 09Apr2019. Event vertigo recovered on 28Feb2019. Event sternum pain recovered on 23Apr2019. Event dorsal pain recovered on 11Jun2019. On 11Jun2019, the patient experienced shortness of breath considered non-serious and rated grade 1. No action was taken for bosutinib in response to the event shortness of breath. The event recovered on 08Jul2019. On 11Jun2019, the patient experienced epigastralgia considered non-serious and rated grade 1. No action was taken for bosutinib in response to the event. The event recovered on 08Jul2019. On 08Jul2019, the patient experienced skin eruption considered non-serious and rated grade 2. Course of the event was on 08Jul2019, skin eruption and pruritus were reported and desloratadine (AERIUS) was prescribed. On 15Jul2019, cutaneous aggravation was noted, bosutinib was withdrawn and prednisolone (SOLUPRED) was prescribed. The action taken with bosutinib in response to the event skin eruption was dose reduced. Bosutinib was received at 300 mg, daily to 15Jul2019. Bosutinib was resumed on 23Jul2019 at 200 mg, daily. The patient presented with anxiety on 22Aug2019 which was considered as non-serious and rated as grade 1. No action was taken in response to this event. Anxiety resolved in Aug2019. On 15Oct2019, the patient recovered from the skin eruption. Skin eruption did not recur upon reintroduction of study drug. On the same day, the patient started to experience cough considered non-serious and rated grade 1. No action was taken on study drug as a result of this event. The patient recovered from cough on 16Dec2019. The patient experienced asthenia on 16Dec2019 which was considered as non-serious and rated as grade 1. No action was taken in response to this event. Asthenia resolved on 13Dec2021. On 27Jul2020, the patient developed skin rash, rated grade 2 and considered as not serious. The event skin rash resolved on 04Aug2020. Last action taken for bosutinib was dose reduced, for urapidil was permanently withdrawn.

The reporter considered "digestive infectious syndrome", "epigastralgia" (onset 28Feb2019), "vertigo", "abdominal meteorism", "skin rash" related to bosutinib and unrelated to concomitant drugs. The reporter considered "fever sensation", "shortness of breath", "epigastralgia"(onset 11Jun2019), "sensation of cold", "polyphagia", "sternum pain", "dorsal pain", "cough", "anxiety" and "asthenia" not related to bosutinib and concomitant medications.
The investigator considered the event skin eruption as possibly related to the study drug bosutinib and to concomitant medication urapidil.

Follow-up attempts are completed. No further information is expected.

Follow-up (27Mar2019): New information received from the CRO includes new events (fever sensation, sternum pain, epigastralgia, dorsal pain and vertigo).

Follow-up (21Jun2019): New information received from the investigator included: indication and dosage regimens of bosutinib; new

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

event (abdominal meteorism).

Follow-up (27Aug2019): New information received via the CRO includes: as reported causality of the event "abdominal meteorism" (related to bosutinib and unrelated to concomitant drugs), outcome of event fever sensation (updated to recovered on 23Apr2019), new adverse events (skin eruption, shortness of breath, Epigastralgia, Cardiomegaly, Hypothyroidism, sensation of cold, Polyphagia).

Follow-up (03Sep2019): New information received from the study site includes: The event cardiomegaly was deleted.

Follow-up (10Sep2019): new information reported includes grade of skin eruption, reporter's assessment for the events skin eruption, shortness of breath and epigastralgia (previously missing).

Follow-up (27Sep2019): New information received includes: Action taken (confirmed as dose reduced for bosutinib in response to the event skin eruption), Reaction data (updated event term hypothyroidism to aggravation of hypothyroidism) and Causality assessment for events sensation of cold and polyphagia.

Follow-up (25Oct2019): New information received from clinical team is as follows: medical history, event outcome.

Follow-up (24Jan2020): New information reported includes further details about bosutinib therapy, recovery date of skin eruption and new event cough.

Follow-up (26Mar2020): new information received from CRO includes: outcome and recovery date of event cough.

Follow-up (26May2020): New information includes strength of concomitant medications pantoprazole, bisoprolol and levothyroxine sodium, onset date of vertigo updated from 28Feb2019 to Feb2019, updated outcome of sternum pain, dorsal pain and vertigo.

Follow-up (05Oct2020): New information received from CRO included: new event "skin rash" added.

Follow-up (02Mar2021): New information received from the CRO included: causality for event skin eruption updated as related to bosutinib and urapidil (previously unrelated to bosutinib).

Follow-up (23Mar2021): New information received from the study site includes: event Fever sensation outcome, new events (anxiety, asthenia).

Follow-up (29Jun2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: event term updated from 'aggravation of hypothyroidism' to 'hypothyroidism', previously event 'Condition aggravated' removed.

Follow-up (31Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Other HCP) for protocol B1871047.
Updated information included: event hypothyroidism deleted.

Follow-up (14Nov2023) : This is a follow-up to a non-interventional study for protocol B1871047 received from the clinical team.
Updated information Following reconciliation includes: outcome of event asthenia was updated to resolved on 13Dec2021.
No follow-up attempt is needed. No further information is expected.

Case Comment: Digestive infectious syndrome (PT: gastrointestinal infection) is unlisted in the RSI of IB of the suspect, bosutinib, and related per Company assessment.

Based on the myelosuppressive effect of the suspect drug, bosutinib, its contributory effect to the occurrence of digestive infectious syndrome cannot be excluded. Based on the limited information provided and known product safety profile, a contributory role cannot be excluded for the events epigastralgia, skin eruption and pruritus/skin rash, fever sensation, sensation of cold, shortness of breath, polyphagia for bosutinib. The other events, sternum pain, dorsal pain, vertigo, cough and abdominal meteorism are assessed as unrelated to bosutinib. New events anxiety and asthenia are assessed as unrelated to bosutinib; the prolonged drug-event temporal association does not suggest a causal relationship. The follow-up information received does not alter the previous company clinical evaluation.

The impact of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to RAs, Ethics Committees, and Investigators, as appropriate.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	06-FEB-2019	C-reactive protein	51.8 mg/l	5
2	06-FEB-2019	White blood cell count	13.8 x10 9/l	11

Mfr. Control Number: 2019075415

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
			3.8	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	08-FEB-2019 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	11-FEB-2019 / 15-JUL-2019; 155 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	23-JUL-2019 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
Unknown to Ongoing	Relevant Med History	Fibromyalgia (Fibromyalgia);
Unknown	Relevant Med History	Pericardial effusion (Pericardial effusion); cardiomegaly was a symptom of pericardial effusion

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		NOV	1955	63 Years	Female	111.00 kg	04	DEC	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

diarrhea [Diarrhoea]
diarrhea [Diarrhoea]
Ptosis [Eyelid ptosis]
bronchitis [Bronchitis]
Urticaria [Urticaria]
Laryngitis [Laryngitis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosutinib (BOSUTINIB) Unknown

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 100 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☒ NO ☐ NA

18. THERAPY DATES(from/to)
#1) 12-NOV-2018 / 18-NOV-2018

19. THERAPY DURATION
#1) 7 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) IRBESARTAN (IRBESARTAN) ; 2012 / Ongoing
#2) ANASTROZOLE (ANASTROZOLE) ; SEP-2015 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
APR-2015 to Ongoing	Relevant Med History	Breast adenoma (Breast adenoma)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019077185

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
23-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 63-year-old female patient received bosutinib (BOSUTINIB), first regimen from 12Nov2018 to 18Nov2018 at 100 mg daily, second regimen from 19Nov2018 to 25Nov2018 at 200 mg daily, third regimen from 26Nov2018 to 02Dec2018 at 300 mg daily and fourth regimen since 03Dec2018 at 400 mg daily. The patient's relevant medical history included: "Hypertension arterial" (ongoing); "Breast adenoma", start date: Apr2015 (ongoing). Concomitant medication(s) included: IRBESARTAN oral taken for hypertension, start date: 2012 (ongoing); ANASTROZOLE taken for breast cancer, start date: Sep2015 (ongoing). The subject experienced ptosis, grade 1, non serious, on an unspecified date recovered on 15Jan2019, bronchitis in Dec2018 with outcome of recovered in Dec2018, diarrhea on 04Dec2018 with outcome of recovered on 04Dec2018, diarrhea on 16Jan2019 with outcome of not recovered, urticaria on 08Apr2019 with outcome of recovered on 03May2019, and laryngitis on 08Apr2019 with outcome of recovered in May2019. Events ptosis, grade 1, bronchitis was grade 2, urticaria grade 2, laryngitis grade 1. In response to the event "ptosis" bosutinib was withdrawn and did not reappear after reintroduction. For other events, dose was not changed.

According to the investigator, the ptosis, bronchitis, urticaria and laryngitis were not related to study drug or concomitant medication while the episodes of diarrhea were related to study drug but not related to concomitant medications.
As of 15May2023, Investigator Initial Awareness Dates for Urticaria and Laryngitis: 16May2019; Investigator Initial Awareness Dates for Eyelid disorder and Bronchitis: 06Dec2018; Investigator Initial Awareness Dates for Diarrhea and Diarrhea: 07Feb2019

Follow-up (25Jun2019): New information received from the investigator included added new events urticaria and laryngitis.

Follow-up (22Jul2019): New information received includes outcome of event laryngitis (updated to resolving).

Follow-up (18Jan2022): This is a follow-up report for a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL). Updated information included: outcome of event Laryngitis (updated from recovering to recovered).

Follow-up(15May2023): This is a follow-up of non-interventional study report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: Investigator Initial Awareness Dates added.

Follow-up attempts are completed. No further information is expected.

Follow-up (06Sep2023). This is a follow-up of non-interventional study report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: event details ("Left eyelid anomaly" updated to "ptosis" and grade).

Follow-up(23Nov2023): This is a non-interventional study follow-up report received from investigational site via CRO for protocol B1871047. Updated information included: bosutinib action taken.

Case Comment: Based on available information and known safety profile of the suspect product, the reported diarrhea episodes were considered related to bosutinib. The reported ptosis, bronchitis, urticaria and laryngitis, in concurrence with the investigator's assessment were considered intercurrent medical condition unrelated to bosutinib.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #2	200 mg, daily; Unknown	Unknown	19-NOV-2018 / 25-NOV-2018; 7 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	300 mg, daily; Unknown	Unknown	26-NOV-2018 / 02-DEC-2018; 7 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	400 mg, daily; Unknown	Unknown	03-DEC-2018 / Unknown; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAR	1986	32 Years	Female	55.00 kg	20	OCT	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

DIARRHEA [Diarrhoea]
hyperthyroidism [Hyperthyroidism]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE.

This is a report from a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL). This is a Non-Interventional Study report with non-serious event only.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 300 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 18-OCT-2018 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	none ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019079681

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
29-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 32-year-old female subject started to receive bosutinib (BOSULIF), from 18Oct2018 at 300 mg once daily, and ongoing for chronic myeloid leukemia. Medical history was none and the subject did not receive concomitant medications.
On 20Oct2018, the subject experienced diarrhea, which was rated grade 1 and assessed as non-serious. The event was described as 2 to 3 stools in the morning.
On 08Jul2019, the subject experienced hyperthyroidism rated non-serious and grade 1. The hyperthyroidism was biological without clinical manifestation. Laboratory analysis performed on 29Jul2019 found thyroid stimulating hormone (TSH) at 0.01 mIU/l (normal range: 0.27 - 4.20 mIU/l), Antidodies anti - TPO was normal, less than 30 U/ml (normal range: normal high 60U/ml) and LUMItest TRAK human was normal, less than 1 IU/l (normal range: normal high 1 IU/l). Action taken on study drug was reported dose not changed. On 14Oct2019, the subject recovered from hyperthyroidism while recovered from diarrhea on 03May2019.

The investigator considered there was a reasonable possibility that the event diarrhea was related to bosutinib.
According to the investigator, the event hyperthyroidism was not related to study drug.

Follow-up (24Apr2019): Follow-up attempts completed. No further information expected.

Follow-up (26Dec2019): New information received from investigator included: lab data; indication and dosage regimens; new event (hypothyroidism).

Follow-up (20Apr2020): New information received from the investigator via the CRO includes updated clinical outcome for diarrhea (from 'not recovered' to 'recovered') with recovery date.

Follow-up (26Aug2020): New information received from the investigator via the CRO included: onset date of hypothyroidism was changed from 29Jul2019 to 08Jul2019.

Follow-up (26Oct2022): This is a follow-up report received from the CRO.

Updated information included: study name was added; patient details updated; lab tests details added; bisutinib dosage details updated.
Additional information: Biological hyperthyroidia no clinical signs. Two to three stools in the Morning

Amendment: This follow-up report is being submitted to amend previously reported information: Event term "hypothyroidism" corrected to "hyperthyroidism".

Case Comment: Based on the temporal association and known product safety profile, the event diarrhea was related to bosutinib. There was not a reasonable possibility that the event Hyperthyroidism was related to bosutinib, but most likely represents patient intercurrent or underlying medical condition.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	29-JUL-2019	Blood thyroid stimulating hormone low	0.01 mIU/l	4.20 0.27
2	29-JUL-2019	Investigation normal	< 1 IU/l	1 1
3	29-JUL-2019	Investigation normal	< 30 IU/ml	60 30

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
PRIVACY	FRANCE		JUL	1947	71 Years	Female	Unk	26	NOV	2018	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

CONSTIPATION [Constipation]
Dry skin [Dry skin]
Reflux gastritis [Reflux gastritis]
rhinopharyngitis [Nasopharyngitis]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety

(Continued on Additional Information Page)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, daily	#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 28-JUN-2018 / Ongoing	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	none ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019115441

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
18-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 71-year-old female subject started to receive bosutinib (BOSULIF) via an unspecified route, from 28Jun2018 at 300 mg daily for an unspecified indication. Medical history was reported as none. The subject did not receive concomitant medication.
The patient experienced constipation, grade 1 on 26Nov2018, dry skin, grade 1 and reflux gastritis, grade 1 both on 11Mar2019. On 01Dec2019, the subject experienced rhinopharyngitis. All events were non-serious. The action taken in response to the event for bosutinib was dose not changed. The event dry skin grade 1 and reflux gastritis were recovered on 19Jun2019, rhinopharyngitis resolved on 18Mar2020 and constipation was recovered on 19Sep2019.

According to the reporter, the event rhinopharyngitis was unrelated to study drug and to concomitant drug. The investigator considered constipation, dry skin and reflux gastritis as possibly related to bosutinib and not related concomitant medications.

Follow-up (14May2019): Follow-up attempts completed. No further information expected.

Follow-up (29Aug2019): New information includes updated outcome of constipation from recovered to recovering.

Follow-up (11May2020): New information received from CRO includes medical history was reported as none and new event rhinopharyngitis

Follow-up (25Oct2021): New information received includes: Clinical outcome (constipation recovered on 19Sep2019).

Follow-up (05Jan2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: new reporter, reaction data (outcome of events Reflux gastritis and Dry Skin).

Follow-up (06Mar2023): This is a follow-up report received from the CRO providing the investigator's awareness date.

Amendment: case is being re-submitted to amend the gender in the narrative.

Case Comment: Based on the clinical information currently provided, the company concurs with the causality assessment expressed by the investigator, considering there is a reasonable possibility that constipation, dry skin, and reflux gastritis, are related to the suspect, study drug bosutinib. Event rhinopharyngitis represents an intercurrent medical condition and unrelated to bosutinib.
The follow-up information received does not alter the previous company clinical evaluation.

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		APR	1960	58 Years	Male	82.00 kg		SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea [Diarrhoea]
Diarrhea [Diarrhoea]
Intermittent diarrhea [Diarrhoea]
Alanine aminotransferase increased [Alanine aminotransferase increased]
gastrointestinal fragility [Gastrointestinal disorder]
Muscle pain under the scapulars [Myalgia]
Great fatigue [Fatigue]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 500 mg, 1x/day

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 08-AUG-2018 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LOPERAMIDE (LOPERAMIDE) ; 08-AUG-2018 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019117574

24c. DATE RECEIVED BY MANUFACTURER
25-AUG-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL). This is a non-interventional clinical study case reporting non-serious events only.

A 58-year-old male subject started to receive bosutinib (BOSULIF; film-coated tablet), via an unspecified route of administration from 08Aug2018 at 500mg once daily for an unspecified indication. The subject did not have relevant medical history. The subject's concomitant medication included loperamide since 08Aug2018 by oral route for diarrhea. The subject experienced diarrhea in Sep2018. The event was Grade 1 and was assessed as non-serious. The action taken in response to the event for bosutinib was dose not changed. The subject received LenoDiar, oral from 28Oct2018 and ongoing for diarrhea. The event diarrhea resolved in Oct2018. The reporter reported additional non-serious event of diarrhea rated grade 1 with onset in Oct2018. He presented with diarrhea during 6 weeks with 3 to 4 stools a day, resolving for about a month, but still treated with 1 DF of food supplement LenoDiar per day. No action was taken with bosutinib in response to this event. The event resolved on 01Nov2018. In May2019, the subject experienced diarrhea, assessed as non-serious and rated grade 1. The subject presented with a few episodes of moderate-volume liquid stool. Action taken with bosutinib in response to diarrhea (onset date May2019) was reported as dose not changed. On 09Jan2020, the subject had recovered from this episode of diarrhea. On 15May2019, the subject experienced alanine aminotransferase increased, assessed as non-serious and rated grade 2. The subject presented with uninterpretable increase of ALAT (alanine aminotransferase) and ASAT (aspartate aminotransferase) because hemodiluted sample. Action taken with bosutinib was reported as dose not changed. On 08Jan2020, the subject had recovered from alanine aminotransferase increased.

According to the investigator the diarrhea (onset date Sep2018 and Oct2018) was related to study drug. The investigator considered the events diarrhea (onset date May2019) and alanine aminotransferase increased as possibly related to the study drug bosutinib and unrelated to the concomitant medication.

Follow-up (18Apr2019): New information received from the study site includes clarification that the patient had no concomitant medication. Diarrhea resolved on 28Oct2018.

Follow-up (03May2019). New information from the study coordinator included: suspect product data (dosing added), medical history (none).

Follow-up (28Aug2019): New information includes updated start date and recovery date of event diarrhea, additional non-serious episode of diarrhea rated grade 1.

Follow-up (01Oct2019): New information includes: start date of bosutinib (updated from 08Aug2018 to 01Sep2018) and the start date of first episode of diarrhea updated (reaction start date is earlier than the drug start date).

Follow-up (29Oct2019): New information reported includes onset date of the first event of diarrhea (updated from Aug2018 to Sep2018).

Follow-up (13May2020): New information received includes start date of bosutinib (previously reported as 01Sep2018), concomitant drug loperamide, new episode of diarrhea reported as non-serious event, new event alanine aminotransferase increased, relevant lab data.

Follow-up (17Jun2020): New information received includes the clarification that Aspartate aminotransferase increased should not be considered as an additional event.

Follow-up (01Jul2020): New information received includes start date of bosutinib (updated from 08Aug2018 to 01Sep2018). Concomitant medication included food supplement (LENODIAR) for diarrhea via oral route ongoing from Sep2018 (previously reported as loperamide from 08Aug2018 and ongoing). The event diarrhea in Sep2018 resolved in Nov2018 (previously reported in Sep2018). The event diarrhea in May2019 was replaced by intermittent diarrhea occurred in Nov2018. At the time of reporting, the event has not resolved. The onset date of the event alanine aminotransferase increased was on 06Feb2019 (previously reported on 15May2019). In Feb2019, the subject experienced digestive fragility, muscle pain under the scapulars and great fatigue; all assessed as non-serious and rated grade 1. The action taken with bosutinib was dose not changed. The events digestive fragility, muscle pain under the scapulars and great fatigue resolved in Feb2019. The investigator considered the event, digestive fragility, muscle pain under the scapulars and great fatigue as possibly unrelated to the study drug and concomitant medications.

Follow-up (15Nov2021): This is a Non-Interventional Study follow-up report. Updated information included: Bosutinib start date was 08Aug2018. Concomitant medication included loperamide orally from 08Au2018 for diarrhea. Intermittent diarrhea (onset date Nov2018), grade 1, resolved in Jan2020.

Amendment: This follow-up report is being submitted to amend previously reported information: onset date of event "digestive fragility" was provided as Feb2019.

Case Comment: Based on the known drug safety profile, the Company concurs with the investigator that the causal association

Mfr. Control Number: 2019117574

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

between the events, episodes of diarrhea and alanine aminotransferase increased, and bosutinib administration cannot be excluded. Conversely, the reported digestive fragility, muscle pain under the scapulars and great fatigue are considered unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	15-MAY-2019	Alanine aminotransferase	increased	
		uninterpretable because hemodiluted sample		
2	15-MAY-2019	Aspartate aminotransferase	increased	
		uninterpretable because hemodiluted sample		

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		NOV	1984	34 Years	Male	122.00 kg	30	JAN	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrheas [Diarrhoea]
Intermittent diarrheas [Diarrhoea]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)
#1) 300 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) 18-DEC-2018 / 26-DEC-2018

19. THERAPY DURATION
#1) 9 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) HYPERIUM (RILMENIDINE PHOSPHATE) ; 30-OCT-2018 / Ongoing
#2) HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) ; 27-SEP-2018 / Ongoing
#3) LERCANIDIPINE (LERCANIDIPINE) ; 27-SEP-2018 / Ongoing
#4) NEBIVOLOL (NEBIVOLOL) ; 24-FEB-2018 / Ongoing
#5) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; 24-APR-2018 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension) treated, unrelated to tyrosine kinase inhibitor
Unknown to Ongoing	Relevant Med History	Adrenal hypercorticism (Hyperadrenocorticism) not treated, unrelated to tyrosine kinase inhibitor

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019129720

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
07-JUN-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 34-year-old male patient received bosutinib (BOSULIF), first regimen from 18Dec2018 to 26Dec2018 at 300 mg daily, second regimen from 26Dec2018 to 19Mar2019 at 400 mg daily, third regimen from 20Mar2019 to 26Jun2019 at 300 mg daily, fourth regimen from 26Jun2019 to 18Sep2019 at 400 mg daily and fifth regimen since 18Sep2019 (ongoing) at 300 mg daily, all oral for chronic myeloid leukaemia. The patient's relevant medical history included: "arterial hypertension" (ongoing), notes: treated, unrelated to tyrosine kinase inhibitor; "hypercorticism" (ongoing), notes: not treated, unrelated to tyrosine kinase inhibitor; "hypothyroidism" (ongoing), notes: treated, unrelated to tyrosine kinase inhibitor; "CML" (ongoing); "CUSHING SYNDROME" (ongoing). Concomitant medication(s) included: HYPERIUM taken for hypertension, start date: 30Oct2018 (ongoing); HYDROCHLOROTHIAZIDE taken for hypertension, start date: 27Sep2018 (ongoing); LERCANIDIPINE taken for hypertension, start date: 27Sep2018 (ongoing); NEBIVOLOL taken for hypertension, start date: 24Feb2018 (ongoing); LEVOTHYROX taken for hypothyroidism, start date: 24Apr2018 (ongoing).
The following information was reported: DIARRHOEA (non-serious) with onset 30Jan2019, outcome "recovered" (20Mar2019), described as "Diarrheas"; DIARRHOEA (non-serious) with onset 26Jun2019, outcome "recovered" (17Jun2020), described as "Intermittent diarrheas". The action taken for bosutinib was dosage not changed.

Additional information:On 30Jan2019, the subject experienced diarrhea assessed as non-serious and grade 2. No action was taken with bosutinib. No laboratory tests were provided. On 20Mar2019, diarrhea resolved.diarrhea on 26Jun2019 was grade 2.

The investigator considered there was a reasonable possibility that the event was related to bosutinib and unrelated to a concomitant medication.

Follow-up (10May2019): Follow-up attempts are completed. No further information is expected.

Follow-up (15May2019): New information received includes subject's medical history included arterial hypertension, hypercorticism, and hypothyroidism, all ongoing at report time and unrelated to tyrosine kinase inhibitor. Hypercorticism was not under treatment. Ongoing concomitant medications included rilmenidine phosphate (HYPERIUM) since 30Oct2018 for arterial hypertension, hydrochlorothiazide since 27Sep2018 for arterial hypertension, lercanidipine since 27Sep2018 for arterial hypertension, nebivolol since 24Feb2018 for arterial hypertension, and levothyroxine sodium (LEVOTHYROX) since 24Apr2018 for hypothyroidism. No complementary examination was realized.

Follow-up (24Sep2019): New information received from CRO is as follows: The subject developed diarrhea grade 1 on 26Jun2019. In response to the event, no action was taken with bosutinib. At reporting time, the event was not resolved. According to the reporter the event was related to study drug and unrelated to concomitant drug. The reporter stated: the subject signaled some very episodic diarrhea episodes from 26Jun2019.

Follow-up (19Dec2019): New information received from the study site includes: The event term 'diarrhea' with onset date 26Jun2019 was updated to 'Intermittent diarrhea'.

Follow-up (19Feb2020): New information received from the study coordinator includes that the subject received bosutinib 300 mg from 18Dec2018 to 26Dec2018, 400 mg from 26Dec2018 to 20Mar2019, 300 mg from 20Mar2019 to 26Jun2019, 400 mg from 26Jun2019 to 18Sep2019, and 300 mg since 18Sep2019.

Follow-up (06Jul2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. New information received from the study site via CRO includes:
Verbatim as reported for diarrhea of 30Jan2019 was updated to 'diarrheas' and for intermittent diarrhea of 26Jun2019 to 'intermittent diarrheas'. Intermittent diarrheas of 26Jun2019 recovered on 17Jun2020.

Follow-up (10May2023): This is a non-interventional study report (Post Authorization Safety Study) received from contactable Physician and Other HCP for protocol B1871047.
Updated information includes patient's height.

Follow-up (07Jun2023): This is a non-interventional study report received from the investigational site via the CRO. Updated information included: The patient's initials were updated. diarrhea on 26Jun2019 was grade 2. Relevant medical history includes ongoing CUSHING SYNDROME and CML. Bosutinib was received at 400 mg, dailyfrom 26Dec2018 to 19Mar2019 (reported previously as 20Mar2019)

Follow-up attempts are completed. No further information is expected.

Case Comment: Based on the temporal relationship and known drug safety profile, the causal association between the reported episodes of diarrhea and bosutinib administration cannot be excluded.
The follow-up information received does not alter the previous company clinical evaluation.

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	26-DEC-2018 / 19-MAR-2019; 85 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	20-MAR-2019 / 26-JUN-2019; 99 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	26-JUN-2019 / 18-SEP-2019; 2 months 24 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	18-SEP-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism); treated, unrelated to tyrosine kinase inhibitor
Unknown to Ongoing	Relevant Med History	CML (Chronic myeloid leukaemia);
Unknown to Ongoing	Relevant Med History	Cushing's syndrome (Cushing's syndrome);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUL	1950	68 Years	Male	82.00 kg	25	FEB	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

intestinal occlusion [Intestinal obstruction]
respiratory distress [Respiratory distress]
ANEMIA [Anaemia]
rectal bleeding [Rectal haemorrhage]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) HYDREA (HYDROXYCARBAMIDE)
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, 1x/day	#1) Unknown
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) Unknown

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 30-JAN-2019 / 15-FEB-2019	#1) 17 days
#2) Unknown	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LACOSAMIDE (LACOSAMIDE) ; Ongoing
#2) RAMIPRIL (RAMIPRIL) ; Ongoing
#3) BISOPROLOL (BISOPROLOL) ; Ongoing
#4) PLAVIX (CLOPIDOGREL BISULFATE) ; Unknown

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History	Chronic renal failure (Chronic kidney disease)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019141363

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
31-JUL-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.
A 68-year-old male patient received bosutinib (BOSULIF), first regimen from 30Jan2019 to 15Feb2019 at 200 mg 1x/day, second regimen from 16Feb2019 to 2019 at 300 mg 1x/day and third regimen from 2019 to 17Sep2019 at 400 mg 1x/day, oral for chronic myeloid leukaemia; hydroxycarbamide (HYDREA), (Batch/Lot number: unknown). The patient's relevant medical history included: "arterial hypertension" (ongoing); "chronic renal failure" (ongoing); "epilepsy" (ongoing); "lower limbs arthropathy" (ongoing), notes: Lower limbs. Concomitant medication(s) included: LACOSAMIDE oral taken for epilepsy (ongoing); RAMIPRIL oral taken for hypertension (ongoing); BISOPROLOL oral taken for cardiac failure (ongoing); PLAVIX taken for arterial occlusive disease. On 01Mar2019, the subject experienced anemia (assessed Grade 3). The subject experienced rectal bleeding on 25Feb2019, reported as non-serious and rated grade 1. The subject experienced respiratory distress on 20Mar2019, reported as serious and rated grade 4. The subject experienced intestinal occlusion on 20Mar2019, reported as serious (hospitalization) and rated grade 3. No action was taken with bosutinib for events rectal bleeding, respiratory distress and intestinal occlusion. The action taken in response to the event anemia was reported as dose not changed for the study drug BOSULIF. On 30Jul2019, the subject experienced lack of effect of bosutinib which was considered as non-serious and rated as grade 2. The last action taken in response to the events for bosutinib was permanently withdrawn on 17Sep2019. The action taken in response to the events for hydroxycarbamide was unknown. The subject recovered from anemia on 21Mar2019. The event rectal bleeding resolved on 25Feb2019. The event respiratory distress resolved on 23Apr2019. The event intestinal occlusion resolved on 29Mar2019.

According to the investigator, the event intestinal occlusion was related to bosutinib and unrelated to concomitant drugs.
According to the investigator, the event respiratory distress and rectal bleeding was unrelated to bosutinib and to concomitant drugs.
According to the investigator, the event anemia was unrelated to the study drug bosutinib, but related to concomitant drug hydroxycarbamide.
According to the investigator, the lack of effect was considered as related to study drug but not related to concomitant medication.

Follow-up attempts completed. No further information expected.

Follow-up (24Sep2019 and 25Sep2019): New information received from the study site included: clinical course; dosage regimens and action taken of bosutinib.

Follow-up (22Jan2020): New information received includes an updated clinical course (the subject had lack of efficacy with ponatinib and palpitations).

Follow-up (25May2020): New information received from the investigator via contract research organization (CRO)includes: The previously reported events of lack of efficacy with ponatinib and palpitations have been deleted.

Follow-up (12Jan2021): New information received inlcuded: dosage regimens of bosutinib; event leukocytosis of 30Jan2019 was deleted; new events (rectal bleeding); onset date of respiratory distress updated; event "occlusion" updated to "intestinal occlusion".

Follow-up (31Jul2023): This is a follow-up report from the investigator via CRO. New information received included: dosage regimens and action taken of bosutinib to the event anemia.

No Follow-up attempts are needed. No further information is expected.

Case Comment: Intestinal obstruction is unlisted i the RSI of suspect drug bosutinib and unrelated per company assessment.

In concurrence with the reporting investigator, the Company attributes the reported anemia, with the respiratory distress associated to the anemia, to the patient's underlying chronic myeloid leukemia, therefore unrelated to bosutinib. Similarly, the company also deems there is not a reasonable possibility that rectal bleeding and intestinal obstruction are related to bosutinib, being considered self-supporting intercurrent conditions in the setting of the underlying clinical picture characterized by progressive chronic myeloid leukemia and medical history of arterial hypertension, chronic renal failure, epilepsy and lower limbs arthropathy, all ongoing. Also important to note that GI bleeding is reported in the safety profile of concomitant clopidogrel.

The impacts of this report on the benefit/risk profile of the Pfizer product is evaluated as part of Pfizer procedures for safety evaluation, including the review and analysis of aggregate data for adverse events. Any safety concern identified as part of this review, as well as any appropriate action in response, will be promptly notified to Regulatory Authorities, Ethics Committees and Investigators, as appropriate.

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet;	300 mg, 1x/day; Unknown	Chronic myeloid leukemia	16-FEB-2019 / 2019;

Mfr. Control Number: 2019141363

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
Regimen #2		(Chronic myeloid leukaemia)	Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, 1x/day; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	2019 / 17-SEP-2019; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Epilepsy (Epilepsy);
Unknown to Ongoing	Relevant Med History Lower limbs	Arthropathy (Arthropathy);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1976	42 Years	Male	50.00 kg		FEB	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

diarrhea [Diarrhoea]
Intermittent arthritic pain [Arthralgia]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 07-JAN-2019 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) BACLOFEN (BACLOFEN) ; Ongoing
#2) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNESIUM) ; Ongoing
#3) ARCOXIA (ETORICOXIB) ; Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1976 to Ongoing	Relevant Med History	Cerebral atrophy (Cerebral atrophy)
Unknown	Relevant Med History due to the immobility	Constipation (Constipation)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
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Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019170804

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
07-NOV-2022

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 42-year-old male subject started to receive bosutinib (BOSULIF; Film-coated tablet) via an unspecified route, at 400 mg daily from 07Jan2019 for unspecified indication. Medical history included diffuse cerebral atrophy, ongoing since 1976 and constipation due to the immobility. Concomitant medication included ongoing BACLOFEN for atrophy, as muscle relaxant, ongoing esomeprazole magnesium (INEXIUM) for gastroesophageal reflux, and ongoing etoricoxib (ARCOXIA) as anti-inflammatory. The patient experienced diarrhea, grade 2, in Feb2019. On 10Apr2019, the subject developed intermittent arthritic pain, rated grade 2 and not serious. It seems that the subject presented with muscular pain, it was complicated to evaluate the pain. The subject was systematically treated by paracetamol, codeine (EFFERALGAN CODEINE). No action was taken with bosutinib or baclofen in response to the reported events. Diarrhea was resolved on 08Nov2019. Intermittent arthritic pain was not recovered.

The investigator considered the events diarrhea and intermittent arthritic pain as related to bosutinib and not related concomitant medications.

Follow-up (27Aug2019): New information reported from the site includes: details on the medical history cerebral atrophy, bosutinib dose, frequency and start date, indication for use of concomitant Baclofen, additional event 'Suspect diffuse pain', event treatment, BACLOFEN selected as co-suspect drug for the event 'Suspect diffuse pain'.

Follow-up (14Nov2019): New information reported from the site includes: investigator initial aware date, event verbatim 'Suspected diffuse pain' updated to 'Muscle pains', outcome of the events diarrhea and muscular pain updated from recovering to recovered, events stop date provided, investigator' s causality assessment of the event muscle pains updated to unrelated to concomitant drugs, baclofen no more considered a co-suspect product.

Follow-up (03Feb2021). New information received from the CRO included: Muscle pain was not recovered.

Follow-up(25Oct2022): This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter (Physician) for protocol B1871047. Updated information: event "muscle pains" changed to "intermittent arthritic pain".

Follow-up (07Nov2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter (Physician) for protocol B1871047
Updated information included: updated stop date for event diarrhea (from 10Jul2019 to 08Nov2019).

Case Comment: Considering the plausible drug-event temporal association and the consistency of the events with the known safety profile of the suspect product, a reasonable possibility that diarrhea and intermittent arthritic pain are related to bosutinib administration cannot be excluded

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Immobile (Immobile);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1947	71 Years	Male	87.00 kg	08	MAR	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Pain in legs [Pain in extremity]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 19-OCT-2018 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetes (Diabetes mellitus)
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
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Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019172357

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
28-OCT-2021

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2019172357

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a Non-Interventional Study report with non-serious events only.
A 71-year-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 19Oct2018 and ongoing at 400 mg, daily for an unspecified indication. Medical history included ongoing diabetes mellitus, ongoing arterial hypertension, ongoing diarrhoea, and ongoing creatinine increased grade 1. The subject's concomitant medications were not reported. The subject experienced pain in legs on 08Mar2019. The event was rated grade 1. The action taken in response to the events for bosutinib was dose not changed. Outcome of the event was recovered on 28Jun2019.

According to the investigator, the event was unrelated to the introduction of bosutinib (BOSULIF) and to concomitant drugs.

Follow-up (07Sep2020): New information received includes reaction data (event "pain in legs and scapular girdle" updated to "pain in legs").

Follow-up (28Oct2021): This is a follow up Non-Interventional Study report for protocol B1871047. Updated information included: Patient' initials updated to PRIVACY, outcome of event updated to "recovered on 28Jun2019".

Case Comment: Limited information was provided. Pending further details, at this moment, in agreement with the reporting investigator, the Company considers the reported pain in legs and scapular girdle are unlikely related to the study drug, bosutinib. The follow-up information removes the event pain in scapular girdle and does not alter the previous company clinical evaluation for the remaining event Pain in extremity.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Blood creatinine	increased grade 1	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diarrhea (Diarrhoea);
Unknown to Ongoing	Relevant Med History	Creatinine increased (Blood creatinine increased);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JAN	1960	58 Years	Male	Unk		OCT	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

DIARRHEA [Diarrhoea]
abdominal pain [Abdominal pain]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

15. DAILY DOSE(S)
#1) 400 mg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) Unknown

18. THERAPY DATES(from/to)
#1) 01-OCT-2018 / Ongoing

19. THERAPY DURATION
#1) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	none ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
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Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019180732

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
22-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 58-year-old male patient received bosutinib (BOSULIF), since 01Oct2018 (ongoing) at 400 mg daily. The subject had no relevant medical history and did not receive any concomitant medications. In Oct2018 the first days of treatment were associated with some diarrhea and abdominal pain. The events were rated grade 1 (non-serious) and resolved on 24Oct2018. No dose change was required in response to the events, bosutinib was ongoing at the time of report.

According to the reporter, the events were related to bosutinib.

Follow-up (28Aug2019): New information received from the CRO includes an update about relevant medical history and concomitant medications.

Follow-up (14Nov2019): New information received from the CRO includes updated onset date and recovery date of both events.

Follow-up (05Nov2021): New information received from the study site via CRO includes updated recovery date of both events diarrhea and abdominal pain from 31Oct2018 to 24Oct2018.

Follow-up (03Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: Investigator Initial Aware Date added.

Follow-up (22Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.
Updated information: dosage information of Bosutinib.

No Follow-up attempts are needed. No further information is expected.

Case Comment: Based on the known drug safety profile and temporal relationship, the causal association between the events, diarrhea and abdominal pain, and bosutinib administration cannot be excluded.The follow-up information received does not alter the previous company clinical evaluation.

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUL	1986	32 Years	Male	96.00 kg		NOV	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Diarrhea grade1/ Diarrhea grade 2 [Diarrhoea]
Fatigue [Fatigue]
Rhinitis [Rhinitis]
Gastroenteritis [Gastroenteritis]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, daily	#1) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 12-NOV-2018 / 26-DEC-2018	#1) 45 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Penicillin allergy (Drug hypersensitivity)
Unknown	Relevant Med History	Appendicitis (Appendicitis)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
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26. REMARKS

24b. MFR CONTROL NO.
2019185456

24c. DATE RECEIVED BY MANUFACTURER
27-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from contactable reporter(s) (Physician and Other HCP) from product quality group for protocol B1871047.

A 32-year-old male patient received bosutinib (BOSULIF), first regimen from 12Nov2018 to 26Dec2018 at 200 mg daily, oral, second regimen from 27Dec2018 to 14Jan2019 at 300 mg daily, oral, third regimen from 15Jan2019 to 23Jan2019 at 400 mg daily, oral, fourth regimen from 05Feb2019 to 20Mar2019 at 400 mg daily, oral and fifth regimen since 21Mar2019 (ongoing) at 500 mg daily for chronic myeloid leukaemia. The patient's relevant medical history included: "Penicillin Allergy" (unspecified if ongoing); "Appendicitis" (unspecified if ongoing); "non-significant hepatic cytolysis" (ongoing), notes: grade 1. PS 0; "Chronic myeloid leukemia" (ongoing). There were no concomitant medications.On 12Nov2018 AST was 43 and ALT was 67. PS 0. There was no hepatosplenomegaly. Cytolysis remained grade 1 until the discontinuation of bosutinib. There were no concomitant medications. The subject experienced one or two episodes of diarrhea grade 1, on an unspecified date in Nov2018, at the beginning of treatment with bosutinib. At that time bosutinib daily dose was at 200 mg daily. The subject occasionally received loperamide (trade name unspecified) as corrective treatment. Despite the event, bosutinib was pursued and the dosing regimen was increased according to protocol. On 22Jan2019, the subject started to experience gastroenteritis and diarrhea grade 2. As a result of these events, bosutinib was not administered on 23Jan2019 and 24Jan2019. Bosutinib was temporarily withdrawn on 23Jan2019. Treatment received for diarrhea included loperamide. The subject underwent lab tests which included: ASAT (N 0-34): 49 on 29Jul2019, 40 on 02Sep2019, 55 on 15Oct2019 and 44 on 25Nov2019, ALAT (N 10-49): 77 on 29Jul2019, 80 on 02Sep2019, 88 on 15Oct2019, 62 on 25Nov2019. The subject experienced rhinitis, rated grade 2 and not serious in Aug2019 (on the week prior to 02Sep2019). No dose change was done with bosutinib in response to the event. The subject received paracetamol. The subject experienced fatigue on 25Nov2019, grade 1 and non-serious. In the consultation record of 25Nov2019, it was reported that the subject "felt a little more tired, including in the morning. Nevertheless, he had a good sleep and good appetite". No action was taken with bosutinib in response to the event fatigue. The subject experienced loss of major molecular response on 02Mar2020, not considered as a lack of efficacy of the study drug, he was a poor responder. In response to the event, bosutinib was permanently withdrawn on 29Mar2020 and switched to dasatinib monohydrate on 30Mar2020. BCR/ABL transcript was 0.024 % on 25Nov2019, 0.24% on 02Mar2020 (loss of major molecular response), 0.56% on 31Mar2020 (confirmation of loss of major molecular response). Myelogram on 12Mar2020 revealed chronic phase. The outcome of the event gastroenteritis was resolved on 24Jan2019. The outcome of the event diarrhea grade 1/ diarrhea grade 2 was resolved on 03Mar2020. The outcome of the event rhinitis was resolved on 02Sep2019. The outcome of the event fatigue was resolved on 02Mar2020.

The investigator considered the grade 1 diarrhea was related to study drug bosutinib but there was not a reasonable possibility that the remaining events were related to bosutinib or to concomitant treatment.

Follow-up (14May2019): New information received from the clinical research associate (CRA) includes: indication and dosage of bosutinib, medical history.

Follow-up (12Sep2019): New information received includes updated details about therapy dates and doses of bosutinib and new event (rhinitis).

Follow-up (17Jan2020): New reported information received from the CRO included updated event verbatim from "Pharyngitis in a context of fever" to "viral like fever".

Follow-up (28Feb2020): New information received from the investigator via CRO included: reaction data (added new events fatigue and hepatic cytolysis), lab data and clinical course details.

Follow-up (06Mar2020): New information received from the investigational site includes: baseline ASAT and ALAT values provided. Investigator's causality for hepatic cytolisis updated from related to unrelated.

Follow-up (19Mar2020): New information received from the investigational site includes: Baseline ASAT and ALAT were performed on 12Nov2018 (previously reported 15Nov2018).

Follow-up (05May2020): New information received from CRO includes information on drug ineffective with lab tests and change of therapy.

Follow-up (26May2020 and 27May2020): New information received from clinical team includes clarification that loss of major molecular response was not considered as a lack of efficacy of the study drug.

Follow-up (29Oct2020): New information reported includes 'hepatic cytolysis' removed as event and details on medical history provided.

Follow-up (02Mar2021): New information received from CRO includes the event fatigue resolved on 02Mar2020. The event diarrhea grade 1 resolved on 03Mar2020 - the investigator assessed this event as related to study drug bosutinib.

Follow-up (02Mar2021): New information received from CRO includes: "viral like fever" was changed to "gastroenteritis with diarrhea, fever and vomiting" rated grade 2, occurred from 22Jan2019 and recovered on 24Jan2019. No action was taken for the study drug in response to the event. The investigator considered that the events gastroenteritis with diarrhea, fever and vomiting was unrelated to

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

study drug or to any concomitant drug.

Follow-up (20Sep2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from CRO. Updated information includes: reaction data (event verbatim updated to "Gastroenteritis" from "gastroenteritis with diarrhea, fever and vomiting").

Follow-up (27Sep2023): This is a non-interventional study follow up report from the investigational site via the CRO. Updated information includes:Relevant medical history includes ongoing chronic myeloid leukemia.

Case Comment: Based on the information currently available, a possible contributory role of bosutinib to the reported diarrhea cannot be completely excluded based on temporal association and known drug safety profile. The reported fatigue is considered associated the patient's pre-existing medical condition, unrelated to bosutinib. Events rhinitis, gastroenteritis is most likely intercurrent medical condition and unrelated to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Alanine aminotransferase	67 IU/l	49
2	12-NOV-2018	Alanine aminotransferase	67	49 10
3	29-JUL-2019	Alanine aminotransferase	77	49 10
4	02-SEP-2019	Alanine aminotransferase	80	49 10
5	15-OCT-2019	Alanine aminotransferase	88	49 10
6	25-NOV-2019	Alanine aminotransferase	62	49 10
7		Aspartate aminotransferase	43 IU/l	34
8	12-NOV-2018	Aspartate aminotransferase	43	34 0
9	29-JUL-2019	Aspartate aminotransferase	49	34 0
10	02-SEP-2019	Aspartate aminotransferase	40	34 0
11	15-OCT-2019	Aspartate aminotransferase	55	34 0
12	25-NOV-2019	Aspartate aminotransferase	44	34 0
13	25-NOV-2019	Cytogenetic analysis	0.024 %	
14	02-MAR-2020	Cytogenetic analysis loss of major molecular response	0.24 %	
15	31-MAR-2020	Cytogenetic analysis confirmation of loss of major molecular response	0.56 %	
16	12-MAR-2020	Spinal myelogram complete cytogenetic response	chronic phase	

Mfr. Control Number: 2019185456

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	300 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	27-DEC-2018 / 14-JAN-2019; 19 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	15-JAN-2019 / 23-JAN-2019; 9 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	05-FEB-2019 / 20-MAR-2019; 44 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	500 mg, daily; Unknown	Chronic myeloid leukemia (Chronic myeloid leukaemia)	21-MAR-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hepatic cytolysis (Hepatic cytolysis); grade 1. PS 0
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		MAY	1973	45 Years	Female	59.50 kg		FEB	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Abdominal pain [Abdominal pain]
Eosinophilia edemato-congestive colitis [Eosinophilic colitis]
Diarrhea grade 1 [Diarrhoea]
Asthenia [Asthenia]
digestive disorders [Functional gastrointestinal disorder]
Palpitations [Palpitations]
vagal malaise [Presyncope]
Cystitis [Cystitis]
Painful ankilosys at elbow level with morning rustling [Joint ankylosis] **(Continued on Additional Information Page)**

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) METRONIDAZOLE (METRONIDAZOLE) Tablet **(Continued on Additional Information Page)**

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 100 mg, daily	#1) Oral
#2) UNK	#2) Oral

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) vaginal burning with suspicion of infection **(Continued on Additional Information Page)**

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 04-FEB-2019 / 21-FEB-2019	#1) 18 days
#2) FEB-2020 / FEB-2020	#2) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Dolichocolon (Dolichocolon)
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019185788

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

chest pain [Chest pain]
vaginal burning with suspicion of infection [Vulvovaginal burning sensation]
vaginal burning with suspicion of infection [Vaginal infection]
epigastric pain [Abdominal pain upper]
urinary disorders (pollakiuria and lower back pain) [Pollakiuria]
urinary disorders (pollakiuria and lower back pain) [Back pain]
iron deficiency [Iron deficiency]
Diarrhea grade 2 [Diarrhoea]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 45-year-old female subject (sbj) (unknown if pregnant) received bosutinib (BOSULIF), first regimen from 04Feb2019 to 21Feb2019 at 100 mg daily, second regimen from 22Feb2019 to 04Jun2019 at 200 mg daily, third regimen from 05Jun2019 to 03Jul2019 at 300 mg daily, fourth regimen from 29Nov2019 to 02Jan2020 at 400 mg daily, fifth regimen from 03Jan2020 to 23Feb2020 at 300 mg daily, sixth regimen from 24Feb2020 to 12Mar2020 at 400 mg daily, seventh regimen from 13Mar2020 to 18Mar2020 at 500 mg daily, eighth regimen from 19Mar2020 to Mar2020 at 400 mg daily, ninth regimen from Mar2020 to 18Feb2022 at 500 mg daily and tenth regimen since 28Feb2022 (ongoing) at 400 mg daily, all oral for chronic myeloid leukaemia. The sbj also received concomitant suspect medication metronidazole (METRONIDAZOLE), from Feb2020 (Batch/Lot number: unknown) to Feb2020, oral for vulvovaginal burning sensation, vaginal infection; ferrous sulfate (TARDYFERON), (Batch/Lot number: unknown); nefopam hydrochloride (ACUPAN), (ongoing) (Batch/Lot number: unknown). The sbj's relevant medical history included: 'Dolichocolon' (unspecified if ongoing); 'chronic myeloid leukemia' (ongoing). The sbj's concomitant medications were not reported. The following information was reported: DIARRHOEA (non-serious) with onset Feb2019, outcome 'recovered' (18Nov2019), described as 'Diarrhea grade 1'; POLLAKIURIA (non-serious), BACK PAIN (non-serious) all with onset Feb2019, outcome 'recovered' (May2019) and all described as 'urinary disorders (pollakiuria and lower back pain)'; CYSTITIS (non-serious) with onset 01May2019, outcome 'recovered' (06Jun2019); ASTHENIA (non-serious) with onset 05Jun2019, outcome 'recovered' (15Jun2019); ABDOMINAL PAIN (medically significant) with onset 29Jun2019, outcome 'recovered' (04Jul2019); PRESYNCOPE (non-serious) with onset 03Jul2019, outcome 'recovered' (03Jul2019), described as 'vagal malaise'; JOINT ANKYLOSIS (non-serious) with onset Jul2019, outcome 'recovered' (25Nov2019), described as 'Painful ankilosys at elbow level with morning rustling'; CHEST PAIN (non-serious) with onset Dec2019, outcome 'recovered' (09Mar2020); IRON DEFICIENCY (non-serious) with onset Dec2019, outcome 'recovering'; FUNCTIONAL GASTROINTESTINAL DISORDER (non-serious) with onset 10Feb2020, outcome 'recovered' (17Feb2020), described as 'digestive disorders'; ABDOMINAL PAIN UPPER (non-serious) with onset Feb2020, outcome 'recovered' (Feb2020), described as 'epigastric pain'; VULVOVAGINAL BURNING SENSATION (non-serious), VAGINAL INFECTION (non-serious) all with onset Feb2020, outcome 'recovered' (09Mar2020) and all described as 'vaginal burning with suspicion of infection'; DIARRHOEA (non-serious) with onset 13Mar2020, outcome 'not recovered', described as 'Diarrhea grade 2'; PALPITATIONS (non-serious) with onset 13Mar2020, outcome 'recovered' (18May2020); EOSINOPHILIC COLITIS (non-serious) with onset 27Aug2020, outcome 'recovered' (2021), described as 'Eosinophilia edemato-congestive colitis'.
Clinical course: The sbj experienced non-serious event diarrhea grade 1 in Feb2019, presented with cystitis on 01May2019, grade 2,non-serious. On 06May2019 it was noted 'since 01May2019 clinical picture of cystitis initially treated by D-mannose which allowed a quick relief of vesical symptoms'. She finally took a bag of fosfomycin (MONURIL) on 05May2019 and did not feel completely relieved: pollakiuria remained as well as a few slight burns and especially lumbar pain. On 05Jun2019, the sbj experienced asthenia grade 1, non-serious. The sbj described a notable asthenia through the 10 days following the increase of dosage, that diminished then. On 29Jun2019, the sbj presented with abdominal pain, medically significant condition, grade 3. There was appearance of mucus diarrhea on 29Jun2019 with spasmodic abdominal pain. Absence of rectal bleeding, absence of nausea or vomiting. Progressive onset of diarrhea and pain. On 03Jul2019, diffuse abdominal pain evolving since the morning, predominant on the left flank. Intense diarrhea on this day with several dozen watery stools. No sign of functional urinary tract. He saw a generalist practitioner who prescribed imagery. She came to the emergency room following worsening of pain. On 03Jul2019, at 04:47 pm, the sbj was admitted to the emergency room and was discharged on 04Jul2019 at 05:24 am. Abdomen and pelvis CT scan did not find any anomaly. On 06Jul2019, stool analysis was negative for clostridium difficile, pathogens and parasites. Due to abdominal pain, bosutinib discontinued on 03Jul2019. Consultation on 29Jul2019: abdominal pain resolved, no tolerance problem, no diarrhea, no abdominal pain. She received in the emergency room phloroglucinol/trimethylphloroglucinol (SPASFON) 40 mg once, oxycodone hydrochloride (OXYNORM) 5 mg once oral and nefopam hydrochloride (ACUPAN) once. In Jul2019, the sbj experienced painful ankilosys at elbow level with morning rustling, grade 1, non-serious. Since some time, she had a sensation of painful ankilosys at elbow level with morning rustling at night. There were no signs of local inflammation, no discomfort in other joints. The reason for increase dose of the study drug was a progressive increase until the correct dosage. The sbj presented with chest pain (grade 2) since the end of Dec2019 motivating a consultation and an electrocardiogram that returned normal result. Troponin dosage was also performed and was normal. Symptomatology improved after two sessions of osteopathy. In Feb2020, the sbj also presented with vaginal burning with suspicion of infection (grade 2) leading to the prescription fifteen days ago (reported on 09Mar2020) of an antibiotic treatment with metronidazole (unspecified trade name) tablet and sertaconazole nitrate (MONAZOL, ovule). Following introduction of antibiotic therapy, the sbj developed epigastric pain probably related to metronidazole. The sbj developed epigastric pain reported as non-serious and grade 1 in Feb2020. Cystitis was reported as a recurrent event in this sbj that recovered on

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

06Jun2019. No action was taken with bosutinib in response to 'painful ankilosys at elbow level with morning rustling' and vaginal burning with suspicion of infection. Due to chest pain, bosutinib dose was reduced. On 27Aug2020, the sbj experienced an eosinophilia edemato-congestive colitis, non-serious, grade 2, description of this event: Abdominal pain of the right flank irradiating the right lumbar fossa for 4/5 days. Abdominal scan on 31Aug2020: without significant abnormality. The sbj went to emergency on 31Aug2020 from 3:43 pm to 8:19 pm. She received morphin 3 mg intravenously. Pain at 3/10 at the discharge from the emergency. The sbj refused other morphine. At the sbj's discharge, the physician wrote: non-specific abdominal pain, iatrogenic functional colopathy post treatment. The sbj came back home with symptomatic treatment and monitoring of the evolution. For information: the sbj saw her general practitioner a few times ago for the same reason. She is waiting for an abdominal ultrasound (had an appointment tomorrow) on 22Dec2020: gastroscopy without obvious abnormality. On 15Mar2021: coloscopy without abnormality of the colon mucous and colic rectum biopsies finding discrete images of congestive edemato colitis which could correspond to an allergic mechanism. Vagal malaise following Acupan was noted in the emergency report. In response to vagal malaise, no action was taken with nefopam hydrochloride (ACUPAN). Further information: Abdominal pain on right and left side was replaced with Eosinophilia edemato-congestive colitis. Diagnosis on the report of coloscopy performed on 15Mar2021. On 13Mar2020, the sbj had grade 2 diarrhea, not serious, did not resolve. On 13Mar2020, the sbj had grade 1 palpitations, not serious, resolved on 18May2020. Due to both events, bosutinib dose was reduced. The investigator assessed event diarrhea and palpitations as related to bosutinib and unrelated to concomitant drug. In report of 18May2020, it was suggested to increase the dose of bosutinib from 400 to 500 mg in one daily intake. Very quickly, within few days, the sbj felt palpitations with sensation of cardiac arrhythmia in the context of hypotension (consultation with prescribing physician, normal ECG at examination). Posology of bosutinib was then reduced to 400 mg daily from 19Mar2020 and the sensation of palpitations has regressed (in the meantime, the sbj had taken magnesium). The increase of posology to 500 mg/day was possible since end of Mar2020 without tolerance problem. The treatment is taken in the evening. The sbj experienced urinary disorders (pollakiuria and lower back pain) from Feb2019 to May2019; vagal discomfort 03Jul2019 to 03Jul2019; digestive disorders from 10Feb2020 to 17Feb2020 due to ferrous sulfate; epigastric pain on 30Nov2020 and iron deficiency in Dec2019 with unknown result. The event digestive disorder was grade 1, urinary disorders was grade 2, event iron deficiency was grade 2. On 01Jun2022, it was reported that the sbj went to emergency care unit for abdominal pain on right and left side. The sbj experienced flank pain on unknown date (not considered clinically significant by site staff). Event diarrhea (grade 2, onset 13Mar2020) recurred upon resumption of bosutinib (action taken was dose reduced for this event). No action was taken on bosutinib due to the events epigastric pain (Feb2020), gastrointestinal disorders (10Feb2020) and due to chest pain. After resumption of bosutinib, the event abdominal pain (29Jun2019) re-occurred (rechallenge was positive). Metronidazole dose was not changed regarding the event epigastric pain (Feb2020). As of 30Aug2023, it was reported lower back pain was related to urinary disorder. The sbj underwent the following laboratory tests and procedures: Biopsy colon: (15Mar2021) discreet images of oedematous congestive colitis, notes: that may correspond to an allergic mechanism; Colonoscopy: (15Mar2021) no anomaly of the colon and rectum mucosa; Computerised tomogram abdomen: (03Jul2019) No anomaly; (31Aug2020) normal, without a significant anomaly; Computerised tomogram pelvis: (03Jul2019) No anomaly; Electrocardiogram: (unspecified date) normal; (Mar2020) normal; Endoscopy upper gastrointestinal tract: (22Dec2020) No obvious anomaly; Stool analysis: (06Jul2019) negative; (06Jul2019) negative; (06Jul2019) negative; Troponin: (unspecified date) normal. The last action taken for bosutinib was dosage reduced; for metronidazole and nefopam hydrochloride was dosage not changed, for ferrous sulfate was dosage permanently withdrawn. Ferrous sulfate was withdrawn due to digestive disorders, it was reported that she also had a prescription of TARDYFERON which she only took for about a week due to digestive problems. Therapeutic measures were taken as a result of abdominal pain, eosinophilic colitis, cystitis, diarrhoea, palpitations, chest pain, vulvovaginal burning sensation, vaginal infection.

The reporter considered 'abdominal pain', 'eosinophilia edemato-congestive colitis', 'diarrhea grade 1', 'asthenia', 'palpitations' and 'diarrhea grade 2' related to bosutinib. The reporter considered 'digestive disorders', 'vagal malaise', 'cystitis', 'painful ankilosys at elbow level with morning rustling', 'chest pain', 'vaginal burning with suspicion of infection', 'epigastric pain', 'urinary disorders (pollakiuria and lower back pain)' and 'iron deficiency' not related to bosutinib.

The investigator considered the events abdominal pain, diarrhea grade 1 and grade 2, asthenia, cystitis, painful ankilosys at elbow level with morning rustling, palpitations, eosinophilia edemato-congestive colitis, vaginal burning with suspicion of infection, chest pain were unrelated to any concomitant drug. The events urinary disorders (pollakiuria and lower back pain), and iron deficiency was reported unrelated to concomitant drug. The event epigastric pain was related to concomitant drug metronidazole. The investigator assessed event digestive disorder, grade 1, was related to ferrous sulfate. The investigator assessed event vagal malaise, grade 1, related to concomitant drug nefopam hydrochloride. The site reported 'vagal malaise following ACUPAN as per emergency report'.

FU (22May2019): New information received includes: new event (cystitis) added.

FU (04Jul2019 and 05Jul2019): New information received includes new event enteritis and clinical course.

FU (12Aug2019): New information received via CRO includes: reaction data (new events asthenia, painful ankilosys at elbow level with morning rustling) and clinical course.

FU (10Sep2019): New information received clarified the reason for increase dose of the study drug and confirmed no action taken as the result of the event painful ankylosis at elbow level with morning rustling.

FU (28Oct2019): New information received includes: action taken for bosutinib updated to permanently withdrawn.

FU (31Oct2019): New information received includes event ('possible enteritis' was changed to 'abdominal pain') with outcome (resolved on 04Jul2019).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

FU (17Jan2020): New information received included: causaity for event 'painful ankilosys at elbow level with morning rustling'.

FU (09Mar2020): New information received via the CRO included: route of administration, indication, dosage regimen of bosutinib, outcome of event, new events (chest pain, vaginal burning with suspicion of infection), action taken, clinical course, lab data, causality assessment, event (cystitis) recurred.

FU (23Mar2020 and 23Mar2020): New information reported includes: product data (updated administration dates for bosutinib), additional suspect product (metronidazole), lab data, concomitant medication data, reaction data (updated onset date for event abdominal pain (form 03Jul2019 to 29Jun2019) and added non-serious event epigastric pain), and causality assessment for abdominal pain (unrelated).

FU (14Aug2020): New information received via the CRO included: medical history (none), stop date of the event 'cystitis' updated, and investigator's causality for the event 'abdominal pain' (onset 29Jun2019) updated from unrelated to related.

Amendment: This FU report is being submitted to amend previously reported information: product - event details updated.

FU (22Sep2020): New information received includes: suspect drug details (additional therapy date and dosing regimen; action taken updated) and reaction data (new event 'abdominal pain on right and left side'; stop date of event cystitis).

FU (29Oct2020): New information reported includes: resolution date of the event cystitis updated from 06Jun2019 to 2019 and date of treatment with fosfomycin updated from 04May2019 to 05May2019.

FU (17Feb2021): New information received includes: updated outcome for the events 'Painful ankilosys at elbow level with morning rustling', 'abdominal pain on right and left side (27Aug2020)', action taken and new event 'Palpitations.'

FUs (19Feb2021 and 24Feb2021): New information received from the CRO and the clinical team includes: updated the outcome of event diarrhea, additional concomitant suspect drug, and new events (pollakiuria, lower back pain, vagal discomfort, digestive disorders, epigastric pain (30Nov2019) and iron deficiency).

FU (02Mar2021): New information includes: updated therapy dates of bosutinib, updated recovery date of cystitis, specification of action taken in response to chest pain (dose reduced).

FU (08Jun2021): New information received includes: medical history (dolichocolon), new event (sensitive abdomen), and lab data.
Amendment: This FU report is being submitted to amend previously reported information: causality as reported updated for back pain, iron deficiency, pollakiuria and presyncope.
FU (29Oct2021): New information received from CRO included: medical history, event sensitive abdomen deleted (corresponded to the abdominal pain on right and left side).

FU (02Dec2021): This is a FU report via the CRO. Update information: digestive disorder and urinary disorders severity, new suspect drug nefopam hydrochloride (ACUPAN), abdominal CT scan result, action taken for Ferrous sulfate, causality between event digestive disorder and ferrous sulfate, causality between event vagal malaise and nefopam hydrochloride.

FU (15Dec2021): This is a report for protocol B1871047.Updated information included: onset date of epigastric pain updated to 30Nov2020 (previously 30Nov2019) and martial deficiency added as medical history.

FU (01Jun2022): This is a FU report combining information from duplicate reports AER 202101834306 and AER 2019185788. The current and all subsequent FU information will be reported under manufacturer report number AER 2019185788. The new information received from investigator includes: adverse event abdominal pain on right and left side was assessed as serious since the sbj went to emergency care unit. Flank pain from AER 202101834306 added in this case.

Amendment: This FU report is being submitted to amend previously reported information: diarrhea grade 2 on 13Mar2020 should be reported as an event.

FU (12Jul2023): This is a FU report (Post Authorization Safety Study) for protocol B1871047.Updated information included: clinical details.

FU (26Jul2023): This is a FU report received via the CRO for protocol B1871047.Updated information: Sbj's weight update, event abdominal pain on right and left side from 27Aug2020 updated to eosinophilia edemato-congestive colitis and stop date updated and its clinical course updated, outcome of event iron deficiency updated from unknown to resolving, action taken with metronidazole regarding event epigastric pain added.

FU (28Jul2023): This is a FU report via the CRO for protocol B1871047. Updated information: medical history CML added, dose regimen of bosutinib.

FU (30Aug2023): This is a FU report from CRO following BOSEVAL reconciliation. New information included: clinical course.

FU (28Sep2023): This is a FU report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Updated information included: nine dosing regimen stop date updated (previous 17feb2022) and ten dosing regimen start date updated, abdominal pain details added (re-occurred after bosutinib resumption), chest pain detail and acupan details.

FU (12Oct2023): This is a follow up report from the clinical team. Updated information included: confirmed by the site, Epigastric pain from 30Nov2020 to Dec2020 was a symptom of Digestive disorders and Blood pressure decrease and Asthenia both from Mar2020 to Mar2020 were symptoms of event Palpitation (not considered as additional events).

FU (14Nov2023): This is a follow-up to a non-interventional study for protocol B1871047 received from the clinical team. Updated information following reconciliation includes: event "flank pain" deleted as not considered clinically significant by site staff, does not have to be reported. Medical history and event coding updated.

No follow-up attempt is needed. No further information is expected.

Case Comment: Based on compatible temporal association and/or known drug safety profile, the causal association between the events, diarrhea (both episodes), abdominal pain, Eosinophilic colitis, asthenia and bosutinib administration cannot be excluded. The events, Functional gastrointestinal disorder, palpitations, vagal malaise, cystitis, Painful ankylosis at elbow level with morning rustling, chest pain, vaginal burning with suspicion of infection, epigastric pain (both episodes), urinary disorders (pollakiuria and lower back pain) and iron deficiency are most likely intercurrent medical conditions and unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	15-MAR-2021	Biopsy colon that may correspond to an allergic mechanism	discreet images of oedematous congestive colitis	
2	15-MAR-2021	Colonoscopy	no anomaly of the colon and rectum mucosa	
3	03-JUL-2019	Computerised tomogram abdomen	No anomaly	
4	31-AUG-2020	Computerised tomogram abdomen	normal, without a significant anomaly	
5	03-JUL-2019	Computerised tomogram pelvis	No anomaly	
6		Electrocardiogram	normal	
7	MAR-2020	Electrocardiogram	normal	
8	22-DEC-2020	Endoscopy upper gastrointestinal tract	No obvious anomaly	
9	06-JUL-2019	Stool analysis Negative	negative	
10	06-JUL-2019	Stool analysis Negative	negative	
11	06-JUL-2019	Stool analysis Negative	negative	
12		Troponin	normal	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	200 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	22-FEB-2019 / 04-JUN-2019; 105 days

Mfr. Control Number: 2019185788

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	05-JUN-2019 / 03-JUL-2019; 29 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	29-NOV-2019 / 02-JAN-2020; 1 month 5 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	03-JAN-2020 / 23-FEB-2020; 1 month 21 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	24-FEB-2020 / 12-MAR-2020; 18 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	500 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	13-MAR-2020 / 18-MAR-2020; 6 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #8	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	19-MAR-2020 / MAR-2020; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #9	500 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	MAR-2020 / 18-FEB-2022; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #10	400 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	28-FEB-2022 / Ongoing; Unknown
#2) METRONIDAZOLE (METRONIDAZOLE) Tablet; Regimen #1	UNK; Oral	vaginal burning with suspicion of infection (Vulvovaginal burning sensation) vaginal burning with suspicion of infection (Vaginal infection)	FEB-2020 / FEB-2020; Unknown
#3) TARDYFERON (FERROUS SULFATE) ; Regimen #1	UNK; Unknown	Unknown	Unknown; Unknown
#4) ACUPAN (NEFOPAM HYDROCHLORIDE) ; Regimen #1	UNK; Unknown	Unknown	Ongoing; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		OCT	1969	48 Years	Female	57.00 kg	27	SEP	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

acute cholecystitis [Cholecystitis acute]
Bigeminy [Extrasystoles]
diarrhea [Diarrhoea]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☒ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) AUGMENTIN [AMOXICILLIN SODIUM;CLAVULANATE POTASSIUM] **(Continued on Additional Information Page)**

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 500 mg, 1x/day	#1) Oral
#2) 1000 mg, 3x/day	#2) Unknown

17. INDICATION(S) FOR USE
#1) CHRONIC MYELOID LEUKEMIA (Chronic myeloid leukaemia)
#2) Unknown

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 05-JUL-2017 / 06-NOV-2018	#1) 1 year 4 months 2 days
#2) OCT-2018 / NOV-2018	#2) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	None ()

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019195605

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-SEP-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2019195605

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047.

A 48-year-old female subject started to receive bosutinib (BOSULIF; film-coated tablet) at 500 mg once daily by oral route on 05Jul2017 to 06Nov2018, for chronic myeloid leukemia. Additional co-suspect included amoxicillin sodium / clavulanic acid (AUGMENTIN) received from Oct2018 to Nov2018 at 1000 mg thrice daily (3x/day). She had no relevant medical history. In Oct2018, the subject developed bigeminy rated grade 2. The investigator added as comment that the subject presented with dyspnea related to bigeminy but did not capture dyspnea as event. It was confirmed on 20Apr2020, that dyspnea was not considered as a supplemental adverse event but as a symptom of bigeminy. On 02Oct2018, abdominal ultrasound found vesicular lithiasis, and cholecystectomy was performed on 06Nov2018. Following cholecystectomy, the subject complained of pain at the level of the surgical scar. Following cholecystectomy reported pain on the scar operative date of awareness of 1 on 04Oct2018 and 2 21Dec2018. The SAEs were reported as acute cholecystitis, grade 3 (led to hospitalization or prolongation of hospitalization) on 27Sep2018, diarrhea rated grade 2 (assessed as non-serious) on 04Oct2018, and grade 2 bigeminy (assessed as non-serious) in Oct2018. Bosutinib was temporarily stopped from 06Nov2018 to 08Nov2018 in response to acute cholecystitis. Bosutinib was resumed on 09Nov2018, and acute cholecystitis did not recur. The action taken with Augment was dose not changed. No action was taken for bosutinib in response to the event Bigeminy. Treatment received for acute cholecystitis included cholecystectomy and amoxicillin sodium / clavulanic acid (AUGMENTIN). The subject recovered from acute cholecystitis on 06Nov2018 and from diarrhea in Nov2018. Bigeminy was resolved on 29Apr2019. As of 19Sep2023, bosutinib was ongoing.

The investigator considered the events bigeminy and acute cholecystitis as unrelated to bosutinib or to a concomitant medication; and diarrhea as unrelated to bosutinib and as related to the concomitant amoxicillin sodium / clavulanic acid.

Follow-up (20Apr2020): New information received from the investigator via the clinical team included: concomitant medication/treatment dates for Augmentin, confirmation that dyspnea is not an adverse event; treatment data (cholecystectomy on 06Nov2018), stop dates of bosutinib

Follow-up (28Oct2021): New information received from the investigator via CRO includes onset date of the event acute cholecystitis updated from 02Oct2018 to 27Sep2018.

Follow-ups (19Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site via CRO for protocol B1871047.
Updated information includes: updated patient initials, updated outcome of bigeminy, and clinical course.

Case Comment: In concurrence with the reporting investigator, the Company considers there is not a reasonable possibility that the reported acute cholecystitis associated with diarrhea, bigeminy, are related to the study drug, bosutinib. Events are more likely inter-current diseases. The mentioned "vesicular lithiasis" identified at ultrasound was likely the cause of acute cholecystitis.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02-OCT-2018	Ultrasound abdomen	vesicular lithiasis	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#2) AUGMENTIN [AMOXICILLIN SODIUM;CLAVULANATE POTASSIUM] (AMOXICILLIN SODIUM, CLAVULANATE POTASSIUM) ; Regimen #1	1000 mg, 3x/day; Unknown	Unknown	OCT-2018 / NOV-2018; Unknown

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		JUN	1947	71 Years	Female	Unk	23	APR	2019

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
AST increase [Aspartate aminotransferase increased]
ALT increase [Alanine aminotransferase increased]
meteorism [Flatulence]
Anorexia [Decreased appetite]
Nausea [Nausea]
Abdominal pain [Abdominal pain]

Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☒ YES ☐ NO ☐ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, daily	#1) Oral

17. INDICATION(S) FOR USE
#1) Chronic myeloid leukemia (Chronic myeloid leukaemia)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 18-MAR-2019 / Unknown	#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) METFORMIN (METFORMIN) ; Ongoing
#2) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#3) TENORMINE (ATENOLOL) ; Ongoing
#4) PRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE] (INDAPAMI
#5) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing
#6) OMEPRAZOLE (OMEPRAZOLE) ; Ongoing

(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History currently treated	Arterial hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History currently treated, all types	Diabetes (Diabetes mellitus)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019209248

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
16-MAY-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 71-year-old female subject started to receive bosutinib (BOSULIF) orally on 18Mar2019 to an unknown date, and then from 10Apr2019 to 30Apr2019 for chronic myeloid leukemia. The most recent dose before the event was administered at 400 mg daily on 30Apr2019.
Medical history included arterial hypertension ongoing (currently treated), diabetes all types ongoing (currently treated), herniated disc ongoing (not treated), vestibular neuritis ongoing (not treated), thyroidectomy (currently treated), right carpal canal surgery (not treated), varicose vein surgery (not treated), and gonarthrosis ongoing (not treated). The patient had no family history of hepatic disease. Before the diagnosis of chronic myeloid leukemia, the patient drink alcohol 5 times a week, 1 glass of wine daily. It was unknown if the alcohol consumption lasted for more than 1 year. Concomitant medications included metformin at 1000 (unit not provided) per day ongoing for diabetes, levothyroxin sodium (LEVOTHYROX) daily ongoing for thyroidectomy, atenolol (TENORMINE) 50 (unit not provided) per day ongoing for arterial hypertension, perindopril arginine/ indapamide (PRETERAX) unknown dose, daily ongoing for arterial hypertension, atorvastatin calcium (TAHOR) 10 (unit not provided) 1 day out of 3 ongoing for cardiovascular prophylaxis, and omeprazole (manufacturer unknown) daily ongoing for gastroesophageal reflux prophylaxis. The subject previously took dasatinib and experienced alopecia.
On 29Apr2019, the subject experienced aspartate aminotransferase (AST) increased. On 30Apr2019, the subject experienced alanine aminotransferase (ALT) increased. The event AST increase was rated grade 3, the event ALT increase was rated grade 4. Both events were reported as serious (important medically events). On 09Oct2018 (within the year before the treatment), AST was 15 IU/l (normal < 32) and ALT was 13 IU/l (normal < 32). At the beginning of the treatment, on 18Mar2019, AST was 24 IU/l and ALT was 7 IU/l. During the treatment, on 30Apr2019, ALT 425 IU/l (Grade 3) (normal range: 0-32) on 29Apr2019 and AST 697 IU/l (Grade 4) (normal range: 0-32). After the treatment, on 03Jun2019, AST was 24 IU/l (normal < 34) and ALT was 25 IU/l (normal < 34). Decision of the investigator to permanently withdraw bosutinib on the day of the consultation (30Apr2019). The subject also experienced anorexia (grade 1), nausea (grade 2), meteorism (grade 2) and abdominal pain (grade 1), assessed as non-serious, with onset date on 23Apr2019. The action taken with bosutinib for nausea, anorexia, meteorism, abdominal pain was dose not changed. The overall action taken with bosutinib was permanently withdrawn on 30Apr2019. The outcome of the events AST/ ALT increase was recovered on 03Jun2019. The outcome of nausea, meteorism, anorexia and abdominal pain was resolved on 13May2019.

The investigator commented: hepatic cytolysis.

The investigator considered events AST/ ALT increase, anorexia, gastrointestinal disorders (meteorism) and nausea were related to study drug bosutinib and unrelated to concomitant medications. The investigator considered the event abdominal pain was unrelated to the study drug bosutinib and unrelated to concomitant drugs.

Follow-up (22May2019 and 23May2019): New information received from the investigator and CRO includes: concomitant medications, medical history, past drug, updated dosage regimen of bosutinib, and new event (gastrointestinal disorders).

Follow-up (16Jul2019): New information received from the study site includes updated event (from gastrointestinal disorders to meteorism, anorexia and nausea, with not provided causality).

Follow-up (16Jul2019): New information received includes updated verbatim of events 'gastrointestinal disorders to meteorism, anorexia and nausea', provided causality.

Follow-up (11Sep2019): New information received from CRO includes: event verbatim, action taken and causality for event gastrointestinal disorders (meteorism).

Follow-up (16Sep2019): New information received from the study site includes: lab data, medical history details.

Follow-up (08Jan2020): New information received from CRO included confirmed the recovery date of aspartate aminotransferase increased and alanine aminotransferase increased (resolved on 03Jun2019).

Follow-up (28Jan2022): New information received from CRO included the verbatim of the event "gastrointestinal disorders (meteorism)" updated to "meteorism", new event (abdominal pain) added.

Follow-up (28Jul2022): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. Updated information includes: AST increased start date updated to 29Apr2019 as well as the date of lab data AST.

Follow-up (21Feb2023): This is a report from a Non-Interventional Study from the investigational site via the CRO.
Updated information: grade of Abdominal pain; outcome of Anorexia.

Follow-up (16May2023): This is a report from a Non-Interventional Study from the investigational site via the CRO. Updated information: event onset date.

Mfr. Control Number: 2019209248

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case Comment: Based on the plausible temporal association, considering the known safety profile of bosutinib, and lacking alternative explanations, the Company cannot completely exclude the possible causality between the reported ALT/AST increased and the administration of bosutinib. Similarly, the Company cannot completely rule out the possible causality between the reported events, meteorism, anorexia and nausea, and bosutinib administration.
Conversely, the assessment of the AE of abdominal pain is considered unrelated both by the reporter and the Company.
The follow up information does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	09-OCT-2018	Alanine aminotransferase	13 IU/l	32 0
2	18-MAR-2019	Alanine aminotransferase	7 IU/l	32 0
3	30-APR-2019	Alanine aminotransferase Grade 3	425 IU/l	32 0
4	03-JUN-2019	Alanine aminotransferase	25 IU/l	34
5	09-OCT-2018	Aspartate aminotransferase	15 IU/l	32 0
6	18-MAR-2019	Aspartate aminotransferase	24 IU/l	32 0
7	29-APR-2019	Aspartate aminotransferase Grade 4	697 IU/l	32 0
8	03-JUN-2019	Aspartate aminotransferase	24 IU/l	34

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	400 mg, daily; Oral	Chronic myeloid leukemia (Chronic myeloid leukaemia)	10-APR-2019 / 30-APR-2019; 21 days

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#4) PRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE] (INDAPAMIDE, PERINDOPRIL ARGININE) ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History not treated	Herniated disc (Intervertebral disc protrusion);
Unknown to Ongoing	Relevant Med History not treated	Vestibular neuronitis (Vestibular neuronitis);
Unknown	Relevant Med History currently treated	Thyroidectomy (Thyroidectomy);
Unknown	Relevant Med History not treated	Carpal tunnel decompression (Carpal tunnel decompression);

Mfr. Control Number: 2019209248

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History not treated	Varicose vein operation NOS (Varicose vein operation);
Unknown to Ongoing	Relevant Med History not treated	Gonarthrosis (Osteoarthritis);
Unknown	Relevant Med History 5 times a week, 1 glass of wine daily	Alcohol use (Alcohol use);
Unknown	Past Drug Event alopecia ongoing	dasatinib (DASATINIB); Drug Reaction: Alopecia (Alopecia)

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	FRANCE		FEB	1964	54 Years	Female	Unk		DEC	2018

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas)

Alanine aminotransferase increased [Alanine aminotransferase increased]
Aspartate aminotransferase increased [Aspartate aminotransferase increased]
Cephalgia [Headache]
Nausea [Nausea]
Vomiting [Vomiting]
Nausea while on CLAMOXYL [Nausea]
Diarrhea while on CLAMOXYL [Diarrhoea]
Pulmonary superinfection [Pneumonia]
Positive Hepatitis E [Hepatitis E]

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Bosulif (BOSUTINIB) Film-coated tablet
#2) CLAMOXYL [AMOXICILLIN] (AMOXICILLIN)
(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg, 1x/day	#1) Oral
#2) UNK	#2) Unknown

17. INDICATION(S) FOR USE
#1) chronic myeloid leukemia (Chronic myeloid leukaemia)
#2) pulmonary superinfection (Pneumonia)

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 20-NOV-2018 / 26-MAR-2019	#1) 4 months 7 days
#2) DEC-2018 / 07-JAN-2019	#2) Unknown

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ATROVENT (IPRATROPIUM BROMIDE) ; Ongoing
#2) BRICANYL (TERBUTALINE SULFATE) ; Ongoing
#3) BECLOSPIN (BECLOMETASONE DIPROPIONATE) ; Ongoing
#4) OXEOL (BAMBUTEROL HYDROCHLORIDE) ; Ongoing
#5) SINGULAIR (MONTELUKAST SODIUM) ; Ongoing
#6) AERIUS [DESLORATADINE] (DESLORATADINE) ; Ongoing
(Continued on Additional Information Page)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History treated	COPD (Chronic obstructive pulmonary disease)
Unknown to Ongoing	Relevant Med History treated	Hepatitis B (Hepatitis B)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
2019211022

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
14-NOV-2023

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Anxiety [Anxiety]

Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE

This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 54-year-old female subject received bosutinib (BOSULIF), first regimen from 20Nov2018 to 26Mar2019 at 300 mg 1x/day and second regimen, all oral for chronic myeloid leukaemia. The subject received amoxicillin (CLAMOXYL) from Dec2018 to 07Jan2019 for pulmonary superinfection. The subject had a medical history of ongoing chronic obstructive pulmonary disease (COPD) (treated), ongoing hepatitis B (treated), ongoing emphysema (treated), ongoing chronic renal failure (treated) since Aug2010, multiple allergies (no treated at the report time), cholecystectomy, appendicectomy, ongoing chronic myeloid leukemia, all not related to a past tyrosine kinase inhibitors. The subject did not have a family history of liver disease.
Concomitant medications included ipratropium bromide (ATROVENT) ongoing for COPD, terbutaline sulphate (BRICANYL) ongoing for COPD, beclometasone (BECLOSPIN) ongoing for COPD, bambuterol (OXEOL) ongoing for COPD, montelukast (SINGULAIR) ongoing for COPD, desloratadine (AERIUS) ongoing for COPD, esomeprazole magnesium (INEXIUM) ongoing for gastrooesophageal reflux prophylaxis, mepolizumab (NUCALA) ongoing for COPD.
In Dec2018, the subject experienced nausea while on CLAMOXYL (grade 2), diarrhea while on CLAMOXYL (grade 2) and pulmonary superinfection (grade 2). These events were assessed as non-serious. In the result of the events, bosutinib was continued at the same dose. Action taken regarding amoxicillin was unknown.
On 26Mar2019, the subject experienced positive hepatitis E (grade 2), which was assessed as non-serious. In the result of the event, bosutinib was continued at the same dose. The subject received tenofovir disoproxil (VIREAD) daily, ongoing from 09May2019 for hepatitis B and ribavirin (COPEGUS) 200 (unit not provided) ongoing from 09May2019 for hepatitis E.
The subject developed cephalgia from 07Mar2019 to 18Mar2019, nausea from 26Mar2019 to 15May2019, vomiting from 26Mar2019 to 15May2019, anxiety (onset date in May2019) was noted in the consultation report of 20May2019, and malaise (onset date in 2019) was noted in the consultation report of 31Jul2019.
On 22Mar2019, the subject experienced alanine aminotransferase (ALAT) increased and aspartate aminotransferase (ASAT) increased. The events were assessed respectively with a grade 3 and 2 and non-serious. The physician was aware of these events on 23Mar2019 based on analysis performed on the same day and the subject was convoked on 26Mar2019. Bosutinib was temporarily withdrawn on 26Mar2019. The reporter stated: improvement after bosutinib withdrawal then increase of cytolysis when bosutinib was resumed before definitive withdrawal.
The subject developed asthenia at the beginning of the treatment by bosutinib, from Oct2019 to 09Dec2019.
No action was taken with amoxicillin in response to the events nausea and diarrhea (nausea and diarrhea resolved at the end of the treatment with amoxicillin), and in response to other events was unknown. The last action taken for bosutinib was dosage permanently withdrawn.
On 07Jan2019, the events nausea (Dec2018), diarrhea and pulmonary superinfection resolved. Outcome was reported as resolved for Alanine aminotransferase increased on 08Aug2019 and for aminotransferase increased on 25Jul2019. The outcome of events anxiety was recovered on May2019. The outcome of positive hepatitis E was not recovered, the outcome of Cephalgia was recovered on 18Mar2019, nausea (26Mar2019) was recovered on 15May2019, Vomiting was recovered on 15May2019, Asthenia was recovered on 09Dec2019. Therapeutic measures were taken as a result of pneumonia, hepatitis E.
The subject presented with hepatic cytolysis which was considered as a symptom. Alanine aminotransferase results (normal value < 32IU/l) were 15 IU/l on 03Apr2018, 22 IU/l on 01Oct2018, 375 IU/l on 23Mar2018, 277 IU/l on 26Mar2019 and 61 IU/l on 23Sep2019. Aspartate aminotransferase results (normal value < 32IU/l) were 19 IU/l on 03Apr2018, 21 IU/l on 01Oct2018, 136 IU/l on 23Mar2018, 106 IU/l on 26Mar2019 and 31 IU/l on 23Sep2019. On 26Mar2019, hepatitis B and C serologies were negative. On 26Mar2019, hepatitis E serology (ratio HEV/IgG) was 25. 989 (normal value <1).

The investigator considered the events alanine aminotransferase increased and aspartate aminotransferase increased as related to bosutinib and unrelated to concomitant medications.
The investigator considered the events nausea (Dec2018) and diarrhea as unrelated to bosutinib and related to the concomitant amoxicillin.
The investigator considered the events pulmonary superinfection and positive hepatitis E as unrelated to bosutinib and concomitant medications.
The investigator considered the events headache, nausea (26Mar2019) and vomiting as related to bosutinib and the event anxiety as unrelated to bosutinib.

Follow-up (03Jun2019): New information received includes: start date of bosutinib updated, medical history and concomitant medications updated, action taken with amoxicillin added.

Follow-up (16Jul2019): New information received includes: deleted event vomiting.

Follow-up (02Dec2019): New information received from the investigational site includes relevant medical history, symptom of event, relevant lab data.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (09Sep2020 and 10Sep2020): New information received from the clinical team includes: new event (cephalgia, nausea and vomiting, anxiety, malaise, and asthenia) added.

Amendment: This follow-up report is being submitted to amend previously reported information: Causality for events headache, nausea (in Apr2019), vomiting, anxiety, malaise, and asthenia are unknown, a statement is added in narrative to clarify the causality is based on company assessment for these events.

Follow-up (07Oct2020): new information received from CRO included: onset date of events (Alanine aminotransferase increased and Aspartate aminotransferase increased, Positive Hepatitis E) updated, and outcome of events (Alanine aminotransferase increased and Aspartate aminotransferase increased) updated as resolved and recovery date added.

Follow-up (21Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047.
Updated information: patient's height added.

Follow-up (08Jun2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047. Updated information included: treatment with bosutinib marked as ongoing, relevant medical history of chronic myeloid leukemia added, start and stop dates updated for events headache, nausea, vomiting and anxiety, outcome of event anxiety updated from unknown to recovered, causality assessment for events headache, nausea (26Mar2019) and vomiting updated as related to bosutinib and the event anxiety updated as unrelated to bosutinib (previously not provided).

Amendment: This follow-up report is being submitted to amend previous information: events ('nausea' and 'vomiting') term updated, patient age updated, dosage regimen of bosutinib updated.

Follow-up (14Nov2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from clinical team following reconciliation between clinical and safety databases.
Updated information included: events asthenia (Oct2019) and malaise (2019) not reportable since AE encountered after 28 days post bosutinib treatment stop.

Case Comment: Based on the information currently available information and the consistency with the known safety profile of the suspect product bosutinib, the events alanine aminotransferase increased, aspartate aminotransferase increased, headache, nausea (second episode), vomiting as related to bosutinib. The events nausea (first episode) and diarrhea are considered as unrelated to bosutinib but related to the concomitant amoxicillin. The events pulmonary superinfection, hepatitis E and anxiety are most likely related to an intercurrent or underlying condition which is not related to the suspected drug.
The follow up information does not alter the previous company clinical evaluation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	03-APR-2018	Alanine aminotransferase	15 IU/l	32
2	01-OCT-2018	Alanine aminotransferase	22 IU/l	32
3	23-MAR-2019	Alanine aminotransferase increased	375 IU/l	32
4	26-MAR-2019	Alanine aminotransferase	277 IU/l	32
5	23-SEP-2019	Alanine aminotransferase	61 IU/l	32
6	03-APR-2018	Aspartate aminotransferase	19 IU/l	32
7	01-OCT-2018	Aspartate aminotransferase	21 IU/l	32
8	23-MAR-2019	Aspartate aminotransferase increased	136 IU/l	32
9	26-MAR-2019	Aspartate aminotransferase	106 IU/l	32
10	23-SEP-2019	Aspartate aminotransferase	31 IU/l	32

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ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
11	26-MAR-2019	Hepatitis B virus test Negative	negative	
12	26-MAR-2019	Hepatitis C virus test Negative	negative	
13	26-MAR-2019	Hepatitis E virus test	25. 989	1

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2	UNK; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	Unknown; Unknown

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION continued

#7) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNESIUM) ; Ongoing

#8) NUCALA (MEPOLIZUMAB) ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History treated	Emphysema (Emphysema);
AUG-2010 to Ongoing	Relevant Med History treated	Chronic renal failure (Chronic kidney disease);
Unknown	Relevant Med History no treated at the report time	Multiple allergies (Multiple allergies);
Unknown	Relevant Med History	Cholecystectomy (Cholecystectomy);
Unknown	Relevant Med History	Appendicectomy (Appendicectomy);
Unknown to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);