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		PRIVACY		76 Years	Male	Unk	29	JAN	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
acute pancreatitis [Pancreatitis acute]
functional disability related to inguinal hernia [Physical disability]
inguinal hernia [Inguinal hernia]
heavy head in the morning [Head discomfort]
nausea [Nausea]
Nausea [Nausea]
Vomiting [Vomiting]
decrease of appetite [Decreased appetite]
headache [Headache]

(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, UNK	#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) 14-AUG-2018 / 08-NOV-2018	#1) 87 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) BISOPROLOL (BISOPROLOL) ; 20-JAN-2017 / Ongoing
#2) DIFFU K (POTASSIUM CHLORIDE) ; 2016 / Ongoing
#3) METFORMIN (METFORMIN) ; Ongoing
#4) INIPOMP (PANTOPRAZOLE SODIUM SESQUIHYDRATE) ; Ongoing
#5) LANTUS (INSULIN GLARGINE) ; Ongoing
#6) NISIS (VALSARTAN) ; 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	Diabetes (Diabetes mellitus)
Unknown to Ongoing	Relevant Med History currently treated	Arterial 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.
2019211077

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
10-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

dysequilibrium [Balance disorder]
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 contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 76-year-old male subject received bosutinib (BOSULIF), from 14Aug2018 to 08Nov2018 at 300 mg (300 mg, unk), oral, from 28Nov2018 to 02Apr2019 at 400 mg daily, oral and since 02Apr2019 (ongoing) at 300 mg daily for chronic myeloid leukaemia. The subject's relevant medical history included: "diabetes (all types)" (ongoing), notes: currently treated; "arterial hypertension" (ongoing), notes: currently treated; "chronic cirrhosis" (unspecified if ongoing), notes: no treatment, past history; "hepatocarcinoma" (unspecified if ongoing), notes: no treatment, past history; "cholecystectomy" (unspecified if ongoing), notes: no treatment; "arthrosis" (ongoing), notes: no treatment; "cervical osteoarthritis" (unspecified if ongoing). Concomitant medication(s) included: BISOPROLOL taken for arterial hypertension, start date: 20Jan2017 (ongoing); DIFFU K taken for hypokalaemia, start date: 2016 (ongoing); METFORMIN taken for diabetes (ongoing); INIPOMP taken for gastrooesophageal reflux prophylaxis (ongoing); LANTUS taken for diabetes (ongoing); NISIS taken for arterial hypertension(ongoing); TAREG taken for arterial hypertension; FUROSEMIDE taken for prophylaxis (ongoing); SETOFILM taken for nausea prophylaxis, start date: 29Jan2019 (ongoing). Past drug history included: Dasatinib, reaction(s): "anemia due to martial deficiency", notes: no treatment, past history; Dasatinib, reaction(s): "digestive hemorrhage", notes: no treatment, past history; Imatinib, reaction(s): "Angiodysplasia", notes: no treatment, past history; Tardyferon, stop date: 08Nov2018, for anemia due to martial deficiency, notes: 240 daily. The following information was reported: HEAD DISCOMFORT (non-serious) with onset 29Jan2019, described as "heavy head in the morning"; NAUSEA (non-serious) with onset 29Jan2019; PHYSICAL DISABILITY (medically significant) with onset Mar2019, described as "functional disability related to inguinal hernia"; INGUINAL HERNIA (medically significant) with onset Mar2019, outcome "not recovered"; NAUSEA (non-serious) with onset Oct2019; DECREASED APPETITE (non-serious) with onset Oct2019, described as "decrease of appetite"; VOMITING (non-serious) with onset 18Feb2020; BALANCE DISORDER (non-serious) with onset 18Jun2020, described as "dysequilibrium"; HEADACHE (non-serious) with onset 18Jun2020; ABDOMINAL PAIN (non-serious) with onset 19Aug2020; PANCREATITIS ACUTE (hospitalization) with onset 19Aug2020, described as "acute pancreatitis". The subject was hospitalized for pancreatitis acute (start date: 19Aug2020, discharge date: 24Aug2020, hospitalization duration: 5 day(s)). Clinical course: On 29Jan2019, the subject experienced heavy head in the morning and nausea, both assessed as non-serious and grade 1. The subject described a feeling of heavy head in the morning that he thought to be related to bosutinib but that could also be related to cervical arthrosis. The subject also complained of rare episodes of nausea. In response to those events, the investigator reduced the dose of bosutinib from 400 to 300 mg daily. The latter dose was previously well tolerated. In Mar2019, the subject developed inguinal hernia and functional disability related to inguinal hernia. The events functional disability related to inguinal hernia and the event inguinal hernia were assessed as medically significant. The subject went to the emergency unit close to his home (not in the investigational site) due to functional disability while walking related to inguinal hernia. He was not hospitalized. No action was taken with bosutinib in response to functional disability and inguinal hernia. Inguinal hernia was not operated and was still ongoing at report time. On 02Apr2019, the subject had fully recovered from heavy head in the morning, nausea, and functional disability. The subject developed nausea from Oct2019 to 18Feb2020 and decrease of appetite from Oct2019 to 18Jun2020. The event decrease of appetite on Oct2019 rated grade 1, and unrelated to bosutinib or to any concomitant drug. No action was taken for bosutinib in response to the event. On 18Feb2020, the subject experienced vomiting grade 1. The subject presented with headache and disequilibrium related to cervical arthrosis (medical history) on 18Jun2020. These separate events were assessed as non-serious and rated grade 1. No action was taken in the result of these events. These events resolved on 19Aug2020. On 19Aug2020, the subject experienced acute pancreatitis, which led to hospitalization and rated grade 3. No action taken was taken with bosutinib as result of the event. On 19Aug2020, abdominal pelvic computed tomography was normal. The subject was hospitalized from 19Aug2020 to 24Aug2020 in a nearby hospital for acute pancreatitis flare-up in a context of diabetes. The event resolved on 24Aug2020. The referent physician was aware of the information during the consultation of 07Sep2020. On 19Aug2020, the subject experienced abdominal pain assessed as non-serious and rated grade 2. No action was taken with bosutinib as result of the event. The event resolved on 24Aug2020. The referent physician was aware of the information during the consultation of 07Sep2020. As of 12Oct2022, it was reported that an echo endoscopy was performed following the pancreatitis on 22Jun2021 with normal result except 2 millimetric pancreatic cystic images. The event vomiting resulted as resolved on 18Jun2020. At the time of the report, the subject had not recovered from the event inguinal hernia. The subject underwent the following laboratory tests and procedures: Computerised tomogram: (19Aug2020) normal; Endoscopy: (22Jun2021) NORMAL, notes: NORMAL RESULT EXCEPT 2 CYSTIC PANCREATIC MILLIMETRIC IMAGES. The last action taken for bosutinib was dosage reduced. Therapeutic measures were not taken as a result of inguinal hernia. The outcome of head discomfort was recovered on 02Apr2019; nausea on 29Jan2019 and physical disability were recovered on 02Apr2019; nausea on Oct2019 was recovered on 18Feb2020; decreased appetite and vomiting were recovered on 18Jun2020; balance disorder and headache were recovered on 19Aug2020; abdominal pain and pancreatitis acute were recovered on 24Aug2020; and inguinal hernia was not recovered.

The investigator considered there was a reasonable possibility that the events acute pancreatitis, heavy head in the morning, nausea (two epidoses) and vomiting were related to bosutinib and unrelated to the concomitant medications. Heavy head in the morning was also considered as possibly related to cervical arthrosis.
The investigator considered there was not a reasonable possibility that the events functional disability and inguinal hernia, headache,

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

disequilibrium, decreased appetite and abdominal pain were related to bosutinib or to concomitant medications.

Follow-up (21May2019): New information reported includes additional details about bosutinib regimens, medical history, past drugs, concomitant medications and clinical outcome of inguinal hernia.

Follow-up (26Mar2020): New information reported includes additional events occurred on 18Feb2020: nausea grade 1, and vomiting grade 1.

Follow-up (09Sep2020): New information reported includes new event decreased appetite with a feeling of full stomach at mealtimes and disgust for meat, headache and disequilibrium.

Follow-up (30Sep2020 and 01Oct2020): New information reported includes updated onset of the second episode of nausea (occurred in Oct2019, previously reported 18Feb2020), new events decrease of appetite (non-serious and rated grade 1), updated verbatim for the event headache and disequilibrium (updated to separate event headache and disequilibrium, assessed as non-serious and rated grade 1), acute pancreatitis which led to hospitalization, relevant test, new event abdominal pain (assessed as non-serious and rated grade 2) and updated event verbatim for functional disability (updated to functional disability related to inguinal hernia) and updated seriousness for functional disability related to inguinal hernia and the event inguinal hernia (assessed as medically significant).

Follow-up (23Apr2021): New information received from the investigational site via the CRO includes: subject's height added, dose regimen of bosutinib added, event verbatim "decreased appetite with a feeling of full stomach at mealtimes and disgust for meat" was changed to "decrease of appetite" and its recovery date updated, and event decrease of appetite from 18Feb2020 removed.

Follow-up (12Oct2022): New information received from investigational site via CRO reporting the stop date for event nausea was 18Jun2020.

Follow-up (13Oct2022): 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 included: Endoscopy added in lab data section and outcome of the event vomiting updated as resolved.

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

Follow-up (10May2023): This is a non-interventional follow-up study report (Post Authorization Safety Study) from contactable reporter(s) (Physician and Other HCP) for protocol B1871047 from the investigational site via the CRO.
Updated information included: event details (previous event nausea with start date of Oct2019, stop date was updated from 18Jun2020 to 18Feb2020).

Case Comment: Based on the available information, the company considers that a causal relationship between heavy head in the morning, nausea (both episodes), vomiting, pancreatitis and bosutinib cannot be excluded due to plausible temporal association and/or known drug safety profile. The Company considers the reported events functional disability, inguinal hernia, headache, disequilibrium, decrease appetite and abdominal pain are unrelated to suspect drug bosutinib but more likely inter-current medical conditions. This case will be updated when new information becomes available. 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-AUG-2020	Computerised tomogram	normal	
2	22-JUN-2021	Endoscopy	NORMAL	
		NORMAL RESULT EXCEPT 2 CYSTIC PANCREATIC MILLIMETRIC IMAGES		

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)	28-NOV-2018 / 02-APR-2019; 146 days
#1) Bosulif (BOSUTINIB) Film-coated tablet;	300 mg, daily; Unknown	chronic myeloid leukemia	02-APR-2019 /

Mfr. Control Number: 2019211077

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)	Ongoing; Unknown

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

#7) TAREG (VALSARTAN) ; Unknown

#8) FUROSEMIDE (FUROSEMIDE) ; Ongoing

#9) SETOFILM (ONDANSETRON) ; 29-JAN-2019 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History no treatment, past history	Cirrhosis liver (Hepatic cirrhosis);
Unknown	Relevant Med History no treatment, past history	Liver carcinoma (Hepatic cancer);
Unknown	Relevant Med History no treatment	Cholecystectomy (Cholecystectomy);
Unknown to Ongoing	Relevant Med History no treatment	Arthrosis (Osteoarthritis);
Unknown	Relevant Med History	Osteoarthritis of cervical spine (Spinal osteoarthritis);
Unknown	Past Drug Event no treatment, past history	dasatinib (DASATINIB); Drug Reaction: Iron deficiency anaemia (Iron deficiency anaemia)
Unknown	Past Drug Event no treatment, past history	dasatinib (DASATINIB); Drug Reaction: Hemorrhage of digestive tract (Gastrointestinal haemorrhage)
Unknown	Past Drug Event no treatment, past history	imatinib (IMATINIB); Drug Reaction: Angiodysplasia (Angiodysplasia)
Unknown to 08-NOV-2018	Past Drug Event 240 daily	tardyferon (TARDYFERON); Drug Indication: Anemia iron deficiency (Iron deficiency anaemia)

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		PRIVACY		56 Years	Male	70.00 kg		FEB	2019

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

Other Serious Criteria: Medically Significant
pyelonephritis [Pyelonephritis]
lipase increased [Lipase increased]
postprandial diarrhea [Diarrhoea]
episode of lung infection [Pneumonia]
lower limb pain [Pain in extremity]
Meteorism (grade 1) [Flatulence]
Fever (grade 2) [Pyrexia]

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

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) 22-JAN-2019 / Ongoing

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	Renal calculus (Nephrolithiasis)
17-FEB-2019 to FEB-2019	Relevant Med History rated grade 2	Fever (Pyrexia)

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.
2019222241

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
21-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

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 56-year-old male subject started to receive oral bosutinib (BOSULIF) at 400 mg daily from 22Jan2019 for chronic myeloid leukemia. Relevant medical history included renal calculus, and fever rated grade 2 from 17Feb2019 to Feb2019, ongoing chronic myeloid leukemia. He received unspecified concomitant medications. In Feb2019, the subject experienced an episode of lung infection rated grade 2 and lower limb pain rated grade 1. On 20Feb2019, she presented with pyelonephritis rated grade 3. In Apr2019, the subject experienced postprandial diarrhea grade 1. The site described postprandial diarrhea at noon not requiring symptomatic treatment. Episode of lung infection, lower limb pain and postprandial diarrhea were assessed as non-serious. Pyelonephritis required hospitalization from 20Feb2019 to 22Feb2019 due to medical history of renal calculus. On 21Mar2019, ureteroscopy was performed. No action was taken with bosutinib in response to the events lung infection, lower limb pain, pyelonephritis and postprandial diarrhea. On 10Jan2020, the subject experienced lipase increased rated grade 4 and considered as medically significant. The site described lipase increased but subject was completely asymptomatic. Due to a departure abroad, the investigator stopped the treatment for 1 week, with resumption at 2 tablets a day to avoid an episode of real pancreatitis abroad. On 10Jan2020, lipase increased to 417 IU/L (normal ranges: 13-60). On 16Jan2020, lipase was 120 IU/L. On 29Jan2020, lipase was 37 IU/L. In response to the event lipase increased, bosutinib was temporarily withdrawn. The subject fully recovered from the episode of lung infection on 14Feb2019 (duration: 14 days), from pyelonephritis on 22Feb2019 and from lower limb pain on 23Apr2019. The event postprandial diarrhea was recovered on 08Oct2019. The event lipase increased recovered on 29Jan2020 and did not reoccur at treatment resumption. The subject experienced Fever (grade 2) on 17Feb2019. The outcome of Fever (grade 2) was resolved on Feb2019. On 25May2020, the subject experienced meteorism, which was assessed as non-serious and rated as grade 1. Meteorism with bloating. The last action taken for bosutinib in response to the event meteorism was dose not changed. The event, meteorism was recovered on 05Oct2020.

The investigator considered there was not a reasonable possibility that the events infection, lower limb pain, pyelonephritis, Fever (grade 2) and Meteorism (grade 1) were related to bosutinib or to a concomitant medication. The investigator considered that the event postprandial diarrhea was related to bosutinib and unrelated to a concomitant drug. The investigator considered that there was a reasonable possibility that the event lipase increased was related to bosutinib and unrelated to a concomitant drug.

Follow-up (03Jul2019): New information includes reaction data (added new event 'postprandial diarrhea').
The report has been upgraded due to new related event 'diarrhea'.

Follow-up (26Mar2020 and 27Mar2020): New information received from the CRO included: lab data; action taken and start date of bosutinib; new event (lipase increased); removed event fever to medical history.

Follow-up (27Apr2020): Follow-up attempts completed. No further information expected.

Follow-up (09Jul2020): New information received from the CRO includes: new event (meteorism) added.

Follow-up (03Aug2020): New information reported includes: event detail (upgrade lipase increased rated grade 4 to serious).

Amendment (07Aug2020): This follow-up report is being submitted to amend previously reported information: to correct last action taken to dose not changed (last action taken in response to last event (meteorism)) and to remove duration of lower limb pain.

Follow-up (07Oct2020): New information received from the CRO includes: reaction data (events outcome for events "meteorism and postprandial diarrhea" were both updated from "not recovered" to "recovered").

Follow-up (28Jan2022): This is a spontaneous follow-up report received from the investigator via the CRO.
Updated information: Bosulif start date updated to 22Jan2019, new events (Fever (grade 2)), event verbatim updated from Meteorism to Meteorism (grade 1), lab data added.

Follow-up (23Feb2023). 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: Medical history included ongoing chronic myeloid leukemia.

Follow-up (21Jul2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the investigator via the CRO for protocol B1871047.
Updated information included: reporter information.

Case Comment: In concurrence with the reporting investigator, the Company attributes pyelonephritis to the pre-existing medical condition of renal calculus, unrelated to bosutinib. Similarly, the reported lower limb pain cannot be excluded as associated to pyelonephritis, and assessed as unrelated to bosutinib. Lung infection fever and meteorism are also evaluated as unrelated to the suspect drug, being considered intercurrent and self-supporting complications, in the clinical setting of the underlying chronic myeloid leukemia. Conversely, due to the known drug safety profile, diarrhea, and lipase increased are assessed as related to bosutinib. The

Mfr. Control Number: 2019222241

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

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

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10-JAN-2020	Lipase	417 IU/l	60 13
2	16-JAN-2020	Lipase	120 IU/l	60 13
3	29-JAN-2020	Lipase	37 IU/l	60 13
4	21-MAR-2019	Ureteroscopy	unknown results	

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);

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		PRIVACY		75 Years	Female	Unk	04	MAY	2019

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

asthenia [Asthenia]
pruritus of extremities [Pruritus]

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.

(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) Oral

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

18. THERAPY DATES(from/to)
#1) 03-MAY-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)

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.
2019259654

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 post-authorization safety study.

A 75-year-old female subject started to receive bosutinib (BOSULIF) at 200 mg daily by oral route ongoing from 03May2019 for chronic myeloid leukemia. Relevant medical history, laboratory tests and concomitant medications were not provided. On 04May2019, the subject experienced asthenia and pruritus of extremities. The events were both assessed as non-serious and grade 1. He complained of asthenia since the initiation of bosutinib that was more marked that it was previously. Pruritus of extremities requiring the application of moisturizing cream and non-daily intake of an antihistaminic treatment (unspecified trade name). No action was taken with bosutinib. At the time of the report, the subject had not recovered yet from asthenia; pruritus of extremities resolved in May2019.

The investigator considered there was a reasonable possibility that the events were related to bosutinib and unrelated to a concomitant medication.

Follow-up (09Dec2020): New information includes updated outcome of event pruritus of extremities.

Follow-up (07May2021): New information received from the investigational site via the CRO includes: recovery date of the event pruritus of the extremities was updated to May2019 (previously 01Aug2019).

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

Follow-up (20Jan2023): 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 included: Study information and patient information.

Amendment: This follow-up report is being submitted to amend previously reported information: the patient was a female subject instead of male.

Case Comment: Based on the known drug safety profile and temporal relationship, the causal association between the reported events asthenia and pruritus and bosutinib administration cannot be excluded.

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		PRIVACY		52 Years	Female	Unk		MAR	2019

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

nausea grade 2 [Nausea]
diarrhea [Diarrhoea]
epigastralgia [Abdominal pain upper]
acid reflux [Gastrooesophageal reflux disease]
Muscular pain [Myalgia]
Constipation [Constipation]
Laryngitis [Laryngitis]

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) 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) 19-MAR-2019 / 25-MAR-2019

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)

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.
2019261868

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

24c. DATE RECEIVED BY MANUFACTURER
06-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

CONDITIONS OF USE

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

A 52-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), first regimen from 19Mar2019 to 25Mar2019 at 300 mg daily, second regimen from 26Mar2019 to 09Apr2019 at 400 mg daily and third regimen from 10Apr2019 to 26Feb2020 at 500 mg daily, all oral for chronic myeloid leukaemia. The patient's relevant medical history was not reported. There were no concomitant medications.
The following information was reported: DIARRHOEA (non-serious) with onset Mar2019, outcome "recovered" (13May2019), described as "diarrhea"; NAUSEA (non-serious) with onset Mar2019, outcome "recovered" (27Feb2020), described as "nausea grade 2"; ABDOMINAL PAIN UPPER (non-serious) with onset 19Mar2019, outcome "recovered" (11Sep2019), described as "epigastralgia"; GASTROOESOPHAGEAL REFLUX DISEASE (non-serious) with onset Jun2019, outcome "recovered" (11Sep2019), described as "acid reflux"; CONSTIPATION (non-serious) with onset Oct2019, outcome "recovered" (27Feb2020); MYALGIA (non-serious) with onset Oct2019, outcome "recovered" (27Feb2020), described as "Muscular pain"; LARYNGITIS (non-serious) with onset Nov2019, outcome "recovered" (Nov2019). Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage permanently withdrawn on 26Feb2020. Therapeutic measures were not taken as a result of nausea. Therapeutic measures were taken as a result of abdominal pain upper, laryngitis.

Additional information: In Mar2019, the subject experienced nausea and diarrhea, (both assessed as non-serious. The diarrhea was rated grade 1). The nausea was rated grade 2. Medical report dated 17Apr2019 stated: "Progressive increase in dose of bosutinib over 3 weeks with occurrence of misdirect digestive tolerance (nausea and diarrhea)." Medical report dated 13May2019 stated: "Misdirect digestive tolerance with occurrence of nausea and diarrhea. The subject did not want to take corrective treatment against nausea." Bosutinib dose was increased in response to the events. On 19Mar2019, the subject developed epigastralgia. Bosutinib dose was increased in response to epigastralgia. In Jun2019, she experienced acid reflux. Epigastralgia and acid reflux were both assessed as non-serious and grade 2. Medical report dated 17Jun2019 stated: "Since the initiation of bosutinib, the subject presented with misdirect digestive tolerance with occurrence of epigastralgia grade 2 for which she received esomeprazole (unspecified trade name). On the day of consultation (17Jun2019), frequent episodes of epigastralgia and sometimes reflux acid were noted." In Oct2019, the subject developed constipation grade 2, and muscular pain, grade 1; both were considered as not serious. In the report of 05Dec2019: since her last visit 3 months prior to the consultation, grade 2 constipation and muscle spasms. In Nov2019, the subject developed laryngitis grade 2, considered as not serious. In the report of 05Dec2019: the episode of laryngitis in Nov was of favorable outcome under amoxicillin sodium, clavulanate potassium (AUGMENTIN). On an unspecified date, the subject developed poor molecular response, considered as not serious. The investigator was advised as of 14Feb2020 that the treatment would be switched because it was discussed in multidisciplinary consultation meetings. In the report of 27Feb2020: initiation of treatment by ponatinib (ICLUSIG) 45 mg per day due to a poor molecular response under bosutinib after 12 months of treatment. Upon follow up on 09Mar2020, it was reported that the investigator considered 'poor molecular response' as lack of efficacy, and therefore was re-encoded. The poor molecular response was described as a myelogram performed on 28Jan2020 and showing polymorphic smear without excess blast and BCR/ABL at 2.8%. The event poor molecular response referred to a lack of clinical effect; the subject lost major molecular response, she was a poor responder and it was not due to a lack of efficacy of the product. There were several treatment lines and it did not question the treatments at each time. Bosutinib was permanently stopped in response to poor molecular response on 26Feb2020 and treatment with ponatinib (ICLUSIG) 45 mg daily was initiated on 27Feb2020. Treatment received for laryngitis included amoxicillin sodium, clavulanate potassium (AUGMENTIN); treatment received for epigastralgia include esomeprazole. As of 30May2023, Additional event "primary Failure to BOSULIF" was reported. BOSULIF withdrawn in response to this event. Event considered related to bosutinib and unrelated to concomitant medication. As of 06Dec2023, The event Primary failure to BOSULIF was updated to drug ineffective.

The reporter considered "nausea grade 2", "diarrhea", "epigastralgia", "acid reflux" and "muscular pain" related to bosutinib. The reporter considered "constipation" and "laryngitis" not related to bosutinib.The investigator considered the events muscular pain, constipation and laryngitis, as unrelated to concomitant medications.

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

Follow-up (20Jun2019): New information received from the investigator via the CRO included new events (epigastralgia and reflux acid).

Follow-up (28Feb2020): New information received from the CRO includes updated dosage regimen of bosutinib, and new events (muscular pain, constipation and laryngitis).

Follow-up (09Mar2020): New information received from the investigational site includes updated event term (from poor molecular response to lack of drug effect), laboratory data (myelogram), action taken with bosutinib (updated to permanently withdrawn).

Follow-up (23Mar2020): New information received from the investigational site includes Study drug data (stop date for bosutinib).

Amendment: This follow-up report is being submitted to amend previously reported information: Causality per company updated to

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

unrelated for event Poor molecular response.

Follow-up (14May2020): New information received from the investigator via the CRO includes height provided, deleted weight, and confirmation that bosutinib was permanently stopped in response to poor molecular response.

Follow-up (27May2020): New information received from the investigational site includes details on the event poor molecular response.

Follow-up (25May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) from product quality group for protocol B1871047. Updated information: reaction data (CTCAE grade, event outcome, onset date).

Follow-up (30May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) via CRO. Updated information: suspect drug data and clinical course.

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

Follow-up (06Dec2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) from product quality group for protocol B1871047.
Updated information: The event Primary failure to BOSULIF was updated to drug ineffective.

Case Comment: Based on the known drug safety profile, there is a reasonable possibility of the causal association between the events nausea, epigastralgia, diarrhea and muscular pain and the suspect drug, bosutinib. A possible contributory role of bosutinib to the reported event acid reflux cannot be completely excluded based on temporal association. The reported constipation and laryngitis are most likely intercurrent conditions and unrelated to bosutinib administration.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	28-JAN-2020	Cytogenetic analysis	2.8 %	
2	28-JAN-2020	Spinal myelogram	polymorphic smear without excess blast	

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-MAR-2019 / 09-APR-2019; 15 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	500 mg, daily; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	10-APR-2019 / 26-FEB-2020; 10 months 17 days

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		PRIVACY		63 Years	Male	Unk		MAY	2019

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

Diarrhea grade 2 [Diarrhoea]
Decrease of appetite grade 1 [Decreased appetite]
Aggravation of spinal pain [Spinal pain]
Aggravation of spinal pain [Condition aggravated]

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

(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) 23-MAY-2019 / 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
20-JUL-2012 to FEB-2019	Relevant Med History treated	Adenocarcinoma (Adenocarcinoma)
Unknown to Ongoing	Relevant Med History	Asthenia (Asthenia)

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.
2019263909

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

24c. DATE RECEIVED BY MANUFACTURER
27-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 (Study alias BOSEVAL). This is a Non-Interventional clinical study case reporting non-serious events only.

A 63-year-old male subject started to receive bosutinib (BOSULIF), orally, at 300 mg daily from 07Jun2019, for chronic myeloid leukaemia. Medical history included adenocarcinoma from 20Jul2012 to Feb2019 (treated), and ongoing asthenia. The subject did not receive any concomitant treatment. On an unknown date in May2019, the subject experienced grade 1 decrease of appetite and grade 2 several diarrhea. No action was taken in response to the events for bosutinib. At the time of the report, the subject had not recovered from the events.

According to the investigator, events were related to study drug.

Follow-up (04Jul2019): New information reported includes that bosutinib was started on 23May2019 at 100 mg daily, then dose increased to 300 mg daily from 07Jun2019.

Follow-up (06Nov2019): New information reported includes that the subject had fully recovered from both events on 05Aug2019.

Follow-up (02Mar2020): New information received from CRO included:
Medical history included ongoing osteoporotic-looking spinal settlement D8D9D11, and persistent back pain.
On 05Dec2019, the CT scan showed an osteoporotic compression fracture of thoracic vertebra (T) T8, T10 and T11.
On 20Jan2020, MRI (magnetic resonance imaging) showed vertebral settlements T8 to T11 with a benign appearance, and no edema. However, there was an inflammatory aspect of posterior joints, on the right and left side at the T8-T9 and T10-T11 levels. Therefore, after a consultation with a hematologist, posterior joint infiltrations were planned, under CT control, at the three levels from T8-T9 up to T10-T11 on the right side, where the pain is located.
On the patient's medical record of 03Feb2020, it appeared that the patient was suffering from back pain for several months. A radiological check-up and a CT (computerized tomography) scan of the rachis were performed.
On 27Feb2020, the subject experienced joint infiltration T8 T9 T10 T11 rated grade 2 and assessed as non-serious. The event was resolved on 27Feb2020. According to the reporter, the event was unrelated to study drug and to concomitant drugs. In response to the event, no action was taken with bosutinib.

Follow-up (13Mar2020): New information received from the investigational site: the event joint infiltration T8 T9 T10 T11 was corrected to Inflammatory aspect of posterior joints, at the T8-T9 and T10-T11 levels, and the onset date was corrected to 20Jan2020 (MRI date). The right-sided spinal back pain were attributed to the inflammatory aspect of posterior joints, at the T8-T9 and T10-T11 levels. The causality assessment, seriousness was unchanged.

Follow-up (13Mar2020): New information received from CRO: The verbatim of the event Inflammatory aspect of posterior joints, at the T8-T9 and T10-T11 levels was updated to right lateral back pain and spinal pain. It was also reported that right lateral back pain and spinal pain could be attributed to posterior inflammatory aspect of T8-T9 to T10-T11 levels on MRI in Jan2020. The causality assessment, seriousness was unchanged.

Follow-up(22Mar2023): New information received from CRO: The verbatim of the event "Right lateral back pain and spinal pain" changed to "spinal pain".

Follow-up (27Mar2023): New information received from CRO: The verbatim of the event "spinal pain" updated to "Aggravation of spinal pain". Previously reported information also amended: event back pain deleted.

Case Comment: Based on the known drug safety profile, the causal association between the events, decrease of appetite and diarrhea, and bosutinib administration cannot be excluded. Conversely, in concurrence with the reporter, the reported aggravation of spinal pain is attributed to posterior inflammatory aspect of T8-T9 to T10-T11 levels on MRI in Jan2020, unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	05-DEC-2019	Computerised tomogram	osteoporotic compression fracture of thoracic vert	
2	03-FEB-2020	Computerised tomogram	unknown result	
3	03-FEB-2020	Investigation	unknown result	
4	20-JAN-2020	Magnetic resonance imaging	vertebral settlements T8 to T11	
		showed vertebral settlements T8 to T11 with a benign appearance, and no edema. However, there was an inflammatory aspect of posterior joints, on the right and left side at the T8-T9 and T10-T11 levels.		

Mfr. Control Number: 2019263909

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; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	07-JUN-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Spinal cord compression (Spinal cord compression);
Unknown	Relevant Med History	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		PRIVACY		70 Years	Male	72.00 kg		JAN	2019

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

Peripheral neuropathy [Neuropathy 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) 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) Bosutinib (BOSUTINIB) 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) 100 mg, daily	#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)	19. THERAPY DURATION
#1) 09-JUL-2018 / 16-JUL-2018	#1) 8 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
OCT-2014 to FEB-2015	Relevant Med History	Guillain-Barre syndrome (Guillain-Barre syndrome)
2009 to 2009	Relevant Med History	Hip prosthesis user (Joint prosthesis user)
	right	

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.
2019273060

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 70-year-old male patient received bosutinib (BOSUTINIB), first regimen from 09Jul2018 to 16Jul2018 at 100 mg daily, second regimen from 17Jul2018 to 24Jul2018 at 200 mg daily, third regimen from 25Jul2018 to 03Oct2018 at 300 mg daily and fourth regimen since 04Oct2018 (ongoing) at 400 mg daily, all oral for chronic myeloid leukaemia. The patient's relevant medical history included: "GUILLAIN-BARRE SYNDROME", start date: Oct2014, stop date: Feb2015; "right hip prosthesis", start date: 2009, stop date: 2009, notes: right. The patient's concomitant medications were not reported.
The following information was reported: NEUROPATHY PERIPHERAL (non-serious) with onset Jan2019, outcome "not recovered", described as "Peripheral neuropathy". The action taken for bosutinib was dosage not changed.

Additional information: The patient experienced peripheral neuropathy in Jan2019. The event peripheral neuropathy was assessed as Grade 1, non-serious.

The investigator considered that the event peripheral neuropathy was unrelated to bosutinib or to any concomitant drug.

Follow-up (22Jul2019): New information received from the investigational site via the CRO included: confirmation outcome of event peripheral neuropathy (unknown).

Follow-up (01Oct2019): New information received from the CRO includes: outcome of event peripheral neuropathy (provided as resolving).

Follow-up (03Dec2019): New information received from the clinical team and from the CRO included: reaction data (the event peripheral neuropathy recovered on an unspecified date in Apr2019).

Follow-up (18Jul2023): 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: outcome (updated to not recovered).

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; Oral	CML (Chronic myeloid leukaemia)	17-JUL-2018 / 24-JUL-2018; 8 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	300 mg, daily; Oral	CML (Chronic myeloid leukaemia)	25-JUL-2018 / 03-OCT-2018; 71 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	400 mg, daily; Oral	CML (Chronic myeloid leukaemia)	04-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
PRIVACY	FRANCE		PRIVACY		43 Years	Female	95.00 kg	08	NOV	2018

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

Intermittent gastralgia [Abdominal pain upper]
Influenza like illness [Influenza like illness]
Asthenia [Asthenia]

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.

(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) 08-NOV-2018 / 15-NOV-2018	#1) 8 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) AMOXICILLIN (AMOXICILLIN) ; 06-AUG-2018 / Ongoing
#2) IBUPROFEN (IBUPROFEN) ; Ongoing
#3) DEPAKOTE (VALPROATE SEMISODIUM) ; 2005 / Ongoing
#4) PAROXETINE (PAROXETINE) ; 2005 / Ongoing

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

From/To Dates	Type of History / Notes	Description
2005 to Ongoing	Relevant Med History	Bipolar disorder (Bipolar disorder)
2008 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.
2019275010

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
15-MAY-2023

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2019275010

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 43-year-old female patient started to receive bosutinib (BOSULIF) via an unspecified route of administration from 08Nov2018 to 15Nov2018 at 100 mg, daily, via an unspecified route of administration from 16Nov2018 to 22Nov2018 at 200 mg, daily, via an unspecified route of administration from 23Nov2018 to 30Nov2018 at 300 mg, daily, via an unspecified route of administration from 01Dec2018 and ongoing at 400 mg, daily for an unspecified indication.
Medical history included bipolar disorder from 2005 and ongoing, hypercholesterolaemia from 2008 and ongoing, tonsillectomy in 2000. Concomitant medication included amoxicillin, ibuprofen, valproate semisodium (DEPAKOTE), and paroxetine. The subject experienced intermittent gastralgia (CTCAE grade 1) on 08Nov2018, influenza like illness (CTCAE grade 2) on 23Feb2019, asthenia (CTCAE grade 1) on 24Feb2019, all assessed as non-serious. Despite the events, bosutinib was pursued unchanged. Outcome of gastralgia was resolved in Dec2019, asthenia was resolved in Mar2019, influenza like illness was resolved on 24Feb2019.

The investigator considered there was a reasonable possibility that the event intermittent gastralgia could be related to the study drug bosutinib and not related to concomitant drug.

The investigator considered there was not a reasonable possibility that the events influenza like illness and asthenia could be related to the study drug bosutinib and concomitant drug.

Follow-up (22Jul2019): new information reported includes updated outcome of event gastralgia and asthenia.

Follow-up (15May2023): This is a non-interventional study follow-up report received from investigational site via CRO.
Updated information included: study name, patient data, reaction data (outcome for Asthenia and Gastralgia).

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	16-NOV-2018 / 22-NOV-2018; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	Unknown	23-NOV-2018 / 30-NOV-2018; 8 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	Unknown	01-DEC-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2000 to 2000	Relevant Med History	Tonsillectomy (Tonsillectomy);

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		PRIVACY		35 Years	Female	59.00 kg		MAR	2019

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

asthenia [Asthenia]
Diarrhea-digestive disorder [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. This is a Non-Interventional Study report with non-serious events 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) 400 mg, 1x/day

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

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

18. THERAPY DATES(from/to)
#1) 05-MAR-2019 / 20-JUN-2019

19. THERAPY DURATION
#1) 108 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	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.
2019286775

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 35-year-old female patient started to receive bosutinib (BOSULIF) via oral at 400 mg, 1x/day from 05Mar2019 to 20Jun2019 for chronic myeloid leukaemia. Medical history included ongoing chronic myeloid leukemia. Concomitant drugs were not reported. No relevant laboratory data was performed. In Mar2019 patient had asthenia, grade 2 and diarrhea-digestive disorder, grade 3. The site described that events asthenia and digestive disorder type diarrhea were reported at medical visit performed on 20Jun2019. The action taken with bosutinib was permanently withdrawn. The event asthenia resolved on 02Dec2019. The event diarrhea-digestive disorder resolved on 02Sep2019.

The investigator considered that the events asthenia and diarrhea-digestive disorder were related to bosutinib and unrelated to any concomitant drug.

Follow-up (07Oct2020): New information received from the CRO included: outcome and stop date of the events.

Follow-up (16May2023): This is a Non-Interventional study follow-up report from the investigational site via the CRO. Updated information included: patient's initials, medical history, suspect drug data (frequency).

Case Comment: Based on the known drug safety profile, the Company concurs with the investigator that there is a reasonable possibility of the causal association between the events, asthenia and diarrhea, and bosutinib administration.

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		PRIVACY		67 Years	Male	86.00 kg		APR	2019

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

Numbness of fingers [Hypoaesthesia]
Infectious episode [Infection]
Joint pain of 3rd finger of hand [Arthralgia]
ST segment depression [Electrocardiogram ST segment depression]
DIFFICULTY BREATHING [Dyspnoea]
lower limb edema [Oedema peripheral]

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) CML (Chronic myeloid leukaemia)

18. THERAPY DATES(from/to)
#1) 15-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) MICARDIS (TELMISARTAN) ; Ongoing
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#3) LERCAN (LERCANIDIPINE HYDROCHLORIDE) ; Ongoing
#4) FUROSEMIDE (FUROSEMIDE) ; 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	Renal failure (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.
2019310092

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:

25b. NAME AND ADDRESS OF REPORTER
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 67-year-old male patient received bosutinib (BOSULIF), since 15Jan2019 (ongoing) at 400 mg daily for chronic myeloid leukaemia. The patient's relevant medical history included: "Hypertension arterial" (ongoing); "Renal failure" (ongoing); "Diabetes" (ongoing). Concomitant medication(s) included: MICARDIS (ongoing); KARDEGIC (ongoing); LERCAN (ongoing); FUROSEMIDE (ongoing). The subject experienced grade 1 infectious episode and grade 1 numbness of fingers, both on an unspecified date in Apr2019. On 13Jan2020 the subject experienced joint pain of 3rd finger of hand, grade 1, non-serious. The subject developed breathing difficulties in Oct2020, grade 2, non-serious; ST segment depression on 14Jan2021, grade 1, non-serious; lower limb edema on 26Jan2021, grade 1, non-serious. Action taken in response to the events with bosulif was dose not changed. The event infectious episode resolved in Apr2019, numbness of fingers resolved on 12Jul2019, joint pain of 3rd finger of hand resolved on 20Apr2020, breathing difficulties resolved on 19Oct2020, ST segment depression outcome was unknown, lower limb edema resolved on 08Mar2021.

According to the investigator, the numbness of fingers was related to study drug but not related to concomitant medication, while the infectious episode, "joint pain of 3rd finger of hand", ST segment depression, breathing difficulties and lower limb edema were not related to study drug or concomitant medication.

Follow-up (12Sep2019): New information received includes updated outcome for event numbness of fingers.

Follow-up (16Jan2020): New information received included dose of bosutinib and new event ("Joint pain of 3rd finger of hand").

Follow-up (23Mar2021): New information includes: updated outcome of event Joint pain of 3rd finger of hand and additional events ST segment shift, breathing difficulties, and lower limb edema.

Follow-up (07Feb2022) and Follow-up (28Feb2022). This is a follow-up to a non-interventional clinical study case.

Updated information: Outcome of lower limb edema was updated to resolved. ST segment shift outcome changed to unknown, Recovery date of Edema lower limb event was updated to 08Mar2021.

Follow-up (09Mar2023): 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 included: Event ST segment shift verbatim was updated to ST segment shift and ST depression.

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

Follow-up (03Aug2023): This is a follow up non-interventional study report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information: verbatim of event "ST segment shift and ST depression" updated to "ST segment depression".

Case Comment: Based on the clinical information currently provided, the company deems there is not a reasonable possibility that all the reported events are related to suspect drug bosutinb, considering the reported events intercurrent and self-supporting episodes, in the setting of medical history including ongoing CML, hypertension, renal failure and diabetes.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	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		PRIVACY		64 Years	Female	50.00 kg	26	FEB	2019

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]
HEPATIC CYTOLYSIS [Hepatic cytolysis]
SKIN REACTION [Skin reaction]

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

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) 13-FEB-2019 / 02-MAR-2019

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)

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

From/To Dates	Type of History / Notes	Description
1992 to 1992	Relevant Med History	Hysterectomy (Hysterectomy)

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.
2019310105

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:

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.

A 64-year-old female subject received bosutinib (BOSULIF), from 13Feb2019 (Batch/Lot number: unknown) to 02Mar2019 at 300 mg daily. Relevant medical history included: "HYSTERECTOMY", start date: 1992, stop date: 1992. There were no concomitant medications. On 26Feb2019, the subject experienced epigastric pain, which was assessed as non-serious and of grade 1. In the result of the event, action taken was reported as dose not changed. In Mar2019, the subject experienced skin reaction, which was assessed as non-serious and of grade 1. In the result of the event, action taken was reported as dose not changed. On 02Mar2019, the subject experienced hepatic cytolysis, which was assessed as non-serious and of grade 3. In the result of the event, bosutinib was withdrawn on 02Mar2019. Subject experienced intermittent epigastric pain from May2019 to Apr2020 and site confirmed that the event epigastric pain (May2019) was to be deleted. The subject experienced thyroid nodule in Apr2020, which was assessed as serious (hospitalization) and rated grade 1 (deleted). Thyroid nodule which was operated led to voice disorder. The action taken for bosutinib was dosage permanently withdrawn on 02Mar2019. The outcome of epigastric pain was resolved on 29Jun2020, hepatic cytolysis was resolved on 23Mar2019 and skin reaction was resolved on 25Mar2019.

The investigator considered there was not a reasonable possibility that the events "hepatic cytolysis" and "skin reaction" were related to bosutinib. The investigator considered there was a reasonable possibility that the event "epigastric pain" was related to bosutinib.

Follow-up (13Dec2021, 27Dec2021, 01Feb2022, 07Feb2022, 14Feb2022): This is a follow-up to a non-interventional clinical study case: EPIGASTRIC PAIN onset date updated to 26Feb2019, stop date updated to 29Jun2019, new event thyroid nodule. The event epigastric pain (May2019) was deleted. The report was upgraded to serious.

Follow-up (28Mar2022): Follow-up information received from the CRO.
Updated information: stop date of hepatic cytolysis updated to 23Mar2019 from 06Apr2019.

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

Follow-up (30May2022): This is a follow-up to a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.
Updated information: Event "Thyroid nodule" was removed from this case.

Follow-up (09Mar2023): This is a follow-up to a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.
Updated information: start date of Bosutinib updated.

Amendment: This follow-up report is being submitted to amend previous information: Recovery date of epigastric pain was updated to 29Jun2020.

Case Comment: In concurrence with the investigator, the company considered that the event epigastric pain is related to bosutinib based on compatible temporal association and known safety profile of the drug. The reported events hepatic cytolysis and skin reaction are more likely due to an intercurrent medical condition and unrelated 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		PRIVACY		58 Years	Male	85.00 kg		JAN	2019

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

pericarditis [Pericarditis]
pericarditis [Pericarditis]
Diarrhea [Diarrhoea]
Flu like syndrome [Influenza like illness]
Tinnitus grade 1 [Tinnitus]
Fatigue grade 1 [Fatigue]
chest rash [Rash]
Insomnia grade 1 [Insomnia]
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

(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) 14-JAN-2019 / 13-SEP-2019

19. THERAPY DURATION
#1) 243 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) ATENOLOL (ATENOLOL) ; 2014 / Ongoing
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 2014 / Ongoing
#3) INEGY (EZETIMIBE, SIMVASTATIN) ; 2014 / 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	Angina pectoris (Angina pectoris)
Unknown 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.
2019344376

24c. DATE RECEIVED BY MANUFACTURER
06-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.
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 report from a Pfizer-sponsored, Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL).
A 58-year-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 14Jan2019 to 13Sep2019 at 300 mg daily, and from 15Oct2019 to 29Nov2019 at 200 mg, for an unspecified indication. The patient's relevant medical history included: "angina pectoris" (ongoing); "hypercholesterolemia" (ongoing); "left hip arthrosis" (unspecified if ongoing); "arterial hypertension" (ongoing); "Chronic myeloid leukemia" (ongoing). The subject's concomitant medications included atenolol from 2014 and ongoing for angina attack, acetylsalicylate lysine (KARDEGIC) from 2014 and ongoing for angina attack, and ezetimibe/simvastatin (INEGY) from 2014 and ongoing for hypercholesterolemia. The subject experienced diarrhea in Jan2019, flu like syndrome, grade 1 in Mar2019, tinnitus grade 1 in Apr2019, fatigue grade 1 on 18Mar2019, insomnia grade 1 in Apr2019. In Mar2019, the patient developed asthenia, grade 1, assessed as non-serious. The bosutinib dose was not changed in response to the events asthenia, flu like syndrome, insomnia, tinnitus, and diarrhea. These events were reported by the nurse but they were considered as not clinically significant by the physician. On 15Jul2019, the subject experienced chest rash rated grade 1 and reported as non-serious. On 12Sep2019, the subject experienced pericarditis rated grade 3.
On 12Sep2019, during a systematic monitoring at cardiologist the subject was found to have asymptomatic circumferential pericardial effusion with signs of compression on right auricle. There was no sign of cardiac failure. The subject was hospitalized the same day in cardio vascular surgery department for drainage of this effusion, around 700 cc was drained. On 13Sep2019, bosutinib was temporarily stopped in response to the pericarditis (onset date 12Sep2019). On 15Oct2019, bosutinib was resumed at 200 mg once daily.
On 18Sep2019, the subject was found to have cardiac arrhythmia by atrial fibrillation, a treatment with rivaroxaban (XARELTO) at 20 mg daily was initiated the same day. The anatomopathological analysis of effusion liquid found inflammatory liquid without suspected cell. The treatment with bosutinib (BOSULIF) was readministered after this effusion, without recurrence. Pericarditis recovered on 19Sep2019. On 07Oct2019, the subject consulted a cardiologist, the sinusal rhythm was normal, therefore rivaroxaban (XARELTO) was discontinued on 08Oct2019.
On 29Nov2019, the subject consulted his cardiologist in order to perform an echocardiography in the context of previous occurrence of pericarditis on 12Sep2019. Echocardiography performed on 29Nov2019, disclosed a circumferential pericardial effusion without obvious sign of compression, the pressures were normal, and the kinetics of the left ventricle was normal. The diagnosis of reappearance of pericarditis was made. Usual medical treatment was maintained and it was decided to stop permanently bosutinib taking into account the recurrence of pericardial effusion, despite a reduced dosage to 200 mg daily. The subject was seen by his cardiologist on 17Dec2019. At that time, a very slight regression of pericardial effusion which was no longer circumferential was noted with a detachment of 9 mm posteriorly and 9-10 mm anterior versus 15 to 18 mm in Nov2019. Significant improvement ensued further bosutinib withdrawal. On 13Jan2020, the second episode of pericarditis had fully resolved. The last action taken in response to the events for bosutinib was permanently withdrawn. Diarrhea resolved on 28Jan2019, flu like syndrome resolved on 18Mar2019, tinnitus grade 1 resolved on 17Jul2019, fatigue grade 1 resolved on 03Apr2019, insomnia grade 1 resolved on 17Jul2019, and chest rash was resolved on 30Sep2019. The event asthenia resolved on 17Jul2019.

According to the reporter, the events chest rash, asthenia, insomnia, tinnitus, and diarrhea were related to bosutinib and unrelated to concomitant drugs. The event pericarditis was considered as related to suspect drug bosutinib and not related to concomitant drug. The investigator assessed the second episode of pericarditis as non-serious, rated grade 1, related to bosutinib and unrelated to concomitant drugs. The event flu like syndrome was considered unrelated to the study drug bosutinib or concomitant medications.

The reporter's assessment of the causal relationship of "fatigue grade 1" 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.

Follow-up (08Aug2019): New information received from CRO includes: subject's information (birth date, gender, weight and height) added, additional medical history and concomitant medications added, dose regimen of bosutinib updated, action taken with bosutinib updated as dose not changed (previously unknown), and event (chest rash rated grade 1) added.

Follow-up (29Oct2019): New reported information included pericarditis, updated action taken, treatment received.

Follow-up (28Jan2020): New information received from the investigator includes subject's weight, relevant medical history, details on bosutinib treatment, lab data, and new episode of pericarditis,outcome and causality assessment (The investigator assessed the second episode of pericarditis as non-serious, rated grade 1, related to bosutinib and unrelated to concomitant drugs.)

Follow-up (31Jan2020): New information includes: updated start date of concomitant drugs atenolol, acetylsalicylate lysine and ezetimibe/simvastatin from 2014 to 2004, and confirmation that bosutinib was temporarily withdrawn upon 1st episode of pericarditis and permanently withdrawn upon the second episode of pericarditis.

Amendment: This follow-up is being submitted to amend previously reported information. The sentence "This is a non-interventional clinical study case reporting non-serious events only." was removed from the narrative.

Follow-up (11Mar2023): new information received from the investigator via the CRO.
Updated information: patient initials updated, start date of concomitant drugs updated, updated outcome of rash and stop date added.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (10Oct2023): This is a follow-up report for a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL). New information received from the investigator via the CRO. Updated information: Reporter causality provided for events asthenia, flu like syndrome, insomnia, tinnitus, and diarrhea (previously not reported) and reaction data (updated onset and recovery dates for events asthenia, insomnia, tinnitus, and diarrhea and additional clinical details for action taken for events asthenia, flu like syndrome, insomnia, tinnitus, and diarrhea).

Amendment: This follow-up report is being submitted to amend previous information: to amend seriousness of event pericarditis (onset 29Nov2019) to non-serious.

Follow-up (06Dec2023): new information received from the investigator via the CRO.
Medical history added: Chronic myeloid leukemia (ongoing).

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

Case Comment: Considering a plausible drug-event temporal association and/or the consistency of this event with the known safety profile of the suspect product, there is a reasonable possibility that the reported events are related to bosutinib. Event insomnia grade 1 is most likely related to an intercurrent or underlying condition and unrelated to suspect 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		Blood pressure measurement	normal	
2	29-NOV-2019	Echocardiogram	pericardial effusion	
3		Pathology test	inflammatory liquid without suspected cell	

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	15-OCT-2019 / 29-NOV-2019; 46 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hip arthrosis (Osteoarthritis);
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
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		PRIVACY		67 Years	Female	98.00 kg		APR	2019

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

Abdominal abscess fistulized in the skin [Abdominal abscess]
Right pleural effusion [Pleural effusion]
Diarrhea [Diarrhoea]
Cramps [Muscle spasms]
Voice hoarseness [Dysphonia]
Weight gain [Weight increased]
Weight loss [Weight decreased]
Left lumbar swelling [Abdominal distension]
Transit disorders preceding the appearance of abscesses [Functional gastrointestinal disorder]

(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) 29-APR-2019 / 16-SEP-2020

19. THERAPY DURATION
#1) 1 year 4 months 19 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) SPIRONOLACTONE (SPIRONOLACTONE) ; Ongoing
#2) NEBIVOLOL (NEBIVOLOL) ; Ongoing
#3) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; DEC-2018 / Ongoing
#4) IMATINIB (IMATINIB) ; 02-FEB-2021 / 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)
DEC-2018 to DEC-2018	Relevant Med History	Thyroidectomy total (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.
2019344966

24c. DATE RECEIVED BY MANUFACTURER
06-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

Persisting abdominal abscess fistulized in the skin [Abdominal abscess]

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 67-year-old female subject entered the study and started to receive bosutinib (BOSULIF), via an unspecified route of administration from 29Apr2019 at 200 mg, once a day for an unspecified indication. Medical history included ongoing arterial hypertension, total thyroidectomy in Dec2018, operated ovarian tumor, abdominal access in January 2015 following a gynecological procedure performed in Apr2014 (bilateral oophorectomy, omentectomy, appendicetomy, peritoneal biopsy), ongoing chronic myeloid leukemia. Then, a CT scan performed in 2015 found cellulitis of the left flank with a sign in the left psoas. She was operated on by laparotomy and had her abscess removed. In 2018 there was another overhaul of a left lumbar collection. Concomitant medications included spironolactone ongoing for arterial hypertension, nebivolol ongoing for arterial hypertension, and levothyroxine sodium (LEVOTHYROX) ongoing from Dec2018 for hypothyroidism, imatinib ongoing from 02Feb2021 for chronic myeloid leukemia. The subject experienced diarrhea on 19May2019, cramps in Apr2019, voice hoarseness on 13Jun2019, weight gain, grade 1 on 30Apr2019. On 07Jul2020, the subject developed right pleural effusion, rated grade 2. The pleural effusion was discovered fortuitously during a thoracoabdominopelvic CT performed on 07Jul2020. A drainage was performed on 10Jul2020. 700 ml was collected. The analysis was in favor of an inflammatory liquid without suspicious cell. The pleural effusion persisted during the consultation on 20Jul2020. The evolution was ongoing. As of 24Sep2020 there was increase of pleural effusion at drainage distance. Bosutinib being maintained, it was decided to temporarily withdrawn it. Effusion had to be drained again. The events had not resolved. As of 11Feb2021, it was reported that in Sep2019, the subject observed left lumbar swelling. The doctor does not wish to declare it as part of the study because it is an event which was already present before. The subject described transit disorders preceding the onset of her abscesses and probably corresponding to an impact of the abscess on the intestine which passes on contact. In 2020, the subject had still left lumbar discharge. Hospitalization from 25Oct2020 to 13Nov2020 for management of chronic anterocutaneous fistula (26Oct2020 placement of a left ureteral catheter, resection of small intestine with anastomosis, sigmoid resection, placement of a colostomy). In surgical suites anemia with transfusion and residual collection. As of 10Dec2020, the subject was doing well, with ostomy that works and still a small healing defect. Note during this period a weight loss of 101kg to 80kg between 28Oct2019 and 12Oct2020. The 07Jul2020 scanner found an abundant right pleural effusion declared in the CRF but not in the SAE. Drainage on 10Jul2020. Talc pleurodesis on 30Sep2020 with hospitalization from 27Sep2020 to 05Oct2020 resulting in stopping bosutinib. The doctor did not wish to report this SAE but had indicated that it was unrelated to bosutinib because the pleural effusion was still present after stopping bosutinib on 16Sep2020. As of 11Mar2023, decision to stop bosutinib on 15Sep2020, hoping for an improvement, the effusion having to be drained again. The patient would finally be hospitalized from 27Sep2020 to 05Oct2020, for a right pleural talc and pleural biopsy on 30Sep2020. At the M21 theoretical follow-up visit, it was decided to discuss with the radiologist. A small residue of the right upper lobe, a pleural cavity with thickened walls and a residual compartmentalized pleural effusion of great abundance, without possible improvement, were noted. Treatment with bosutinib could not therefore be resumed. Exit from the Boseval study was therefore validated during this follow-up visit. The subject experienced abdominal abscess fistulized in the skin on 03Oct2019, rated as grade 3 and considered as serious (hospitalization). The subject also experienced persisting abdominal abscess fistulized in the skin in Jul2020 and was rated as grade 2, non-serious. The last action taken in response to the events was permanently withdrawn on 16Sep2020. The outcome of event right pleural effusion was recovered on 27Jan2021, of event abdominal abscess fistulized in the skin was resolved with sequel on 18Oct2019, of event voice hoarseness was recovered on an unspecified date in Jul2019, of event weight gain was recovered on an unspecified date, of cramps, diarrhea was not recovered, of persisting abdominal abscess fistulized in the skin was resolving, of other events was unknown.

According to the investigator, event right pleural effusion was related to bosutinib and unrelated to concomitant medications, event abdominal abscess fistulized in the skin, voice hoarsenes, persisting abdominal abscess fistulized in the skin was unrelated to bosutinib and concomitant drugs.

The reporter's assessment of the causal relationship of "diarrhea", "cramps", "weight gain", "weight loss", "left lumbar swelling" and "transit disorders preceding the appearance of abscesses" 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.

The adverse events were collected by the nurse during but not clinically significant for the physician.

Follow-up (08Aug2019): This case is being submitted to notify that the initial information for this case was first received by the Company on [08Aug2019] and not on [07Aug2019] as previously reported. Due to safety database technical limitations, the field "Initial Receipt Date" can no longer be modified.

Follow-up (26Jul2020): New information received from the CRO includes: subject's details (age, gender, weight and height), lab data, bosutinib dosage, medical history, concomitant medications, new event (right pleural effusion).

Follow-up (25Sep2020): New information includes: increase of pleural effusion at drainage distance, drained again, updated action taken, updated investigator's causality assessment for pleural effusion.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (11Feb2021): New information received from investigational site via clinical team includes: additional medical history, additional lab data, enter study date, clarification of abundant right pleural effusion, reaction data (seriousness criteria, new events abdominal abscess fistulized in the skin, weight loss, left lumbar swelling, transit disorders preceding the appearance of abscesses).

Follow-up (30Apr2021): New information received from CRO included: Causality updated for pleural effusion (related to bosutinib).

Follow-up (11Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from study site for protocol B1871047.
Updated information included: lab data (pleural biopsy), action taken for Bosutinib updated to permanently withdrawn.

Follow-up (12Oct2023 and 13Oct2023): This is a non-interventional study follow-up report received from CRO.
Updated information included: medical history, suspect drug data (start date), new concomitant medication imatinib, reaction data (reporter causality of event abdominal abscess fistulized in the skin, voice hoarsenes, outcome of event right pleural effusion, voice hoarseness, outcome and seriousness of event abdominal abscess fistulized in the skin), new event (persisting abdominal abscess fistulized in the skin).

Follow-up (14Nov2023): This is a non-interventional study follow-up report for protocol B1871047 received from the clinical team.
Updated information following reconciliation included: seriousness of event right pleural effusion was updated to not serious: this right pleural effusion was discovered fortuitously. It cannot be considered as serious. The notion of "drainage" does not make this event serious. The drainage is mandatory to caracterize the type of effusion, to adapt the treatment of the effusion and to decide if bosutinib is to be stopped or not

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

Follow-up (06Dec2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician) for protocol B1871047.
Updated information: event details (Abdominal abscess fistulized in the skin was rated as grade 3 and considered as serious (hospitalization); Persisting abdominal abscess fistulized in the skin occurred in Jul2020 and was rated as grade 2).

Case Comment: Based on available information the company cannot exclude a contributory role of bosutinib to the reported non serious pleural effusion.
Based on the reasonable temporal association and considering no alternative explanations for the reported, diarrhea, cramps, voice hoarseness, and weight gain, the Company cannot completely rule out the possible causality between the reported events and bosutinib administration. Abdominal abscess fistulized in the skin, weight loss, left lumbar swelling, transit disorders preceding the appearance of abscesses, and persisting abdominal abscess fistulized in the skin are not related to bosutinib but are most likely related to the underlying malignancy. This case will be updated when new information becomes available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	APR-2014	Biopsy peritoneum	Unknown results	
2	30-SEP-2020	Biopsy pleura	Unknown results	
3	2015	Computerised tomogram left psoas	cellulitis of the left flank with a sign in the	
4	07-JUL-2020	Computerised tomogram	Right pleural effusion	
5	JUL-2020	Pleural fluid analysis	inflammatory liquid without suspicious cell	
6	30-APR-2019	Weight	Gain kg	
7	28-OCT-2019	Weight	101 kg	
8	12-OCT-2020	Weight	80 kg	

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Ovarian neoplasia (Ovarian neoplasm);
Unknown	Relevant Med History operated ovarian tumor	Cancer surgery (Cancer surgery);
APR-2014 to APR-2014	Relevant Med History gynecological procedure (bilateral oophorectomy, omentectomy, appendicetomy, peritoneal biopsy)	Bilateral oophorectomy (Oophorectomy bilateral);
APR-2014 to APR-2014	Relevant Med History gynecological procedure (bilateral oophorectomy, omentectomy, appendicetomy, peritoneal biopsy)	Omentectomy (Omentectomy);
APR-2014 to APR-2014	Relevant Med History gynecological procedure (bilateral oophorectomy, omentectomy, appendicetomy, peritoneal biopsy)	Appendectomy (Appendicectomy);
JAN-2015 to JAN-2015	Relevant Med History abdominal access	Abdominal wall operation (Abdominal wall operation);
2015 to 2015	Relevant Med History cellulitis of the left flank with a sign in the left psoas	Cellulitis (Cellulitis);
2015 to 2015	Relevant Med History operated on by laparotomy and had her abscess removed.	Laparotomy (Laparotomy);
2015 to 2015	Relevant Med History operated on by laparotomy and had her abscess removed.	Abscess (Abscess);
2018 to 2018	Relevant Med History another overhaul of a left lumbar collection	Back surgery (Spinal operation);
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		PRIVACY		53 Years	Male	73.00 kg		MAY	2018

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

Transient decreased appetite [Decreased appetite]
transit acceleration [Intestinal transit time increased]
Hot flush [Hot flush]
Diffuse back pain related to physical activity [Back pain]
forearm infection [Infection]
Diarrhea [Diarrhoea]
abdominal pain [Abdominal pain]
RHINOPHARYNGEAL INFECTIONS [Nasopharyngitis]

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)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, daily	#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-MAY-2018 / 13-JUN-2018	#1) 31 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) ALLOPURINOL (ALLOPURINOL) ; Ongoing
#2) TAHOR (ATORVASTATIN CALCIUM) ; Ongoing
#3) HYDROCORTISONE (HYDROCORTISONE) ; Ongoing
#4) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#5) TESTOSTERONE (TESTOSTERONE) Injection ; 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	Panhypopituitarism (Hypopituitarism)
Unknown 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.
2019345012

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: 2019345012

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) (Nurse) for protocol B1871047. This is a Non-Interventional Study report with non-serious events only.

A 53-year-old male subject started to receive bosutinib (BOSULIF, Film-coated tablet) via an unspecified route of administration from 14May2018 to 13Jun2018 at 200 mg daily and from 14Jun2018 to 20Apr2021 at 300 mg daily for ongoing chronic myeloid leukemia. The subject had a relevant history of ongoing panhypopituitarism, ongoing hypercholesterolaemia, and hyperuricaemia. Concomitant medications included ongoing allopurinol for panhypopituitarism, ongoing atorvastatin calcium (TAHOR) for hypercholesterolemia, ongoing hydrocortisone for panhypopituitarism, ongoing levothyroxine sodium (LEVOTHYROX) for panhypopituitarism, and ongoing testosterone for panhypopituitarism by injection. The subject experienced hot flush from May2018 and resolved on 11Jun2018, diffuse back pain related to physical activity from May2018 and resolved on 07Dec2018, forearm infection from 01Jun2018 and resolved on an unspecified date in Jun2018, diarrhea from Sep2018 and resolved on 07Dec2018, transient decreased appetite from May2018 and resolved on 11Jun2018, abdominal pain from unspecified date in Dec2018 and resolved on 07Dec2018. The events were considered not clinically significant for the physician (not reported during consultation). In May2018, the subject also experienced transit acceleration rated grade 2 and reported as non-serious. The event was resolved on 20Aug2018. In Dec2018, the subject experienced rhinopharyngeal infections rated grade 2 and reported as non-serious. The event was resolved in 2019. The action taken in response to events for bosutinib was dose not changed.

The reporter considered transit acceleration rated grade 2, diarrhea and abdominal pain rated grade 1related to bosutinib. The reporter considered transient decreased appetite, hot flush, diffuse back pain related to physical activity, forearm infection rated garde 2 and rhinopharyngeal infections not related to bosutinib.
The reporter considered all the events unrelated to concomitant drugs.

Follow-up (08Aug2019): New information received from CRO includes: subject's information (birth date, gender, height and weight) added, medical history updated, dose regimen of bosutinib updated, concomitant medications added, and new events (transit acceleration rated grade 2, rhinopharyngeal infections rated grade 2) added.

Follow-up (03Oct2023): This is a follow-up to a non-interventional study for protocol B9991045 received from the investigator site via the CRO. Updated information includes: bosutinib details, event 'diffuse pain related to physical activity' was updated to 'diffuse back pain related to physical activity', causality for all events.

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

Case Comment: The Company considers the reported transient decreased appetite might be related to the administration of bosutinib, based on the reasonable temporal association and the known safety profile of bosutinib. Similarly, the Company cannot completely exclude the possible causality between the reported transit acceleration rated grade 2 and bosutinib administration. Conversely, the reported hot flush, Diffuse pain related to physical activity, forearm infection, diarrhea (occurred 4 months after bosutinib initiation), rhinopharyngeal infections rated grade 2, and abdominal pain are unlikely related to bosutinib. Those events are more likely inter-current disease.

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)	14-JUN-2018 / 20-APR-2021; 2 years 10 months 7 days

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	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		PRIVACY		55 Years	Female	85.00 kg	09	JUL	2018

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

Diarrhea [Diarrhoea]
COPD [Chronic obstructive pulmonary disease]

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 case reporting non-serious event

(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) 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) 12-APR-2017 / 25-JUL-2018	#1) 470 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TRACLEER [BOSENTAN] (BOSENTAN) ; Ongoing
#2) LASILIX [FUROSEMIDE] (FUROSEMIDE) ; 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	
Unknown	Relevant Med History	Obesity (Obesity)

(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.
2019345107

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

24c. DATE RECEIVED BY MANUFACTURER
09-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

only.
A 55 years female patient started to receive oral bosutinib (BOSULIF), 300 mg once daily, from 12Apr2017 to 25Jul2018, and 400 mg once daily ongoing from 26Jul2018, for an unknown indication.
Medical history included pulmonary arterial hypertension (ongoing) and obesity.
Concomitant medications included ongoing oral tracleer (BOSENTAN) for pulmonary arterial hypertension, and ongoing oral furosemide (LASILIX) for pulmonary arterial hypertension.
The subject experienced bronchitis from 14Jun2018 to Jun2018 and the following events related to tracleer: palpitation, chest pain, diarrhea, muscle cramps, fatigue, malaise between Jul2018 and Mar2019. These events were mentioned by the nurse during the phone call and were not considered as significant by the physician as they were not mentioned in the consultation. The reporter asked that these events should not be reported.
The patient experienced also cough from Nov2017 to Nov2017, anxiety attack Nov2017 to Nov2017, upper respiratory tract infection Nov2017 from Feb2019 to Feb2019, episode of false road with cough and paresthesia with cough from Feb2019 to Feb2019, feeling of chest tightness from Feb2019 to Feb2019. These events were reported by the pneumologist in the context of following of her pulmonary arterial hypertension and not reported by the physician in the CRF.
The subject presented with weight gain grade 2 on 14Feb2019 not related to bosutinib and not no declared by the physician because this was an obese subject who had voluntarily lost weight.
The subject experienced chronic obstructive pulmonary disease (COPD) on 09Jul2018 and diarrhea on 26Jul2018. Action taken for bosutinib was dose not changed. The outcome of event diarrhea was not recovered, of event COPD was recovered on 29May2019.

The investigator considered the events COPD as not related to bosutinib and concomitant medications. He considered the event diarrhea as related to bosutinib and not recovered related to concomitant medications.

Follow-up (09Mar2023): This is a Non-Interventional Study follow-up report received from the investigational site via CRO. Updated information included: medical history "pulmonary arterial hypertension" was ongoing, outcome of event diarrhea updated from recovered to not recovered and causality updated to not related to concomitant treatments.

Case Comment: Based on the information provided and the known safety profile of the suspect drug, there is a reasonable possibility that the reported event diarrhea is related to bosutinib administration. The reported event chronic obstructive pulmonary disease (COPD) is more likely due to an underlying medical condition and is 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	400 mg, 1x/day; Oral	Unknown	26-JUL-2018 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Pulmonary arterial hypertension (Pulmonary 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		PRIVACY		65 Years	Male	115.00 kg	13	JUN	2019

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

Heartburn [Dyspepsia]
cold [Nasopharyngitis]

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. This is a non-interventional clinical study case reporting non-serious events 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, daily

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

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

18. THERAPY DATES(from/to)
#1) 02-MAY-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) IRBESARTAN (IRBESARTAN) ; Ongoing
#2) AMLODIPINE (AMLODIPINE) ; Ongoing
#3) ATORVASTATIN (ATORVASTATIN) ; Ongoing
#4) KARDEGIC (ACETYLSALICYLATE LYSINE) ; 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	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.
2019373850

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

24c. DATE RECEIVED BY MANUFACTURER
25-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

A 65-year-old male subject started to receive bosutinib (BOSULIF) on 02May2019 at 300 mg daily for unspecified indication. Medical history included ongoing arterial hypertension, ongoing type 2 diabetes mellitus, renal failure from 2017 and aortic aneurysm from 2013. Concomitant medications included irbesartan oral for arterial hypertension, amlodipine oral for arterial hypertension, atorvastatin oral for dyslipidemia and acetylsalicylate lysine (KARDEGIC) oral for cardiac prophylaxis. The subject experienced heartburn grade 1 on 13Jun2019. The action taken in response to the event heartburn was dose not changed. The subject experienced cold, grade 1 on 03Feb2020. The action taken in response to the event cold was dose not changed. The outcome of the event heartburn was recovered on 11Jul2019. The outcome of the cold was recovering.

The investigator considered the event heartburn as related to the study drug bosutinib and not related to concomitant medications. The investigator considered the event cold was unrelated to the study drug bosutinib.

Follow-up (02Mar2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. New information received includes: reaction data (added non-serious event cold).

Follow-up (25May2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. New information received from the investigational site via the CRO includes: event cold resolved in Feb2020.

Case Comment: Based on the plausible temporal association, a contributory role cannot be excluded for the event heartburn for bosutinib. The event cold is most likely an intercurrent medical condition, unrelated to the suspect drug.
This case will be updated when new information becomes available.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2017 to Unknown	Relevant Med History	Renal failure (Renal failure);
2013 to Unknown	Relevant Med History	Aortic aneurysm (Aortic aneurysm);

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		PRIVACY		51 Years	Female	97.50 kg	30	MAY	2019

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

NAUSEA [Nausea]
VOMITNG grade 1 [Vomiting]
DIARRHEA grade 3 [Diarrhoea]
PYROSIS [Dyspepsia]
epigastralgia [Abdominal pain upper]

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) 200 mg, daily	#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)	19. THERAPY DURATION
#1) 28-MAY-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) IMATINIB (IMATINIB) ; Unknown / 19-MAY-2019

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.
2019427526

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

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

A 51-year-old female patient received bosutinib (BOSULIF), first regimen since 28May2019 at 200 mg daily, oral, second regimen from 24Jun2019 to 07Mar2020 at 300 mg daily, oral and third regimen since 07Mar2021 (ongoing) at 200 mg daily for chronic myeloid leukaemia. The patient had no relevant medical history. Concomitant medication(s) included: IMATINIB, stop date: 19May2019.
The subject experienced nausea grade 1 on 30May2019. The event nausea was grade 1 on 30May2019 and became grade 2 on 08Jun2019. The subject also experienced vomiting grade 1 on 02Jun2019, diarrhea grade 3 on 02Jun2019. In Sep2019, the subject experienced pyrosis considered non-serious and rated grade 1. In Sep2019, the subject experienced epigastralgia considered non-serious and rated grade 1. Awareness of the events pyrosis and epigastralgia by the doctor on 13Dec2019. The outcome of nausea was resolved on 15Jun2019, vomiting grade 1 was recovered on 24Jun2019, diarrhea grade 3 was resolved on 08Jun2019, epigastralgia was resolved on 18Jun2020 and pyrosis was resolved on 18Jun2020. The action taken in response to the event for bosutinib was dosage reduced, for imatinib was permanently withdrawn.

The reporter considered "nausea", "vomitng grade 1", "diarrhea grade 3", "pyrosis" and "epigastralgia" related to bosutinib.

The investigator considered that events vomiting, diarrhea and nausea (2 episodes) were related to bosutinib and unrelated to imatinib.

Follow-ups (03Dec2019): New information received from the CRO and clinical team includes updated reporter causality for bosutinib (from unrelated to related) and updated outcome for the event nausea grade 1 (from not recovered to recovered)

Follow-up (23Jan2020): New information received from the CRO includes new adverse events epigastralgia and pyrosis.

Follow-up (07Jan2021): New information received from the CRO includes: additional dosing regimen of study drug bosutinib and event details.

Follow-up (07Sep2022): This is a non-interventional study report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information: new dosage for bosutinib added, weight updated, outcome of events pyrosis and epigastralgia updated to (previously not resolved) and both events considered related to bostinib; action taken with bostunib changed to dose reduced.

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 included: First dose regimen of bosutinib was updated to from 28May2019 at 200 mg daily (previously from 20May2019 at 300 mg daily).

Case Comment: Based on the known product safety profile, the Company concurs with the investigator that reported events nausea, vomiting and diarrhea are related to bosutinib. Based on follow up information and on resolution of events as response to dose reduction the events epigastralgia and pyrosis are considered 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	300 mg, daily; Oral	CML (Chronic myeloid leukaemia)	24-JUN-2019 / 07-MAR-2020; 8 months 13 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	CML (Chronic myeloid leukaemia)	07-MAR-2021 / 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		PRIVACY		79 Years	Male	77.00 kg		MAY	2019

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

Constipation [Constipation]
Fatigue [Fatigue]
Diarrhea following the treatment against constipation [Diarrhoea]
Epigastric pain [Abdominal pain upper]

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)
#1) 200 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) 15-MAY-2019 / 02-JUN-2019

19. THERAPY DURATION
#1) 19 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	Abdominal cramps (Abdominal pain)
Unknown to Ongoing	Relevant Med History	Anxiety (Anxiety)

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.
2019469382

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

NAME AND ADDRESS WITHHELD.

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:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
A 79-year-old male patient received bosutinib (BOSULIF), first regimen from 15May2019 to 02Jun2019 at 200 mg 1x/day, second regimen from 03Jun2019 to 28Jul2019 at 300 mg 1x/day, third regimen from 29Jul2019 to 30Nov2020 at 400 mg 1x/day and fourth regimen since 30Nov2020 at 500 mg 1x/day. The patient's relevant medical history included: "abdominal cramps" (ongoing); "anxiety" (ongoing); "Chronic myeloid leukemia" (ongoing). There were no concomitant medications. On 15Jul2019, the subject was rather disturbed by constipation (unspecified onset date in 2019). The event constipation was rated grade 2 and not serious. On 14Oct2019, the tolerance of bosutinib was correct except from a severe constipation still present despite daily intake of 2 bags of lactulose (manufacturer unknown). On unspecified date in 2020, the subject experienced diarrhea grade 1, non serious, following the treatment for constipation. It was reported that diarrhea onset date was between 2 consultations. In May2019, the subject experienced fatigue considered non-serious and rated grade 1. The patient reported on 23May2019 (by email) that he never had any relevant secondary effect of the new treatment, except a slight fatigue in the 2nd to the 3rd hours following the treatment intake. In Dec2019, the subject experienced epigastric pain, grade 1, non-serious. In medical consultation report of 27Jan2020 lactulose was noted not being efficient enough, the treatment was modified by general practitioner. There was diarrhea following this. Consequently the subject was not taking treatment regularly for constipation and was alternating severe constipation and diarrhea. Abdominal discomfort was reported with epigastric pains and significant meteorism. No action was taken with study drug in response to the events. The events diarrhea was resolved in 2020, and epigastric pain was resolved on 27Apr2020, whereas fatigue resolved on 14Oct2019 and constipation recovered on 10Mar2021.

The investigator considered the events constipation, and fatigue were related to study drug bosutinib and unrelated to any concomitant drug. The investigator considered the events diarrhea following the treatment for constipation and event Epigastric pain was unrelated to study drug bosutinib or to concomitant drug.

Follow-up (06Nov2019). New information from the investigational site included: additional non-serious event (fatigue), start and stop date of the new event, outcome and causality for the new event.

Follow-up (13Nov2019): New information received from the investigational site includes: the subject had no concomitant treatment. The event constipation was still ongoing.

Follow-up (30Jan2019): New information reported from the investigational site includes: exact dates when bosutinib regimen at 300 mg daily was stopped and regimen at 400 mg daily was started and additional non-serious events diarrhea and epigastric pain.

Follow-up (24Feb2020): New information received from the study coordinator includes: approximate onset date of diarrhea (between 14Oct2019 and 27Jan2020).

Follow-up (14Aug2020): New information received from the investigator includes diarrhea onset date updated.

Follow-up (01Jun2022): This is a Non-Interventional Study follow-up report.
Updated information: updated outcome for event constipation from not recovered to recovered on 10Mar2021.

Follow-ups (27Dec2022, 27Dec2022, 27Dec2022): This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information:
Bosulif treatment dates updated, outcome of events diarrhea, epigastric pain updated, changed onset date for Epigastric pain, Event assessment for Epigastric pain Causality (changed from Related to Unrelated).

Amendment: This follow-up report is being submitted to amend previous information: onset of constipation (updated from "15Jul2019" to "2019").

Case Comment: Based on the information provided and temporal association, there is a reasonable possibility that the reported events constipation and fatigue are related to the study drug bosutinib. The event "diarrhea following the treatment for constipation" and epigastric pain were unrelated to study drug 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; Regimen #2	300 mg, 1x/day; Unknown	Unknown	03-JUN-2019 / 28-JUL-2019; 59 days

Mfr. Control Number: 2019469382

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	400 mg, 1x/day; Unknown	Unknown	29-JUL-2019 / 30-NOV-2020; 1 year 4 months 2 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	500 mg, 1x/day; Unknown	Unknown	30-NOV-2020 / Unknown; Unknown

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);

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		PRIVACY		69 Years	Female	56.00 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)

Absence of right pedal pulse [Pulse absent]

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-years-old female patient started to receive bosutinib (BOSULIF),

(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) 04-SEP-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 Of both carotids at 30 and 35%	Atheroma coronary artery (Arteriosclerosis coronary artery)

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.
2019471154

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 2019471154

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

via an unspecified route of administration from 04Sep2018 and ongoing at 200 mg, daily for an unspecified indication. Medical history included ongoing arteriosclerosis coronary artery, of both carotids at 30 and 35%. The patient's concomitant medications were not reported. The patient experienced absence of right pedal pulse rated as grade 1 on 25Feb2019 with outcome of not recovered. Relevant test included: On 25Feb2019: left pedal pulse +, right -, no arterial murmur, regular heart sounds. No edema. On 18Oct2019: left pedal pulse +, right -, no carotid or femoral murmur. No claudication. Regular heart sounds. An arterial Doppler of the lower limbs was requested on 18Oct2019. The action taken in response to the event for bosutinib was dose not changed.

According to the investigator, the event was not related to study drug or concomitant medication.

Follow-up (12Jul2023): This is a follow up non-interventional study report (Post Authorization Safety Study) for Protocol B1871047. Updated information included: patient initials updated and added Post Auth. Safety Study classification.

Follow-up (27Jul2023): This is a follow up non-interventional study report (Post Authorization Safety Study) for Protocol B1871047. Updated information included: start date and updated frequency of bosutinib.

Case Comment: There are no elements supporting a causative role of bosutinib for the reported Absence of right pedal pulse (Pulse absent). The event is deemed to be an incidental occurrence.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	25-FEB-2019	Physical examination regular heart sounds	left pedal pulse +, right -, no arterial murmur,	
2	18-OCT-2019	Physical examination	left pedal pulse +, right -, no carotid or femoral murmur. No claudication. Regular heart sounds.	

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		PRIVACY		71 Years	Male	75.00 kg	09	SEP	2019

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

Basithoracic burning at right [Chest pain]
Hepatic cytolysis [Hepatic cytolysis]
Diarrhea grade 3 [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

(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) 26-AUG-2019 / 26-SEP-2019	#1) 1 month 1 day

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) CO-RENITEC (ENALAPRIL MALEATE, HYDROCHLOROTHIAZIDE)
#2) ADVAGRAF (TACROLIMUS) ; 2003 / Ongoing
#3) MOPRAL [OMEPRAZOLE MAGNESIUM] (OMEPRAZOLE MAGNESIUM) ; Unknown
#4) AMLOR (AMLODIPINE BESILATE) ; 2003 / 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
2003 to Ongoing	Relevant Med History	Liver transplant (Liver transplant)
2003 to 2003	Relevant Med History recovered	Hepatitis C (Hepatitis C)

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.
2019473696

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
05-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 non-interventional clinical study case reporting non-serious events only.
A 71-year-old male patient started to receive bosutinib (BOSULIF, film-coated tablet) via an unspecified route of administration from 26Aug2019 to 26Sep2019 at 400mg daily, then from 27Sep2019 to 04Oct2019 at 200 mg daily for an unspecified indication. Medical history included liver transplant from 2003, ongoing, hepatitis C on 2003 (recovered on 2003). Concomitant medications included enalapril maleate, hydrochlorothiazide (CO-RENITEC) from an unspecified date until 2019, tacrolimus (ADVAGRAF) from 2003 and ongoing for anti-liver transplant rejection, omeprazole magnesium (MOPRAL), and amlodipine besilate (AMLOR) from 2003 and ongoing for arterial hypertension. The patient experienced basithoracic burning at right grade 2 on 09Sep2019; hepatic cytolysis grade 3 on 01Oct2019; and diarrhea grade 3 on 09Sep2019. All events were reported as non-serious. Laboratory data was not provided. The action taken with bosutinib was dose reduced in response to basithoracic burning at right and diarrhea; and discontinued in response to hepatic cytolysis on 04Oct2019. It was reported that event didn't reappear after reintroduction. Treatment received was not reported. The outcome of the events basithoracic burning was recovered on 04Oct2019, hepatic cytolysis was recovered on 14Oct2019, diarrhea was recovered on 04Oct2019.

According to the investigator basithoracic burning at right and hepatic cytolysis were related to study drug and unrelated to concomitant treatment, diarrhea was related to study drug, but unrelated to concomitant treatment.

Follow-up (09Apr2020). This follow-up is received from the investigational site. DCA form for hepatic event was completed.
Hepatic cytolysis was new event. The subject presented with following symptoms: abdominal pain of right hypochondrium and diarrhea. Lab test were done in year preceding the start of treatment. On 07May2019 hepatic work-up was normal with bilirubin at 6 umol/l, ASAT 24IU/L, ALAT 26IU/l.
Baseline test at treatment beginning was done. On 30Jul2019 hepatic work-up was normal with bilirubin at 7.9 umol/l, ASAT 18IU/L, ALAT 22IU/l.
During the treatment the test was done 01Oct2019 that showed hepatic work-up was increased with normal bilirubin at 7 umol/ (0-21), ASAT 135IU/L (N 0-50), ALAT 346IU/l (N 0-50), GGT 169 IU/l (N 0-60), PAL 134 IU/l (35-130).
After the treatment was discontinued the test was done on 29Oct2019 and showed normal bilirubin at 7 umol/, ASAT 25 IU/L, ALAT 42 IU/l, GGT 124 IU/L, PAL 96 IU/l.
At event onset the subject taking converting enzyme inhibitor enalapril maleate, hydrochlorothiazide (CO-RENITEC) 1 tablet three times discontinued on unspecified date in 2019, tacrolimus (ADVAGRAF) 3 mg/3 times a day (for liver transplant done in 2003) and omeprazole magnesium (MOPRAL) 40 mg/day.
The subject had medical history of viral hepatitis: hepatitis C recovered in 2004, hypertension, liver transplant in 2003 and then hepatic fibrosis, ongoing dyslipidemia, inguinal hernia (operated eventration), endobrachyoesophagitis in 2016, severe chronic alcoholism 15 years ago.
The subject did not have family history of hepatic pathology. The subject was not drinking alcohol anymore.
On 28Sep2019 eosinophils were 0.94 x10^9/l (N 0.04-0.56), on unspecified date lipase was 17 IU/l (N 13-60).
On 01Oct2019 blood level of concomitant drug tacrolimus (ADVAGRAF) = dose was normal for.

Follow-up (14Apr2020): New information received from investigational site includes bosutinib dose, concomitant details and updated causality for diarrhea as unrelated to concomitant drug.

Follow-up (30Apr2020): New information received from investigational site includes suspect product data (start date of medication added), concomitant product data (added route of administration for amlodipine besilate), and clinical course details.

Follow-up (05May2020): New information received from the CRO includes: stop date of 400 mg regimen (26Sep2019) and new 200 mg dosage regimen added, start date of tacrolimus, and updated indication of amlodipine besilate.

Case Comment: Based on plausible temporal association and known drug safety profile, there is a reasonable possibility that the reported events are related to the study drug, bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	07-MAY-2019	Alanine aminotransferase	26 IU/l	50 0
2	30-JUL-2019	Alanine aminotransferase	22 IU/l	50 0
3	01-OCT-2019	Alanine aminotransferase	346 IU/l	50 0
4	29-OCT-2019	Alanine aminotransferase	42 IU/l	50 0
5	07-MAY-2019	Aspartate aminotransferase	24 IU/l	50 0
6	30-JUL-2019	Aspartate aminotransferase	18 IU/l	50

Mfr. Control Number: 2019473696

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
				0
7	01-OCT-2019	Aspartate aminotransferase	135 IU/l	50 0
8	29-OCT-2019	Aspartate aminotransferase	25 IU/l	50 0
9	01-OCT-2019	Blood alkaline phosphatase	134 IU/l	130 35
10	29-OCT-2019	Blood alkaline phosphatase	96 IU/l	130 35
11	07-MAY-2019	Blood bilirubin	6 umol/l	21 0
12	30-JUL-2019	Blood bilirubin	7.9 umol/l	21 0
13	01-OCT-2019	Blood bilirubin	7 umol/l	21 0
14	29-OCT-2019	Blood bilirubin	7 umol/l	21 0
15	28-SEP-2019	Eosinophil count	0.94 x10 9/l	0.56 0.04
16	07-MAY-2019	Gamma-glutamyltransferase	unknown results IU/l	60 0
17	01-OCT-2019	Gamma-glutamyltransferase	169 IU/l	60 0
18	29-OCT-2019	Gamma-glutamyltransferase	124 IU/l	60 0
19		Lipase	17 IU/l	60 13

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	27-SEP-2019 / 04-OCT-2019; 8 days

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

#1) CO-RENITEC (ENALAPRIL MALEATE, HYDROCHLOROTHIAZIDE) Tablet ; Unknown / 2019

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hepatic fibrosis (Hepatic fibrosis);
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);
Unknown	Relevant Med History operated eventration	Inguinal hernia (Inguinal hernia);
2016 to Unknown	Relevant Med History	Endobrachyoesophagus (Barrett's oesophagus);
Unknown	Relevant Med History 15 years ago	Chronic alcoholism (Alcoholism);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hypertension (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		PRIVACY		65 Years	Male	115.00 kg	11	SEP	2019

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

diarrhea [Diarrhoea]
absence [Petit mal epilepsy]

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) 300 mg, daily

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

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

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

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.
2019497482

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 2019497482

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 65-year-old male subject started to receive bosutinib (BOSULIF), ongoing since 02May2019 at 300 mg daily for an unspecified indication. Medical history and concomitant medication were not provided.
The subject experienced absence grade 3, non-serious on 11Sep2019 and diarrhea grade 1, non- serious in Oct2019 (diarrhea was only one night). The action taken in response to the events was dose not changed. The subject recovered from absence and diarrhea in Oct2019.

The investigator considered the event diarrhea as related to the study drug bosutinib and the event absence as not related to the study drug bosutinib.

Follow-up (13Jan2021). New information reported from the investigational site via CRO includes updated absence onset and recovery date and diarrhea recovery date.

Follow-up (23May2023): This is a follow-up Non-Interventional Study report for protocol B1871047 received from investigational site via CRO. Updated information included: onset and recovery date of absence and investigator's assessment for absence (unrelated).

Case Comment: Based on the information available and the temporal relationship, the Company concurs with the investigator that the causal association between the reported absence and diarrhea and bosutinib administration cannot be excluded. Diarrhoea is consistent with the known drug safety profile.

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		PRIVACY		56 Years	Male	95.00 kg		DEC	2018

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

intermittent diarrhea [Diarrhoea]
Hepatic cytolysis [Hepatic cytolysis]

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 and post authorization safety study for Protocol B1871047. This is a Non-Interventional Study report with non-serious events 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) 400 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) 18-DEC-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) BISOPROLOL (BISOPROLOL) ; Ongoing
#2) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNE
#3) ZOPICLONE (ZOPICLONE) ; Ongoing
#4) OMEXEL (TAMSULOSIN HYDROCHLORIDE) ; 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
21-DEC-2017 to Ongoing	Relevant Med History	Atrial fibrillation (Atrial fibrillation)
Unknown to Ongoing	Relevant Med History for 10 years	Alcoholism (Alcoholism)

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.
2019510644

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
15-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

A 56-year-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 18Dec2018 to unknown date at 400 mg once daily, then from 01Jan2019 and ongoing at 400 mg once daily for an unspecified indication. Medical history included atrial fibrillation ongoing from 21Dec2017 and ongoing alcoholism. Concomitant drug included bisoprolol (unspecified trade name) for atrial fibrillation by oral route and ongoing, esomeprazole magnesium (INEXIUM) ongoing from 28Jan2019 by oral route for oesophagitis, zopiclone (unspecified trade name) ongoing by oral route for sleep disorder, and tamsulosin hydrochloride (OMEXEL) ongoing by oral route for prostate adenoma. In Dec2018, the subject had an intermittent diarrhea and was rated grade 1. In response to this event no action was taken with bosutinib. On 11Oct2019, the subject developed hepatic cytolysis which reported as non-serious and rated grade 3. In response to the event, dose of bosutinib was reduced. On 11Oct2019, ALT was 479 IU/L (normal range 10 - 49) and AST was 177 IU/L (normal range 10 - 34). The outcome of event intermittent diarrhea was recovered on 07May2019; outcome of event hepatic cytolysis was recovered on 14Dec2019. The investigator considered the events intermittent diarrhea and hepatic cytolysis were related to bosutinib and unrelated to concomitant drug.

Follow-up (26Nov2019): New information received from CRO included: medical history, concomitant medication, lab data, and additional event (hepatic cytolysis).

Follow-up (02Dec2019): New information received from the CRO included: new dosage of bosutinib, causality (event intermittent diarrhea was unrelated to concomitant medications).

Follow-up (15May2020) and (16May2020): New information received from the CRO and Clinical team included: Hepatic cytolysis recovered on 14Dec2019. Hepatic function was monitored the year before beginning of the treatment, at the beginning of the treatment and during the treatment. ALT was 24 IU/L on 13Aug2018 (reference value 40 IU/L), 31 IU/L on 17Dec2018 (reference value 40 IU/L), 21 IU/L on 25Jan2019 (reference value 40 IU/L), 232 IU/l on 07May2019 (reference value 49 IU/L), 479 IU/L on 11Oct20149 (reference value 49 IU/L) and 81 IU/L on 17Mar2020 (reference value 41 IU/L). Concomitant drugs included anti-arrhythmic, anticoagulant, other treatment for cardiac disorders or arterial pressure. Medical history included hypertension and alcohol consumption for 10 years.

Case Comment: Based on the known drug safety profile and temporal relationship, there is a reasonable possibility of the causal association between the reported intermittent diarrhea and bosutinib administration. The company considers that a causal relationship between hepatic cytolysis and bosutinib cannot be excluded due to plausible temporal association. However, a contributory role of ongoing alcoholism history may provide alternative explanation.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	13-AUG-2018	Alanine aminotransferase	24 IU/l	40
2	17-DEC-2018	Alanine aminotransferase	31 IU/l	40
3	25-JAN-2019	Alanine aminotransferase	25 IU/l	40
4	07-MAY-2019	Alanine aminotransferase	232 IU/l	49 10
5	11-OCT-2019	Alanine aminotransferase	479 IU/l	49 10
6	17-MAR-2020	Alanine aminotransferase	81 IU/l	41
7	11-OCT-2019	Aspartate aminotransferase	177 IU/l	34 10

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	Unknown	01-JAN-2019 / Ongoing; Unknown

Mfr. Control Number: 2019510644

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

#2) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNESIUM) ; 28-JAN-2019 / Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hypertension (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		PRIVACY		57 Years	Male	95.00 kg	28	JAN	2019

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

oesophagitis [Oesophagitis]

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, reporting non-serious events only. A 57-year-old male subject started to receive bosutinib (BOSULIF), ongoing since 01Jan2019 at 400 mg once daily for an unspecified indication.

(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) 01-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)

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.
2019510738

24c. DATE RECEIVED BY MANUFACTURER
02-DEC-2019

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

The subject had no medical history. Concomitant medications were not provided. The subject experienced oesophagitis grade 2, non serious on 28Jan2019. In response to the event oesophagitis, no action was taken with bosutinib. Symptomatic treatment esomeprazole (INEXIUM) was received. The subject recovered from the event on 06Jun2019.
The investigator considered that the event oesophagitis was unrelated to study drug bosutinib or any concomitant drug.

Follow-up (26Nov2019): New information received included: action taken.

Follow-up (02Dec2019): New information received included causality assessment (event was unrelated to bosutinib or any concomitant drug).

Case Comment: A possible contributory role of bosutinib to the event esophagitis cannot be completely excluded considering temporal association.

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		PRIVACY		74 Years	Male	78.00 kg	06	JUL	2019

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]
Nausea [Nausea]
Rash [Rash]

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) 300 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) 06-JUL-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) LASILIX [FUROSEMIDE] (FUROSEMIDE) ; 1996 / Ongoing
#2) MEDIATENSYL [URAPIDIL] (URAPIDIL) ; 24-MAY-2019 / Ongoing
#3) GLUCOPHAGE (METFORMIN HYDROCHLORIDE) ; 1996 / Ongoing
#4) CARDENSIEL (BISOPROLOL FUMARATE) ; 1996 / Ongoing
#5) COVERAM (AMLODIPINE BESILATE, PERINDOPRIL ARGININE) ; Unknown
#6) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Unknown

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

From/To Dates	Type of History / Notes	Description
1996 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
1996 to Ongoing	Relevant Med History	NIDDM (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.
2019525758

24c. DATE RECEIVED BY MANUFACTURER
10-MAY-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) for protocol B1871047.

A 74-year-old male subject was recruited in the above mentioned study and started to receive bosutinib (BOSULIF), via an unspecified route of administration, from 06Jul2019 and ongoing at dose of 300 mg, daily for an unspecified indication.
Relevant medical history included hypertension ongoing from 1996, non-insulin dependent diabetes (NIDDM) ongoing from 1996, sleep apnoea syndrome ongoing from 2011, and ischaemic cardiomyopathy ongoing from 1996, metabolic disease and hypertriglyceridemia.
Relevant concomitant medications included furosemide (LASILIX) ongoing from 1996 for ischemic cardiopathy and pulmonary arterial hypertension, urapidil (MEDIATENSYL) ongoing from 24May2019 for pulmonary arterial hypertension, metformin hydrochloride (GLUCOPHAGE) ongoing from 1996 for NIDDM and pulmonary arterial hypertension, bisoprolol fumarate (CARDENSIEL) ongoing from 1996 for ischemic cardiopathy and pulmonary arterial hypertension, amlodipine besilate/perindopril arginine (COVERAM) for pulmonary arterial hypertension, acetylsalicylate lysine (KARDEGIC) for pulmonary arterial hypertension. It was also reported that the subject was taking the following unspecified concomitant treatments: anti-arrythmia treatment, treatment modifying the disease, other treatments for cardiac diseases or arterial hypertension, treatments for pulmonary arterial hypertension. On 06Jul2019, the patient developed nausea. On 06Aug2019, the patient developed rash. Nausea and rash were both grade 1. On 18Aug2019, the patient developed diarrhea. On 19Aug2019, the patient developed hepatic cytolysis. Hepatic cytolysis was a new event. The subject did not present with following signs/symptoms: eruption, fever, abdominal pain, coma, flapping tremor, splenomegaly, sepsis, hepatic encephalopathy, pruritus, joint pain, nausea, ascites, weight gain, jaundis, asthenia, vomiting, purpura, abdominal distension, hepatomegaly, hepatic encephalopathy, multi organ failure or other signs. Hepatic function test was done for baseline state at the beginning of treatment on 15Jul2019 and that found AST at 40IU and ALT at 31IU, during the treatment on 19Aug2019 that found AST 75IU (N <40), ALT 105 IU (N <41), GGT 47 IU (N <60), bilirubin total 12umol/l (N < 21), bilirubin conjugated 5 umol/l (N <5), PAL 112 IU (N 40-130). It was unknown if the subject had family history of hepatic pathology. The events were assessed as non-serious by reporter. In response to event rash, bosutinib dose was reduced. The patient had recovered from hepatic cytolysis on 11Sep2019, from diarrhea on 03Oct2019, from nausea on 09Jul2019 and from rash on 03Oct2019.

According to the investigator all events were related to study drug and unrelated to concomitant treatment.

Follow-up (23Jan2020): New information includes updated start date of bosutinib, details on event hepatic cytolysis and lab data, metabolic disease and hypertriglyceridemia added to medical history.

Follow-up (22Jan2021): New information received included confirmed bosutinib start date and concomitant medications updated.

Follow-up (10May2023): This is a report from a Non-Interventional study from the investigational site via the CRO. Updated information included: The patient's initials were updated. Nausea and rash were both grade 1. In response to event rash, bosutinib dose was reduced.

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 hepatic cytolysis, diarrhea, nausea and rash are related to bosutinib cannot be excluded

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	15-JUL-2019	Alanine aminotransferase	31 iU	41
2	19-AUG-2019	Alanine aminotransferase	105 iU	41
3	15-JUL-2019	Aspartate aminotransferase	40 iU	40
4	19-AUG-2019	Aspartate aminotransferase	75 iU	40
5	19-AUG-2019	Bilirubin conjugated	5 umol/l	5
6	19-AUG-2019	Blood alkaline phosphatase	112 iU	130 40
7	19-AUG-2019	Blood bilirubin	12 umol/l	21
8	19-AUG-2019	Gamma-glutamyltransferase	47 iU	60

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2011 to Ongoing	Relevant Med History	Sleep apnea (Sleep apnoea syndrome);
1996 to Ongoing	Relevant Med History	Ischemic cardiomyopathy (Ischaemic cardiomyopathy);
Unknown	Relevant Med History	Metabolic disorder NOS (Metabolic disorder);
Unknown	Relevant Med History	Hypertriglyceridemia (Hypertriglyceridaemia);

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		PRIVACY		73 Years	Male	Unk	02	DEC	2019

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

HEPATITIS [Hepatitis]

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 protocol for 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, daily

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

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

18. THERAPY DATES(from/to)
#1) 07-NOV-2019 / 03-DEC-2019

19. THERAPY DURATION
#1) 27 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 operated	Aneurysm aortic (Aortic aneurysm)

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.
2019527892

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

24c. DATE RECEIVED BY MANUFACTURER
04-NOV-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2019527892

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional clinical study case reporting non-serious event only.

A 73-year-old male subject started to receive bosutinib (BOSULIF; film-coated tablet) via an unspecified route of administration on 07Nov2019 to 03Dec2019, at 500 mg daily for chronic myeloid leukaemia. Medical history included abdominal aorte aneurysm, operated. Concomitant therapy was reported as none. The subject experienced hepatitis (grade 3) on 02Dec2019. The subject had no other sign or symptom. The subject did not consume alcohol. On 18Feb2019, aspartate aminotransferase (AST) was 29, alanine aminotransferase (ALT) was 46, alkaline phosphatase was 97 and gamma-glutamyltransferase (GGT) was 191. On 29Nov2019, AST was 33 IU/l and ALT 52 IU/l ; on 02Dec2019 AST was 350 IU/l and ALT 560 IU/l ; on 10Dec2019, ALT was 220 IU/l and AST was 604 IU/l : on 13Jan2020, AST was 28 IU/l and ALT was 41 IU/l (normal range <50 for AST and ALT). The action taken with bosutinib in response to the event was permanently withdrawn on 03Dec2019. The event was resolved on 13Jan2020.

According to the reporter, the event was related to study drug.

Follow-up (08Apr2020): New information received from investigator includes subject date of birth and gender, updated medical history, start and stop date of bosutinib, concomitant therapy reported as none, updated lab data, updated event outcome.

Follow-up (04Nov2020): New information received from the CRO included: subject data (subject height and initials added), suspect product data (updated bosutinib start date to 07Nov2019 from 05Nov2019) and reaction data (updated grading for hepatitis to grade 3 instead of grade 2).

Case Comment: A possible contributory role of bosutinib to the event hepatitis cannot be completely excluded based on temporal association and the known safety profile.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	18-FEB-2019	Alanine aminotransferase	46	
2	29-NOV-2019	Alanine aminotransferase	52 IU/l	50
3	02-DEC-2019	Alanine aminotransferase	560 IU/l	50
4	10-DEC-2019	Alanine aminotransferase	604 IU/l	50
5	13-JAN-2020	Alanine aminotransferase	41 IU/l	50
6	18-FEB-2019	Aspartate aminotransferase	29 IU/l	50
7	18-FEB-2019	Aspartate aminotransferase	29	
8	29-NOV-2019	Aspartate aminotransferase	33 IU/l	50
9	02-DEC-2019	Aspartate aminotransferase	350 IU/l	50
10	10-DEC-2019	Aspartate aminotransferase	220 IU/l	50
11	13-JAN-2020	Aspartate aminotransferase	28 IU/l	50
12	18-FEB-2019	Blood alkaline phosphatase	97	
13	18-FEB-2019	Gamma-glutamyltransferase	191	

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		PRIVACY		61 Years	Male	Unk	20	MAY	2019

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

Worsening of bilateral femoral stenosis [Peripheral artery stenosis]
Worsening of bilateral femoral stenosis [Condition aggravated]
Hepatic cytolysis [Hepatic cytolysis]

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.

(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) Unknown

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

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

18. THERAPY DATES(from/to)
#1) 03-APR-2019 / 30-MAY-2019

19. THERAPY DURATION
#1) 58 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) TASIGNA (NILOTINIB HYDROCHLORIDE) ; Unknown
#2) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Unknown
#3) ATORVASTATIN (ATORVASTATIN) ; Unknown
#4) SYMBICORT (BUDESONIDE, FORMOTEROL FUMARATE) ; Unknown
#5) IMOVANE (ZOPICLONE) ; Unknown
#6) LASILIX [FUROSEMIDE] (FUROSEMIDE) ; 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	Chronic myeloid leukemia (Chronic myeloid leukaemia)
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.
2020022527

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

A 61-year-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 03Apr2019 to 30May2019 at 400 mg, once a day, via an unspecified route of administration from 04Jun2019 and ongoing at 300 mg, once a day.
The subject had ongoing medical history of chronic myeloid leukemia, hypertension arterial, dyslipidemia and arteriopathy. Concomitant medications included nilotinib hydrochloride (TASIGNA), acetylsalicylate lysine (KARDEGIC), atorvastatine, budesonide/formoterol fumarate (SYMBICORT), zopiclone (IMOVANE), furosemide (LASILIX), omeprazole and angiotensin II receptor blockers.
The subject experienced hepatic cytolysis on 20May2019. The investigator confirmed it was not a recurrence or exacerbation of underlying disease. Monitoring of hepatic function test was done in year before the treatment start. AST, ALT and bilirubin were normal. Hepatic function test at the treatment start was normal. During the treatment hepatic function test showed hepatic cytolysis grade 3 (as reported). Hepatic work-up after the treatment discontinuation was normal. At event onset the subject was taking acetylsalicylate lysine (KARDEGIC) 75 mg, atorvastatine 20 mg, budesonide, formoterol fumarate (SYMBICORT), zopiclone (IMOVANE), furosemide (LASILIX) 20 mg, omeprazole 20 mg and angiotensin II receptor blockers. The subject did not have family history of hepatic pathology. On 30May2019 AST were 90 IU/L (N15-40), ALT 170 IU/L (N 10-40), Gamma GT 38 IU/L (N10-50), bilirubin 5 mg/l (N 1-12). On 02Sep2019, the subject experienced worsening of bilateral femoral stenosis, which led to hospitalization. The event was rated grade 3. CT scan on 02Sep2019 showed a significant increase in stenosis of the 2 superficial femorales to 70% (60% on 19Mar2019). Angioplasty was performed on 29Nov2019. In response to hepatic cytolysis, bosutinib dose was reduced then bosutinib was temporarily withdrawn. The event hepatic cytolysis did not recur with the reintroduction of bosutinib. The event hepatic cytolysis was resolved on 11Jun2019. The event worsening of bilateral femoral stenosis resolved on 29Nov2019.

The investigator assessed the event hepatic cytolysis as grade 2, non-serious and related to bosutinib and unrelated to any concomitant drug.
The investigator considered the event worsening of bilateral femoral stenosis as unrelated to the study drug bosutinib and unrelated to concomitant drugs.

Follow-up (16Jan2020): New information received from the investigator included additional suspect (TASIGNA), medical history added, CT scan, new event worsening of bilateral femoral stenosis, causality for hepatic cytolysis provided, action taken for BOSULIF updated.

Follow-up (06Mar2020): New information included: the causality assessment between bosutinib and the event hepatic cytolusis was updated.

Follow-up (03Jul2020): New information received from investigator includes confirmation on event "hepatic cytolysis" (a new event and not a recurrence or exacerbation of underlying disease), concomitant drugs, lab data relevant to event hepatic cytolysis, recovery date of event hepatic cytolysis.

Follow-up (12Feb2021): New information received from the CRO includes: subject gender, bosutinib action taken, hepatic cytolysis outcome and causality.

Follow-up (19Feb2019). New information received from the clinical team includes recovery date of event Hepatic cytolysis (updated from "27Aug2019" to "11Jun2019").

Follow-up (10May2022): new information received from CRO included:
Start date of AE Hepatic cytolysis updated to 20May2019, patient data (height) updated, nilotinib hydrochloride recoded as concom medication, and confirmed causality of concomitant medications.

Follow-up (23Nov2023): This is a Non-Interventional Study follow report received from the investigatiponal site in response to query. Updated information includes: action taken updated to temporarily withdrawn and rechallenge results updated to Neg.

Case Comment: In concurrence with the investigator, the event worsening of bilateral femoral stenosis is not related to the study drug bosutinib, the concomitant nilotinib hydrochloride (TASIGNA) may contribute to the event occurrence. Similarly, the company does not attribute the event hepatic cytolysis 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	2018	Alanine aminotransferase	normal	
2	30-MAY-2019	Alanine aminotransferase	170 IU/l	40 10
3	2018	Aspartate aminotransferase	normal	

Mfr. Control Number: 2020022527

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
4	30-MAY-2019	Aspartate aminotransferase	90 IU/l	40 15
5	2018	Blood bilirubin	normal	
6	30-MAY-2019	Blood bilirubin	5 mg/l	12 1
7	19-MAR-2019	Computerised tomogram	stenosis to 60%	
8	02-SEP-2019	Computerised tomogram	stenosis to 70%	
9	30-MAY-2019	Gamma-glutamyltransferase	38 IU/l	50 10
10		Liver function test after the treatment discontinuation was normal	normal	
11	APR-2019	Liver function test at the treatment start was normal	normal	
12	2019	Liver function test During the treatment hepatic function test showed hepatic cytolysis grade 3	hepatic cytolysis grade 3.	

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	04-JUN-2019 / Ongoing; Unknown

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

#7) OMEPRAZOLE (OMEPRAZOLE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Dyslipidemia (Dyslipidaemia);
Unknown to Ongoing	Relevant Med History	Arteriopathy (Arterial 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
PRIVACY	FRANCE		PRIVACY		63 Years	Female	111.00 kg		OCT	2019

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

pain of left flank [Flank 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 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

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) 03-DEC-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
1964 to 1964	Relevant Med History	Appendectomy (Appendicectomy)
1985 to Ongoing	Relevant Med History	Blindness (Blindness)
	left ocular prosthesis	

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.
2020036703

24c. DATE RECEIVED BY MANUFACTURER
15-MAY-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 63-year-old female patient started to receive bosutinib (BOSULIF) from 03Dec2018 and ongoing at 400 mg, daily for unknown indication. Medical history included appendicectomy in 1964, blindness (ongoing) from 1985 and requiring left ocular prosthesis, subtotal hysterectomy because of fibroma in Aug2003, pulmonary embolism in Aug2003, arterial hypertension since 2012 and ongoing, breast adenocarcinoma since Apr2015 and ongoing, abscess on vesicovaginal perforation from Sep2003 to Oct2003. Concomitant drugs were unknown.
The subject experienced pain of left flank in Oct2019, considered as non serious and rated grade 1. Action taken with bosutinib was dose not changed. Outcome of event was recovered on 30Oct2019.

The investigator considered the event as unrelated to the study drug bosutinib.

Follow-up (13Mar2020): New reported information included medical history

Follow-up (15May2023): This is a non-interventional study follow up report from the investigational site via the CRO. Updated information includes: new reporter, suspect drug details (frequency of bosutinib updated).

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

Case Comment: The reported flank pain in this report is considered as an inter-current disease in this 64-year-old female patient, unlikely related to bosutinib administration.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History left	Eye prosthesis insertion (Eye prosthesis insertion);
AUG-2003 to AUG-2003	Relevant Med History because of fibroma	Subtotal hysterectomy (Hysterectomy);
Unknown	Relevant Med History	Fibroma (Fibroma);
AUG-2003 to AUG-2003	Relevant Med History	Pulmonary embolism (Pulmonary embolism);
2012 to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
APR-2015 to Ongoing	Relevant Med History	Breast adenocarcinoma (Breast cancer);
SEP-2003 to OCT-2003	Relevant Med History	Abscess (Abscess);
Unknown	Relevant Med History	Vesical rupture (Urinary bladder rupture);

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		PRIVACY		51 Years	Male	87.00 kg	28	OCT	2019

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]
diarrhea [Diarrhoea]
headache intermittent [Headache]
pruritus [Pruritus]
Joint pain [Arthralgia]
Skin lesion [Skin lesion]
Fatigue [Fatigue]
intermittent lumbalgia [Back pain]
gastroesophageal reflux [Gastrooesophageal reflux disease]
Erysipelas [Erysipelas]

(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) NILOTINIB (NILOTINIB)

(Continued on Additional Information Page)

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) Unknown
#2) Unknown

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

18. THERAPY DATES(from/to)
#1) 17-OCT-2019 / 23-OCT-2019
#2) 27-OCT-2021 / Ongoing

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) KLIPAL [CODEINE PHOSPHATE;PARACETAMOL] (CODEINE PHOS
#2) LOPERAMIDE (LOPERAMIDE) ; 2020 / Ongoing
#3) SPASFON [PHLOROGLUCINOL] (PHLOROGLUCINOL) ; JAN-2020 / 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
2014 to Ongoing	Relevant Med History	Myalgia (Myalgia)
2019 to OCT-2019	Relevant Med History	Skin infection (Skin infection)

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.
2020051948

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

Erysipelas [Erysipelas]
muscular pains [Myalgia]
nervousness [Nervousness]
Perianal irritation [Anorectal discomfort]
Erysipelas [Erysipelas]
Bosulif dose omission [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) for protocol B1871047.

A 51-year-old male patient received bosutinib (BOSULIF), first regimen from 17Oct2019 to 23Oct2019 at 200 mg daily and second regimen since 24Oct2019 (ongoing) at 300 mg daily; nilotinib (NILOTINIB), since 27Oct2021 (ongoing) (Batch/Lot number: unknown). The patient's relevant medical history included: "myalgia", start date: 2014 (ongoing); "cutaneous infection", start date: 2019, stop date: Oct2019; "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: KLIPAL [CODEINE PHOSPHATE;PARACETAMOL] oral taken for pain, start date: 2020 (ongoing); LOPERAMIDE oral taken for diarrhoea, start date: 2020 (ongoing); SPASFON [PHLOROGLUCINOL] oral taken for pain, start date: Jan2020 (ongoing).
The following information was reported: ANORECTAL DISCOMFORT (non-serious) with onset 28Oct2019, outcome "recovered" (Nov2019), described as "Perianal irritation"; SKIN LESION (non-serious) with onset Jan2020, outcome "recovered" (13Apr2021); ABDOMINAL PAIN (non-serious) with onset Jan2020, outcome "not recovered"; DIARRHOEA (non-serious) with onset Jan2020, outcome "not recovered", described as "diarrhea"; GASTROOESOPHAGEAL REFLUX DISEASE (non-serious) with onset Jan2020, outcome "recovered" (Mar2020), described as "gastroesophageal reflux"; HEADACHE (non-serious) with onset Jan2020, outcome "not recovered", described as "headache intermittent"; NERVOUSNESS (non-serious) with onset Jan2020, outcome "recovered" (May2020); PRURITUS (non-serious) with onset Jan2020, outcome "not recovered"; BACK PAIN (non-serious) with onset 24Feb2020, outcome "not recovered", described as "intermittent lumbalgia"; ERYSIPELAS (non-serious) with onset 08Mar2020, outcome "recovered" (27Mar2020), ERYSIPELAS (non-serious) with onset 16Jul2020, outcome "recovered" (Jul2020), ERYSIPELAS (non-serious) with onset 24Sep2020, outcome "recovered" (03Oct2020) and all described as "Erysipelas"; ARTHRALGIA (non-serious) with onset 20Apr2020, outcome "not recovered", described as "Joint pain"; PRODUCT DOSE OMISSION ISSUE (non-serious) with onset 2020, outcome "recovered" (2020), described as "Bosulif dose omission"; MYALGIA (non-serious) with onset Oct2020, outcome "not recovered", described as "muscular pains"; FATIGUE (non-serious) with onset 20Oct2020, outcome "not recovered". The action taken for bosutinib was dosage reduced; for nilotinib was dosage not changed.

The reporter considered "abdominal pain", "diarrhea", "headache intermittent", "pruritus", "joint pain", "skin lesion", "fatigue", "gastroesophageal reflux", "erysipelas" and "muscular pains" related to bosutinib. The reporter considered "intermittent lumbalgia", "nervousness", "perianal irritation" and "erysipelas" not related to bosutinib.
According to the reporter, abdominal pain, diarrhea, gastroesophageal reflux, headache, erysipelas (first two episodes), muscular pains, pruritus, skin lesion, joint pain, fatigue were related to bosutinib and unrelated to concomitant drugs. Nervousness, perianal irritation, lumbalgia, erysipelas (onset 24Sep2020) were unrelated to bosutinib and to concomitant drug. The reporter considered headache intermittent related to Nilotonib, GERD with gastritis or ulcer with vomiting, Joint pain, intermittent headaches related to nilotinib. The reporter considered event Bosulif dose omission was non-serious, grade 1, related to study drug bosutinib and unrelated to concomitant drug.

Follow-up (12May2020): New information received from the CRO includes updated outcome of headache, new event erysipelas, concomitant drugs.

Follow-up (17Aug2020): New information received from the investigational site via CRO includes: new events erysipelas and lumbalgia, updated action taken, on unspecified date in 2020 the subject did not take bosutinib.

Follow-up(10Nov2020): New information received from the investigational site via the CRO includes new adverse event muscular pains (non-serious).

Follow-up (19Nov2020): New information received from the investigational site and from the investigational site via the CRO in response to query includes: updated dose of bosutinib.

Follow-ups (15Dec2020): New information received from the investigational site includes clarification on bosutinib dates of administration and dosages, action taken in response to erysipelas.

Follow-up (12Jan2021 and 13Jan2021): New information received from the investigational site via the CRO includes updated start dose of bosutinib, updated event term of skin pruritus (updated to pruritus), nervousness, new events perianal irritation, skin lesion, joint pain, fatigue, new episode of erysipelas (onset 24Sep2020), updated onset date of muscular pains (Oct2020, previously reported as 20Oct2020), updated outcome of gastroesophageal reflux, updated recovery date of Erysipelas (onset 08Mar2020), updated onset date and event term of lumbalgia (to intermittent lumbalgia, onset 24Feb2020),

Mfr. Control Number: 2020051948

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (27Apr2021): New information received from the study site includes: update outcome of events (skin lesion, joint pain and diarrhea), and forgotten dose of bosutinib.

Follow-up(16May2022). This follow-up is received from the investigational site via CRO.
Updated information: outcome of diarrhea was updated.

Follow-up (20Jul2022): This is a follow-up report from a contactable investigator.
Updated information: Clinical outcome of event diarrhea was changed from recovering/resolving to recovered/resolved.

Follow-up (09FEB2023): This is a follow-up report from a contactable investigator. Updated information includes: Bosutinib at 300 mg, daily start date updated to 16Oct2019.

Follow-up(22May2023): This is a follow-up report from a contactable investigator. Updated information includes: Relevant medical history included ongoing Chronic myeloid leukemia.

Follow-up(23May2023): This is a follow-up report from a contactable investigator:
Updated information: bosutinib dosage details and events details added (Verbatim updated from headache to headache intermittent, outcome updated from recovered to not recovered, Joint pain outcome updated from recovered to not recovered), additional suspect Nilotinib added.

Follow-up (16Jun2023): 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 dosages of bosutinib.

Follow-up (03Jul2023): New information received from CRO is as follows: Action taken with bosutinib in response to erysipelas (08Mar2020) was dose not changed.

Follow-up (14Nov2023): This is a non-interventional study follow-up report received from Clinical team following reconciliation.
Updated information included: new event Bosulif dose omission added.

Case Comment: The limited information provided precludes a full clinical assessment of the case. Significant in the assessment of causality would be specific diagnosis of the indication of the suspect product and stage and extent of the underlying malignancy, which were unknown at the time of the report. Based on a the known drug safety profile, the company considers there is a reasonable possibility that abdominal pain, diarrhea, headache, skin pruritus, skin lesion, joint pain, fatigue and lumbalgia are related to suspect drug bosutinib, while, at the present time, with the clinical information provided, nervousness, gastroesophageal reflux, perianal irritation, erysipelas and muscular pain are assessed as unrelated. Important to note medical history of myalgia and skin infection. 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, daily; Unknown	Unknown	24-OCT-2019 / Ongoing; Unknown

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

#1) KLIPAL [CODEINE PHOSPHATE;PARACETAMOL] (CODEINE PHOSPHATE, PARACETAMOL) ; 2020 / Ongoing

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);

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		PRIVACY		74 Years	Male	97.00 kg	09	DEC	2019

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

right knee chondrocalcinosis attack [Chondrocalcinosis]
Popliteal and subpopliteal phlebitis of the right lower limb [Phlebitis]
lipase increased [Lipase increased]
Vitamin C deficiency [Vitamin C deficiency]
Folates deficiency [Folate deficiency]

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) 13-NOV-2019 / 02-DEC-2019	#1) 20 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) COLCHIMAX [COLCHICINE;DICYCLOVERINE HYDROCHLORIDE] (COLCHICINE, DICYCLOVERINE HYDROCHLORIDE) ; DEC-2019 / DEC-2019

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	Chondrocalcinosis (Chondrocalcinosis)
Unknown to Ongoing	Relevant Med History INTERMITTENT	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.
2020075464

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
21-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 reporters (Physician and Other HCP) for protocol B1871047.

A 74-year-old male subject received bosutinib (BOSULIF), first regimen from 13Nov2019 to 02Dec2019 at 100 mg daily, second regimen from 03Dec2019 to 09Dec2019 at 200 mg daily and third regimen since 10Dec2019 (ongoing) at 100 mg daily. The patient's relevant medical history included: "joint chondrocalcinosis" (ongoing); "gout attack" (ongoing), notes: INTERMITTENT; "varicose veins of lower limb", start date: 1999, stop date: 1999; "arterial hypertension" (ongoing); "chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: COLCHIMAX [COLCHICINE;DICYCLOVERINE HYDROCHLORIDE] oral taken for gout, start date: Dec2019, stop date: Dec2019.
In Dec2019 the subject experienced right knee chondrocalcinosis attack. On 09Dec2019, the subject experienced lipase increased. In Jan2020, the subject developed vitamin C deficiency and folate deficiency. On 10Jan2020, the subject experienced popliteal and subpopliteal phlebitis of the right lower limb. The subject was hospitalized due to right knee chondrocalcinosis attack and popliteal and subpopliteal phlebitis of the right lower limb from 10Jan2020 to 20Jan2020.
On 10Jan2020, the subject was hospitalized for joint attacks, which started in the right ankle one month ago, but with a very severe pain in the right knee. The subject had almost complete functional disability and almost did not walk anymore. The subject's general practitioner was consulted for advice on the subject's admission to the hospital. On unknown date, the subject received triamcinolone hexacetonide (HEXATRIONE) infiltration as corrective treatment for right knee chondrocalcinosis attack. The subject's right ankle arthritis, present prior to hospital admission, was not punctured considering the etiology of arthritis was the gout. At subject's hospital admission, doppler ultrasonography was performed, following the infiltration, and the whole right leg and feet tension, and revealed popliteal and infra-popliteal phlebitis, which was favored by the prolonged right lower limb immobilization. It was confirmed that popliteal and subpopliteal phlebitis of the right lower limb developed on 10Jan2020 was an event, serious for hospitalization. The subject was treated with heparin sodium (unspecified trade name) and compression stockings. On an unknown date, heparin sodium was switched to rivaroxaban (XARELTO), by oral route for 3 months. On 20Jan2020, the subject was discharged home. The subject was hospitalized for chondrocalcinosis, phlebitis (start date: 10Jan2020, discharge date: 20Jan2020, hospitalization duration: 10 day(s)). The subject was independent and walked without crutches. The subject's discharge prescription included chronic medication with bosutinib monohydrate (BOSULIF), lercanidipine hydrochloride / enalapril maleate (LERCAPRESS), nicardipine hydrochloride (LOXEN), lorazepam (TEMESTA), pregabalin (LYRICA), cholecalciferol (ZYMAD), tramadol hydrochloride (unspecified trade name) and newly introduced medication with colchicine (unspecified trade name), paracetamol (DAFALGAN), rivaroxaban and venous compression stockings.
The subject underwent the following laboratory tests and procedures: Aspiration joint: (10Jan2020) 5600 WBC/ pyrophosphate crystals, notes: 5600 white blood cells/ pyrophosphate crystals: inflammatory fluid compatible with a gout attack; (15Jan2020) uric acid and pyrophosphate crystals : inflammator, notes: uric acid and pyrophosphate crystals : inflammatory liquid; Lipase: (09Dec2019) increased; Lipase: (10Dec2019) 118 IU/l; Lipase (12-53): (17Feb2020) 64 IU/l; Lipase (13-60): (16Dec2019) 102 IU/l; (30Dec2019) 62 IU/l; (27Jan2020) 100 IU/l; (17Feb2020) 64 IU/l; Ultrasound Doppler: (10Jan2020) popliteal and infra-popliteal phlebitis,, notes: popliteal and infra-popliteal phlebitis, which was favored by the prolonged right lower limb immobilization; (10Jan2020) popliteal and sub-popliteal right phlebitis.
The event right knee chondrocalcinosis attack was rated grade 3. In response to this event, no action was taken with bosutinib. The event lipase increased was reported as non-serious and rated grade 2. In response to this event, dose of bosutinib was reduced. The event popliteal and subpopliteal phlebitis of the right lower limb was rated grade 2, no action was taken with bosutinib. For the events vitamin C deficiency and folate deficiency no seriousness criterion was provide, no action was taken with bosutinib.
The action taken for bosutinib was dosage reduced to 100mg daily due to isolated elevation lipase 118 iu/l and patient was currently on bosutinib. The subject recovered from right knee chondrocalcinosis attack on 17Feb2020, from popliteal and subpopliteal phlebitis of the right lower limb in Apr2020 and from lipase increased on 26Feb2020, from folates deficiency in 2020, while the outcome of vitamin C deficiency was not recovered. No SAE/AE recurred with drug reintroduction.

The reporter considered "right knee chondrocalcinosis attack", "popliteal and subpopliteal phlebitis of the right lower limb" and "folates deficiency" not related to bosutinib or to concomitant medication. The reporter considered "lipase increased" related to bosutinib. The reporter's assessment of the causal relationship of "vitamin c deficiency" 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 (28Feb2020): New information reported includes details on treatment for chondrocalcinosis right knee.

Follow-up (11Aug2020 and 12Aug2020): New information received from the CRO includes new event (popliteal and subpopliteal phlebitis of the right lower limb, serious as per hospitalization, unrelated for reporter). New information received from the clinical team includes new events (vitamin C deficiency and folate deficiency, causality missing).

Follow-up (13Aug2020): New information received from the CRO includes: the onset date of the event chondrocalcinosis right knee was corrected to Dec2019.

Follow-up (24Sep2020): follow-up attempts completed. No further information expected

Follow-up (29Oct2020): new information received from CRO includes: the event term 'chondrocalcinosis right knee' was updated to 'right knee chondrocalcinosis attack'.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Follow-up (22Feb2021): New information received includes updated outcome and recovery date of popliteal and subpopliteal phlebitis of the right lower limb and lipase increased.

Follow-up (20Apr2022): This is a follow-up of a non-interventional study for protocol B1871047. Updated information included: event folates deficiency outcome updated (previously not resolved), recovery date of event lipase increased corrected, causality of event folates deficiency provided (previously unknown).

No follow-up attempts initiated. No further information expected

Amendment: This follow-up report is being submitted to amend previous information: Recovery date of folates deficiency was updated to 2020.

Follow-up (12Jul2023): This is a follow-up of a non-interventional study for protocol B1871047. Updated information included: additional lab test (Lipase on 17Feb2020).

Follow-up (21Jul2023): This is a follow-up of a non-interventional study for protocol B1871047.
Updated information included: RMH updated: chronic myeloid leukemia added and ongoing checkbox checked.

Case Comment: The events chondrocalcinosis right knee and phlebitis are considered unrelated to bosutinib, as the subject had ongoing history of joint chondrocalcinosis and varicose veins. A possible contributory role of bosutinib to the event lipase increased cannot be excluded based on the known safety profile and temporal association. Vitamin C deficiency and folate deficiency are deemed unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	10-JAN-2020	Aspiration joint	5600 WBC/ pyrophosphate crystals	
		5600 white blood cells/ pyrophosphate crystals: inflammatory fluid compatible with a gout attack.		
2	15-JAN-2020	Aspiration joint	uric acid and pyrophosphate crystals : inflammator	
		uric acid and pyrophosphate crystals : inflammatory liquid		
3	09-DEC-2019	Lipase	increased IU/l	60 13
4	10-DEC-2019	Lipase	118 IU/l	
5	16-DEC-2019	Lipase	102 IU/l	60 13
6	30-DEC-2019	Lipase	62 IU/l	60 13
7	27-JAN-2020	Lipase	100 IU/l	60 13
8	17-FEB-2020	Lipase	64 IU/l	53 12
9	17-FEB-2020	Lipase	64 IU/l	60 13
10	10-JAN-2020	Ultrasound Doppler	popliteal and infra-popliteal phlebitis,	
		popliteal and infra-popliteal phlebitis, which was favored by the prolonged right lower limb immobilization		
11	10-JAN-2020	Ultrasound Doppler	popliteal and sub-popliteal right phlebitis	

Mfr. Control Number: 2020075464

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	200 mg, daily; Unknown	Unknown	03-DEC-2019 / 09-DEC-2019; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	100 mg, daily; Unknown	Unknown	10-DEC-2019 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
1999 to 1999	Relevant Med History	Varicose veins of lower extremities (Varicose vein);
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension);
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		PRIVACY		66 Years	Male	63.00 kg		FEB	2020

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

galbladder lithiasis (= cholecystitis) [Cholelithiasis]
galbladder lithiasis (= cholecystitis) [Cholecystitis]
Soft stools [Faeces soft]
Hand and forearm contact eczema [Dermatitis contact]

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) 100 mg, daily	#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) 08-AUG-2019 / 22-AUG-2019	#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
28-SEP-2018 to Ongoing	Relevant Med History	Reflux oesophagitis (Gastrooesophageal reflux disease)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020095002

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
08-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

Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 66-year-old male patient received bosutinib (BOSULIF), first regimen from 08Aug2019 to 22Aug2019 at 100 mg daily, second regimen from 23Aug2019 to 24Sep2019 at 200 mg daily, third regimen from 25Sep2019 to 18Feb2020 at 300 mg daily and fourth regimen since 19Feb2020 (ongoing) at 400 mg daily for chronic myeloid leukaemia. The patient's relevant medical history included: "PEPTIC OESOPHAGITIS", start date: 28Sep2018 (ongoing); "arterial hypertension" (ongoing). The patient's concomitant medications were not reported.
Good tolerance was reported except from the soft stools in the morning. On unknown date in Feb2020 the subject experienced soft stools, which was rated grade 1 and not serious. No intake of antidiarrheics. On 04May2020, the subject experienced hands and forearms contact eczema (manipulated detergent for milking machine), rated grade 1 and not serious. No corrective treatment was given. On 25Jul2020, the subject developed 'gallbladder lithiasis (=cholecystitis)' rated grade 3 and assessed as serious due to hospitalization on the same date. On 25Jul2020 at 00:07 pm, the subject came to the emergency unit due to epigastric pain occurring around 4 am. Epigastric pain was perfectly relieved by morphine sulfate (OXYNORM 10mg). He had no rectorrhagia, no melena, no nausea and no vomiting. In emergency unit, he received esomeprazole (INEXIUM) 40 mg once daily by intravenous route. ECG on 25Jul2020 found regular sinus rhythm with normal axis and diffuse segment elevation in V4 and V5. The subject was valid and autonomous. Blood tests on 25Jul2020 disclosed cytolysis and cholestasis with ASAT at 129, ALAT at 84, lipase at 1088 and CRP at 17.7. Body temperature was at 38 degrees C at 2:35 pm on 25Jul2020. Hence, blood culture was performed twice on 25Jul2020 and returned negative results for herpes simplex virus. The subject was then transferred to digestive surgery unit. At 6:56 pm, he had no more pain. Control abdomino-pelvic CT-scan on 27Jul2020 concluded to the absence of abnormality at pancreas or peripancreatic level, but gallbladder lithiasis with peri-vesicular effusion without other biliary tract abnormalities: beginning cholecystitis. The patient had intravesicular lythiasis with perivesicular effusion without other biliary tract abnormalities: early cholecystitis and diarrhoea (known). On 27Jul2020, feeding was resumed. The subject was much less painful. ASAT was at 16, ALAT was at 36 and CRP was at 29.4 on 27Jul2020. On 28Jul2020, cholecystectomy by laparoscopy was performed. Histology found an aspect of chronic cholecystitis. On 29Jul2020, the subject was discharged home with prescription of paracetamol (unspecified trade name) as required and tramadol (CONTRAMAL) if pain resistant to paracetamol. The action taken in response to the events for bosutinib was dose not changed. The outcome of the event hand and forearm contact eczema was resolved on 25Jul2020. The event soft stools resolved on 04May2020. On 29Jul2020, gallbladder lithiasis (= cholecystitis) was considered as fully resolved.

The investigator considered the event soft stool as related to study drug bosutinib and the event hands and forearms contact eczema as unrelated to study drug.
The investigator considered the event gallbladder lithiasis (= cholecystitis) as neither related to bosutinib nor to a concomitant medication.

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

Follow-up (11Mar2020): New information received from the CRO includes: investigator assessment has been changed.

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

Follow-up (04May2020): New information received from the CRO includes: new dosage regimens for bosutinib, updated stop date of dosage 200 mg, new event hands and forearms contact eczema.

Follow-up (07Aug2020 and 10Aug2020): New information received from the investigator via the CRO includes: reaction data (added events 'gallbladder lithiasis (= cholecystitis)'), product data (updated dosing regimens and indication for bosutinib), lab data, therapeutic intervention data, updated outcome for previously reported event soft stools, medical history data, and clinical course of newly reported event 'gallbladder lithiasis (= cholecystitis)'.

Follow-up (15Dec2021): New information received from the study site via CRO includes:
reaction data (onset date and outcome of Hands and forearms contact eczema were updated).

Follow-up (14Dec2022): This is follow-up non-interventional study report for protocol B1871047 from the investigational site CRO. Updated information includes: new reporter, patient's initials, clinical course.

Follow-up (08Feb2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the investigator via CRO for protocol B1871047. Updated information: details on dosage regimens of bosutinib.

Case Comment: Based on available information and on the known drug safety profile, a possible contributory role of the subject drug bosutinib cannot be excluded for the event of soft stools. Conversely, the forearms contact eczema is assessed as unrelated to bosutinib, since it is reported that it was caused by an external detergent. The reported gallbladder lithiasis (=cholecystitis) are considered unrelated to bosutinib. Of note, histology found an aspect of chronic cholecystitis.

Mfr. Control Number: 2020095002

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	25-JUL-2020	Alanine aminotransferase cytolysis and cholestasis	84	
2	27-JUL-2020	Alanine aminotransferase	36	
3	25-JUL-2020	Aspartate aminotransferase cytolysis and cholestasis	129	
4	27-JUL-2020	Aspartate aminotransferase	16	
5	25-JUL-2020	Blood culture Negative Negative	negative for herpes simplex virus	
6	25-JUL-2020	Blood culture Negative Negative	negative for herpes simplex virus	
7	25-JUL-2020	Body temperature	38 Centigrade	
8	25-JUL-2020	C-reactive protein cytolysis and cholestasis	17.7	
9	27-JUL-2020	C-reactive protein	29.4	
10	27-JUL-2020	Computerised tomogram no abnormality at pancreas or peripancreatic level, gallbladder lithiasis with peri-vesicular effusion without other biliary tract abnormalities: beginning cholecystitis	beginning cholecystitis	
11	25-JUL-2020	Electrocardiogram normal axis, diffuse segment elevation in V4 and V5	regular sinus rhythm	
12	28-JUL-2020	Histology	aspect of chronic cholecystitis	
13	25-JUL-2020	Lipase cytolysis and cholestasis	1088	

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-AUG-2019 / 24-SEP-2019; 82 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	25-SEP-2019 / 18-FEB-2020; 4 months 25 days

Mfr. Control Number: 2020095002

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	400 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	19-FEB-2020 / 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		PRIVACY		41 Years	Female	50.00 kg	26	FEB	2020

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

diarrhea [Diarrhoea]
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 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
#2) TRAMADOL (TRAMADOL)
(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 300 mg/day	#1) Unknown
#2) 50 mg x4 per day	#2) Oral

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

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 20-SEP-2019 / 26-FEB-2020	#1) 160 days
#2) 26-FEB-2020 / Ongoing	#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		

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.
2020108001

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:

Mfr. Control Number: 2020108001

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 41-year-old female patient started to receive bosutinib (BOSULIF) at 300 mg/day from 20Sep2019 to 26Feb2020 for an unspecified indication, and tramadol 50 mg x4 per day ongoing from 26Feb2020 for pain. Medical history and concomitant medications were not reported. The patient experienced diarrhea on 26Feb2020, reported as non-serious and rated grade 2 and gastroenteritis in Mar2021, rated grade 1. Control of diarrhea with decrease of bosutinib dose to 200 mg ongoing since 26Feb2020. On 12Mar2021 the subject experienced entrance to emergency room (unspecified serious event), raison unknown. Action taken for tramadol was not reported, for bosutinib was dose reduced. Diarrhea resolved on 30Mar2021 and gastroenteritis in Mar2021.

According to the reporter, the event diarrhea was related to bosutinib and to concomitant drug tramadol. The reported assessed the event gastroenteritis unrelated to bosutinib or to any concomitant drug.

Follow-up (14Apr2020): New information received from investigational site includes stop date of BOSULIF

Follow-up (12May2020): New information received from investigational site includes
action taken for tramadol and date when reduced dose of bosutinib was started.

Follow-up (17Oct2022): 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: new event gastroenteritis, updated outcome of diarrhea.

Amendment: This follow-up report is being submitted to amend previously transmitted information: The gender of the subject was corrected from male to female.

Follow-up (14Nov2023): This is a follow-up report combining information from duplicate reports AER 202200486416 and AER 2020108001. The current and all subsequent follow-up information will be reported under manufacturer report number AER 2020108001. The new information received from investigator includes: clinical course.

Case Comment: Considering that diarrhea is a known risk with bosutinib and the plausible temporal association, the reported diarrhea is assessed as related to bosutinib. The Company considers the reported event gastroenteritis is unrelated to suspect drug bosutinib but more likely an inter-current medical 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	200 mg, daily; Unknown	Unknown	26-FEB-2020 / 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		PRIVACY		90 Years	Male	88.00 kg	02	FEB	2020

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

ALTERATION OF Comorbidity (diabetes, cardiac failure) [Diabetes mellitus]
ALTERATION OF Comorbidity (diabetes, cardiac failure) [Cardiac failure]

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 Date: 02-FEB-2020
- ☐ 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) 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] (FUROSEMIDE) ; 01-OCT-2013 / Ongoing
#2) TAHOR (ATORVASTATIN CALCIUM) ; 01-OCT-2013 / Ongoing
#3) CORDARONE (AMIODARONE HYDROCHLORIDE) ; 2018 / Ongoing
#4) NEORECORMON (EPOETIN BETA) ; 24-JUN-2019 / 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)
Unknown to Ongoing	Relevant Med History	Cardiac failure (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.
2020121759

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

24c. DATE RECEIVED BY MANUFACTURER
09-DEC-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020121759

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

B1871047, Study alias BOSEVAL. A 90-year-old male subject started to receive bosutinib (BOSULIF)via an unspecified route of administration from 13Mar2018 to 19Jun2018 at 100 mg, once daily, via an unspecified route of administration from 20Jun2018 to 02Feb2020 at 100 mg, twice daily for an unspecified indication. Medical history included diabetes mellitus and cardiac failure. Concomitant medication included furosemide (LASILIX) from 01Oct2013 and ongoing for heart failure, atorvastatin calcium (TAHOR) from 01Oct2013 and ongoing for dyslipidemia, amiodarone hydrochloride (CORDARONE) from 2018 and ongoing for tachycardia, epoetin beta (NEORECORMON) from 24Jun2019 and ongoing for anaemia. On 02Feb2020, the subject experienced alteration of comorbidities (diabetes, cardiac failure) leading to death on the same day. The event was rated grade 5. Eastern cooperative oncology group (ECOG) performance status was 3 on 16Dec2019. The action taken in response to the event for bosutinib was unknown. The subject died on 02Feb2020. The subject died in chronic phase of chronic myeloid leukemia related to comorbidity (diabetes, cardiac failure). The cause of death was comorbidity (diabetes, cardiac failure). No autopsy was performed.

The investigator considered the event as not related to the study drug and concomitant medications.

Follow-up (25Mar2020): New information received from investigator via CRO included: dosage regimen of bosutinib and concomitant drugs.

Follow-up (30Jun2020): New information received from investigator includes: Reaction data (SAE term updated from alteration of general health to alteration of general status) and Death details (No autopsy was performed).

Follow-up (09Dec2020): New information received from investigator via CRO included: update of event verbatim to alteration of general status to alteration of comorbidities.

Case Comment: In concurrence with the reporting investigator, the Company attributed the reported fatal alteration of comorbidities (diabetes, cardiac failure) to the pre-existing medical conditions of diabetes and cardiac failure in this elderly subject with chronic myeloid leukemia and unrelated to the study drug, bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	16-DEC-2019	Eastern Cooperative Oncology Group performance status	3	

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, 2x/day; Unknown	Unknown	20-JUN-2018 / 02-FEB-2020; 593 days

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		PRIVACY		72 Years	Male	100.00 kg	14	FEB	2020

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

CORONARY INSUFFICIENCY [Coronary artery insufficiency]

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) Unknown

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

18. THERAPY DATES(from/to)
#1) 08-JUL-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)

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

From/To Dates	Type of History / Notes	Description
31-AUG-2018 to Ongoing	Relevant Med History	Chronic myelogenous leukemia (Chronic myeloid leukaemia)
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.
2020162233

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

24c. DATE RECEIVED BY MANUFACTURER
21-APR-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

A contactable physician reported that a 72-year-old male patient started to receive bosutinib (BOSULIF; film-coated tablet), via an unspecified route of administration from 08Jul2019 and ongoing at 500 mg, once daily (1x/day) for chronic myeloid leukaemia. Medical history included chronic myeloid leukaemia from 31Aug2018 and ongoing, ongoing hypertension, ongoing diabetes mellitus, and ongoing obesity. The patient's concomitant medications were not reported. The patient experienced grade 3 coronary insufficiency (hospitalization, life threatening) on 14Feb2020. No new thoracic pain. Laboratory data was not provided. The action taken in response to the event for bosutinib was dose not changed. Therapeutic measures were taken as a result of coronary insufficiency included coronarography in emergency and coronary stent insertion on 14Feb2020. The outcome of the event was recovered on 15Apr2020.

The reporter assessed the event coronary artery insufficiency as unrelated to study drug.

Case Comment: The reported event "grade 3 coronary insufficiency" is assessed as serious and unrelated to study drug, bosutinib (BOSULIF). This case will be updated when new information becomes available.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diabetic (Diabetes mellitus);
Unknown to Ongoing	Relevant Med History	Obesity (Obesity);

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		PRIVACY		72 Years	Male	87.00 kg		APR	2020

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

Perineal abscess [Perineal abscess]
Weight loss [Weight decreased]

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) Oral

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

18. THERAPY DATES(from/to)
#1) 19-OCT-2018 / 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) STAGID (METFORMIN EMBONATE) ; Ongoing
#2) APROVEL (IRBESARTAN) ; Ongoing
#3) GALVUS (VILDAGLIPTIN) ; Ongoing
#4) DIAMICRON (GLICLAZIDE) ; 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)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020222779

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-years-old male subject started to receive bosutinib (BOSULIF), oral from 19Oct2018, for chronic myeloid leukaemia. The most recent dose before the events was 400 mg, daily. Medical history included diabetes mellitus, hypertension, blood creatinine increased and diarrhoea. Concomitant medications included irbesartan (APROVEL) for arterial hypertension, metformin embonate (STAGID) for diabetes, vildagliptin (GALVUS) for diabetes, gliclazide (DIAMICRON) for diabetes, all ongoing. The subject experienced perineal abscess and weight loss in Apr2020. The event perineal abscess was rated with grade 3 and it required hospitalization from 23Apr2020 to 30Apr2020. Bacterial culture was positive for Staphylococcus Aureus. Bosutinib was temporarily stopped in response to this event, then resumed without recurrence of perineal abscess. Corrective treatment consisted in flattening of perineal abscess on 23Apr2020, then bandaging under sedation on 27Apr2020. Perineal abscess recovered on 12May2020. The event weight loss was rated by reporter with grade 2, non-serious, resolved on 06Sep2021. Bosutinib was not changed in response to this event.

The investigator considered both events as unrelated to study drug and concomitant medications.

Follow-up (09Jun2020): New information received from investigational site includes grade 3 for event perineal abscess and updated outcome, concomitant medications provided

Follow-up (28Oct2021): New information includes: updated onset date perineal abscess, updated outcome for weight loss.

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

Case Comment: Based on the clinical information currently provided, in agreement with the reporter's opinion, the company does not attribute perineal abscess and weight loss to suspect drug bosutinib, considering the intercurrent conditions in the setting of chronic myeloid leukaemia. 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		Bacterial test Positive	Positive to Staphylococcus Aureus	
2	APR-2020	Weight	Loss	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Creatinine increased (Blood creatinine increased);
Unknown to Ongoing	Relevant Med History	Diarrhea (Diarrhoea);

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		PRIVACY		72 Years	Male	87.00 kg	20	JAN	2020

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

Sepsis [Sepsis]
Bilateral sciatalgia [Sciatica]

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

(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) 19-OCT-2018 / 16-APR-2020	#1) 1 year 5 months 29 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) STAGID (METFORMIN EMBONATE) ; Ongoing
#2) APROVEL (IRBESARTAN) ; Ongoing
#3) GALVUS (VILDAGLIPTIN) ; Ongoing
#4) DIAMICRON (GLICLAZIDE) ; 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)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020222850

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-JUN-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020222850

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-years-old male patient started to receive bosutinib (BOSULIF) via an unspecified route of administration from 19Oct2018 at 400 mg, daily for an unspecified indication. Medical history included ongoing diabetes, ongoing arterial hypertension, ongoing creatinine increased grade 1, ongoing diarrhoea. Concomitant medication included metformin embonate (STAGID) ongoing for diabetes, irbesartan (APROVEL) ongoing for arterial hypertension, vildagliptin (GALVUS) ongoing for diabetes, gliclazide (DIAMICRON) ongoing for diabetes. Perineal abscess found at the pelvic scanner, having justified its transfer to urological surgery department (Perineal abscess reported under AER# 2020222779). The patient experienced sepsis on 16Apr2020, grade 2, requiring hospitalization, bilateral sciatalgia on 20Jan2020, grade 1, non-serious. Patient was hospitalization from 16Apr2020 to 23Apr2020 for dysuria, pelvic pain, pain in miction and right testicular pain, explained by urinary staphylococcus aureus infection, and orchiepididymitis. Setting up a probe and initial treatment with rocephine, then ofloxacin. Added 2 gentamycin injections. Lab tests and procedures included bacterial culture positive to staphylococcus aureus, pelvic scanner perineal abscess. The action taken in response to the events for bosutinib was temporarily withdrawn from 16Apr2020 to 23Apr2020. The outcome of event sepsis was recovered on 23Apr2020, of event bilateral sciatalgia was recovered on 05May2020. It was informed that sepsis did not reappeared after reintroduction.
The reporter considered both events were unrelated to study drug or concomitant medications.

Follow-up (09Jun2020): New information received from investigational site includes updated grade for sepsis (grade 2 instead of grade 3), update of action taken with bosutinib in response to sepsis (from dose not changed to temporarily withdrawn) and confirmation that sepsis did not reappeared after reintroduction.

Follow-up (19Jun2020): New information received from investigational site includes: bosutinib stop dates

Case Comment: Based on the available information, the Company concurs with the reporter that both events sepsis and bilateral sciatalgia are unrelated to study drug or concomitant medications, but more likely inter-current medical conditions.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Bacterial test	positive to staphylococcus aureus	
2		Scan	Perineal abscess	

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	Unknown	23-APR-2020 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Creatinine increased (Blood creatinine increased);
Unknown to Ongoing	Relevant Med History	Diarrhea (Diarrhoea);

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		PRIVACY		70 Years	Female	Unk		DEC	2019

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

DIARRHEA [Diarrhoea]
abdominal pains [Abdominal pain]
hypersensitivity [Hypersensitivity]

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

(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, 1x/day

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) 09-DEC-2019 / 14-APR-2020

19. THERAPY DURATION
#1) 4 months 6 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.
2020222980

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-DEC-2022

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020222980

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

protocol B1871047.
A 70-year-old female patient received bosutinib (BOSULIF), first regimen from 09Dec2019 to 14Apr2020 at 200 mg 1x/day and second regimen from 03Mar2020 to 14Apr2020 at 300 mg 1x/day, all oral for chronic myeloid leukaemia. The patient had no relevant medical history. The patient's concomitant medications were not reported.
On 07Jan2020, the subject presented with diarrhea and abdominal pains. In Apr2020, she experienced hypersensitivity. The events were all assessed as non-serious and rated grade 2. On 14Apr2020, the subject called for informing she had permanently stopped bosutinib due to intolerance: swelling of tongue, feeling of suffocation, diarrhea and abdominal pains. According to the physician, the subject presented with lip and tongue oedema due to hypersensitivity to bosutinib. The subject fully recovered from the events in May2020.

The investigator considered the events as related to bosutinib and unrelated to any concomitant medication.

Follow-up (09Jun2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. The subject stopped bosutinib on 14Apr2020.

Follow-up (01Mar2021). This is a follow-up to a non-interventional clinical study case reporting non-serious events only. Diarrhea and abdominals pains onset date was Dec2019, both recovered on unspecified date in 2020.
Hypersensitivity recovered on unspecified date in 2020.

Follow-ups (19Dec2022): These are follow-up reports of a non-interventional study report (Post Authorization Safety Study) received from contactable reporters (Physician and Other HCP) for protocol B1871047. Updated information included: new dosing regimen for bosulif added, stop date of evens confirmed and lip and tongue edema confirmed as symptoms of hypersensitivity to product.

Case Comment: A causal association between administration of bosutinib and the onset of hypersensitivity, diarrhea and abdominal pains cannot be excluded, considering the temporal association and the known adverse event profile of the suspect product.
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	300 mg, 1x/day; Oral	chronic myeloid leukemia (Chronic myeloid leukaemia)	03-MAR-2020 / 14-APR-2020; 1 month 12 days

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		PRIVACY		43 Years	Male	77.00 kg	30	APR	2020

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
MUTATION T315I [Gene mutation]

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) 500 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) 06-SEP-2019 / 20-MAY-2020

19. THERAPY DURATION
#1) 8 months 15 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) PONATINIB (PONATINIB) ; 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	Chronic myelogenous 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.
2020225154

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

24c. DATE RECEIVED BY MANUFACTURER
18-JAN-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 43 year-old male patient received bosutinib (BOSULIF), from 06Sep2019 (Batch/Lot number: unknown) to 20May2020 at 500 mg daily. Relevant medical history included: "Chronic myelogenous leukemia" (ongoing). Concomitant medication(s) included: PONATINIB.
The patient experienced mutation T315I grade 1, on 30Apr2020. The patient underwent lab tests and procedures which included gene mutation identification test on 30Apr2020. The appearance of mutation T315I was confirmed twice, with one month interval. The action taken in response to the event for bosutinib was permanently withdrawn on 20May2020, and no action taken for ponatinib. The outcome was recovered on 29Jun2021.

The event was not related to bosutinib and concomitant medication.

Follow-up (18Jan2022): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047. Updated information: Outcome updated, Causality assessment updated to not related, concomitant medication.

Case Comment: Based on the limited information provided, and until further detailed data become available, the company deems that, at the present time, there is not a reasonable possibility that the reported gene mutation is caused by bosutinib regimen. 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.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	30-APR-2020	Gene mutation identification test	T315I	

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		PRIVACY		72 Years	Male	87.00 kg			2019

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

Orchiepididymitis [Orchitis]
BENIGN PROSTATIC HYPERPLASIA [Benign prostatic hyperplasia]

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.

(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) 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)
#1) STAGID (METFORMIN EMBONATE) ; Ongoing
#2) APROVEL (IRBESARTAN) ; Ongoing
#3) GALVUS (VILDAGLIPTIN) ; Ongoing
#4) DIAMICRON (GLICLAZIDE) ; 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)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020227149

24c. DATE RECEIVED BY MANUFACTURER
09-JUN-2020

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 72-years-old male patient started to receive bosutinib (BOSULIF), via an unspecified route of administration from 19Oct2018 at 400 mg for an unspecified indication. Medical history included ongoing diabetes mellitus , ongoing hypertension , ongoing blood creatinine increased , ongoing diarrhoea. oncomitant medications included metformin embonate (STAGID) for diabetes mellitus, irbesartan (APROVEL) for arterial hypertension, vildagliptin (GALVUS) for diabetes mellitus, gliclazide (DIAMICRON) for diabetes mellitus. In 2019 the patient experienced benign prostatic hyperplasia, rated grade 2. On 16Apr2020, the patient reported a dysuria for several months and was found to have orchiepididymitis, rated grade1. The action taken in response to the events for bosutinib was dose not changed. The patient recovered from orchiepididymitis on 23Apr2020 while benign prostatic hyperplasia was ongoing. The events were assessed as non serious. The reporter considered the events were unrelated to study drugs or concomitant medications.

Case Comment: In concurrence with the reporter, the events orchiepididymitis and benign prostatic hyperplasia are unrelated to study drugs or concomitant medications.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Creatinine increased (Blood creatinine increased);
Unknown to Ongoing	Relevant Med History	Diarrhea (Diarrhoea);

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		PRIVACY		72 Years	Male	87.00 kg		APR	2020

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

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) for protocol B1871047.

A 72 year-old male patient received bosutinib (BOSULIF), since

(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 / 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) STAGID (METFORMIN EMBONATE) ; Ongoing
#2) APROVEL (IRBESARTAN) ; Ongoing
#3) GALVUS (VILDAGLIPTIN) ; Ongoing
#4) DIAMICRON (GLICLAZIDE) ; 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)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020227229

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 2020227229

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

19Oct2018 (Batch/Lot number: unknown) at 400 mg daily. Relevant medical history included: "Diabetes" (ongoing); "Arterial hypertension" (ongoing); "creatinine increased grade 1" (ongoing); "diarrhea" (ongoing); "benign prostate hyperplasia" (unspecified if ongoing); "urinary catheterization", stop date: 16Apr2020. Concomitant medication(s) included: STAGID taken for diabetes mellitus (ongoing); APROVEL taken for hypertension (ongoing); GALVUS taken for diabetes mellitus (ongoing); DIAMICRON taken for diabetes mellitus (ongoing).
Subject relieved by urinary catheterization on 16Apr2020. Urinary staphylococcus aureus infection was detected. A sepsis has developed on this urinary infection, as well as an orchi-epididymitis, this last having driven a perineal abscess (cross-referenced cases). On Apr2020, the subject experienced urinary infection. Event urinary infection was rated with grade 2 and reported as non-serious. In response to this event bosutinib was temporarily withdrawn and the event did not reappear after reintroduction. Event urinary tract infection was resolved on 23Apr2020. The event urinary tract infection was treated with unspecified treatment.

The investigator considered the event as unrelated to study drug or concomitant medication

Follow-up (21Sep2020): New information received from CRO included: previously reported event acute retention of urine was canceled.

Follow-up (28Oct2021): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information: Event onset date and Bosutinib dosage.

Case Comment: The reported event urinary infection is assessed as unrelated to study drug bosutinib (BOSULIF). Reported urinary catheterization and pre-existing diabetes mellitus provide alternative explanations. This case will be updated when new information becomes available.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Creatinine increased (Blood creatinine increased);
Unknown to Ongoing	Relevant Med History	Diarrhea (Diarrhoea);
Unknown	Relevant Med History	Benign prostatic hyperplasia (Benign prostatic hyperplasia);
Unknown to 16-APR-2020	Relevant Med History	Bladder catheterisation (Bladder catheterisation);

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		PRIVACY		31 Years	Female	68.00 kg		FEB	2020

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

vaginal burns [Vulvovaginal burning sensation]
aphthous [Aphthous ulcer]

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 with non-serious events 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) Bosutinib (BOSUTINIB) Unknown

15. DAILY DOSE(S)
#1)

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

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

18. THERAPY DATES(from/to)
#1) 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)

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.
2020235631

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

24c. DATE RECEIVED BY MANUFACTURER
15-JUL-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

A 31-year-old female subject started to receive bosutinib via an unspecified route of administration from an unspecified date at an unspecified dose for an unspecified indication. The patient's medical history was not reported. There was no concomitant therapy. The subject experienced vaginal burns, and aphthous in Feb2020; both reported as non-serious. The subject reported recent vaginal burns treated by local treatment with econazole nitrate (PEVARYL) and aphthous the week before. The action taken in response to the events for bosutinib was dose not changed. The outcome of the events was resolved on 17Feb2020.

According to the reporter, the event was unrelated to bosutinib and concomitant drug.

Follow-up (15Jul2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only.

The vaginal burns and aphthous were rated grade 1.

Case Comment: The company considered that both events vaginal burns and aphthous are unrelated to bosutinib. The underlying disease and concomitant medication are pending for further assessment.

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		PRIVACY		31 Years	Female	68.00 kg	17	FEB	2020

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

slight hepatic cytolysis [Hepatic cytolysis]

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

(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) 18-NOV-2019 / 25-DEC-2019	#1) 1 month 8 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LOPERAMIDE (LOPERAMIDE) ; Unknown
#2) DESOGESTREL (DESOGESTREL) ; 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	Bilirubin elevated (Blood bilirubin increased)
Unknown	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.
2020235680

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
19-FEB-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 Study report with non-serious events only.
A 31-years-old female subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 18Nov2019 to 25Dec2019 at 200 mg daily, from 26Dec2019 to 30Dec2019 at 300 mg daily, from 31Dec2019 and ongoing at 200 mg daily for an unspecified indication. The subject's medical history and concomitant medications were not reported.
The subject experienced slight hepatic cytolysis on 17Feb2020. The subject underwent lab tests and procedures which included alanine aminotransferase (ALAT) at 2N on 17Feb2020, aspartate aminotransferase (ASAT) at 14 on 20Dec2019, at 44 on 18Jan2020, at 85 on 17Feb2020, at 55 on 06May2020; no unit provided. The action taken in response to the event for bosutinib was dose not changed. The outcome of the event was recovering.
The event hepatic cytolysis was rated grade 1, non-serious, and assessed related to study drug and unrelated to concomitant medication.

Follow-up (10Aug2020): New information reported includes the following: The patient's height was updated. On 10Jul2020, AST was 40, grade 1, and resolving. Bosutinib was still maintained at 200 mg per day.

Follow-up (29Oct2020): New information received from investigational site includes the following: Medical history includes elevated bilirubin and dyslipidemia. It was unknown if the patient had a family history of hepatic disease. Relevant concomitant drugs included loperamide and desogestrel for contraception. Laboratory data included: ALAT was 10 IU/L on 11Mar2019, 27 IU/L on 05Nov2019, 24 IU/L on 15Nov2019 (normal range: 10-49), 85 IU/L on 17Feb2020 (normal range: 10-49), 55 IU/L on 06May2020 (normal range: 10-49), 85 IU/L on 24Aug2020 (normal range: 10-49), 48 IU/L on 06Oct2020 (normal range: 10-49); aspartate aminotransferase: 15 IU/L on 11Mar2019, 18 IU/L on 05Nov2019 (normal range: 0-34), 18 or 16 IU/L on 15Nov2019 (normal range: 0-34), 35 (not 85 as previously reported) IU/L on 17Feb2020 (normal ranges: 0-34), 25 (not 55 as previously reported) IU/L on 06May2020 (normal ranges: 0-34), 35 IU/L on 24Aug20120, (normal ranges: 0-34), 27 IU/L on 06Oct2020 (normal ranges: 0-34); Gamma-glutamyltransferase (normal range: 46-116) 17 IU/L on 15Nov2019, 14 IU/L on 17Feb2020, 16 IU/L on 06May2020, 20 IU/L on 24Aug2020, 17 IU/L on 06Oct2020; total bilirubin (normal range: LT 21) 35.5 umol/l on 15Nov2019, 11 umol/l on 17Feb2020, 18 umol/l on 06May2020, 18 umol/l on 24Aug2020, 8.4 umol/l on 06Oct2020; conjugated bilirubin (normal range: LT 5) 10.1umol/l on 15Nov2019, lipase (normal ranges:12-53), 39 IU/L on 15Nov2019, 52 IU/L on 17Feb2020, 46 IU/L on 06May2020, 83 IU/L on 24Aug2020, 50 IU/L on 06Oct2020. According to the reporter it is a new adverse event, no symptoms related to hepatic cytolysis.

Follow-up (19Feb2021). This follow-up is received from the investigational site via CRO. New information was:

Hepatic cytolysis recovered on 23Nov2020.

Case Comment: The reported event hepatic cytolysis is likely due to bosutinib, considering temporal association and the known hepatotoxicity. 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	11-MAR-2019	Alanine aminotransferase	10 IU/l	
2	05-NOV-2019	Alanine aminotransferase	27 IU/l	
3	15-NOV-2019	Alanine aminotransferase	24 IU/l	49 10
4	17-FEB-2020	Alanine aminotransferase	2N	
5	17-FEB-2020	Alanine aminotransferase	85 IU/l	49 10
6	06-MAY-2020	Alanine aminotransferase	55 IU/l	49 10
7	24-AUG-2020	Alanine aminotransferase	85 IU/l	49 10
8	06-OCT-2020	Alanine aminotransferase	48 IU/l	49 10
9	11-MAR-2019	Aspartate aminotransferase	15 IU/l	
10	05-NOV-2019	Aspartate aminotransferase	18 IU/l	34 0
11	15-NOV-2019	Aspartate aminotransferase	18 or 16 IU/l	34

Mfr. Control Number: 2020235680

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
				0
12	20-DEC-2019	Aspartate aminotransferase	14	
13	18-JAN-2020	Aspartate aminotransferase	44	
14	17-FEB-2020	Aspartate aminotransferase	35 IU/l	34 0
15	06-MAY-2020	Aspartate aminotransferase	25 IU/l	34 0
16	10-JUL-2020	Aspartate aminotransferase	40 IU/l	
17	24-AUG-2020	Aspartate aminotransferase	35 IU/l	34 0
18	06-OCT-2020	Aspartate aminotransferase	27 IU/l	34 0
19	15-NOV-2019	Bilirubin conjugated	10.1 umol/l	5
20	15-NOV-2019	Blood bilirubin	35.5 umol/l	21
21	17-FEB-2020	Blood bilirubin	11 umol/l	21
22	06-MAY-2020	Blood bilirubin	18 umol/l	21
23	24-AUG-2020	Blood bilirubin	18 umol/l	21
24	06-OCT-2020	Blood bilirubin	8.4 umol/l	21
25	15-NOV-2019	Gamma-glutamyltransferase	17 IU/l	116 46
26	17-FEB-2020	Gamma-glutamyltransferase	14 IU/l	116 46
27	06-MAY-2020	Gamma-glutamyltransferase	16 IU/l	116 46
28	24-AUG-2020	Gamma-glutamyltransferase	20 IU/l	116 46
29	06-OCT-2020	Gamma-glutamyltransferase	17 IU/l	116 46
30	15-NOV-2019	Lipase	39 IU/l	53 12
31	17-FEB-2020	Lipase	52 IU/l	53 12
32	06-MAY-2020	Lipase	46 IU/l	53 12
33	24-AUG-2020	Lipase	83 IU/l	53 12
34	06-OCT-2020	Lipase	50 IU/l	53 12

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, daily; Unknown	Unknown	26-DEC-2019 /

Mfr. Control Number: 2020235680

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			30-DEC-2019; 5 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	31-DEC-2019 / 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		PRIVACY		31 Years	Female	68.00 kg		NOV	2019

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 report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. This is a Non-Interventional Study report with non-serious events 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) 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) 18-NOV-2019 / 25-DEC-2019	#1) 1 month 8 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.
2020235729

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
16-JUN-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020235729

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 31-year-old female subject started to receive bosutinib (BOSULIF) at 200 mg daily from 18Nov2019 to 25Dec2019, at 300 mg daily from 26Dec2019 to 30Dec2019 for an unspecified indication. Relevant medical history was not reported. The subject was not receiving any concomitant treatment.
On an unspecified date in Nov2019, the subject experienced diarrhea and abdominal pain, both rated grade 1, non-serious, The patient reported at the beginning of the treatment abdominal pain with a few diarrhea, and no constipation, this abdominal pain persisted for a few days and reappeared when it was proposed to increase BOSULIF dose from 200 to 300 mg per day. She reported that she did not take her treatment every day at that time due to the severity of this pain. She resumed at dose 200 mg every day from 31Dec2019, bosutinib was ongoing. Diarrhea was recovered on an unspecified date in 2019 while abdominal pain recovered on 17Feb2020.
The reporter considered the events related to study drug.

Case Comment: Based on a positive drug-event temporal association and on the known safety profile of the suspect drug, the company concurs with the causality assessment expressed by the investigator, considering there is a reasonable possibility that diarrhea and abdominal pain are related to the 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	300 mg, daily; Unknown	Unknown	26-DEC-2019 / 30-DEC-2019; 5 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	31-DEC-2019 / 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		PRIVACY		53 Years	Male	90.00 kg	23	MAR	2020

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

diarrheas [Diarrhoea]
hepatic cytolysis [Hepatic cytolysis]
DRY SKIN [Dry skin]
Ecchymosis [Ecchymosis]
Folliculitis [Folliculitis]

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) 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) 19-DEC-2019 / 07-JAN-2020	#1) 20 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) GAVISCON [SODIUM ALGINATE;SODIUM BICARBONATE] (SODIU
#2) LOPERAMIDE (LOPERAMIDE) ; 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 23-MAR-2020	Relevant Med History	Dry eczema (Eczema asteatotic)
Unknown	Relevant Med History	Tachycardia (Tachycardia)

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.
2020238927

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
13-DEC-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 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.

A 53-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 19Dec2019 to 07Jan2020 at 200 mg, daily, via an unspecified route of administration from 08Jan2020 to 18Feb2020 at 300 mg, daily, via an unspecified route of administration from 19Feb2020 and ongoing at 400 mg, daily for an unspecified indication. Medical history included dry eczema of lower limb stasis from an unknown date to 23Mar2020. Concomitant medications were not reported. The medical report of 23Mar2020 stated slight dry skin. The subject experienced dry skin on 23Mar2020. The event dry skin was reported a minimal and assessed as non-serious and rated grade 1. The action taken in response to the event for bosutinib was dose not changed. The outcome of the dry skin was recovered on 22Jun2020.

The investigator considered the event was not related to the study drug and concomitant medications.

Follow-up (03Jul2020): additional information received from the investigational site via the CRO was as follows:
In Jun2020, the subject experienced diarrheas and ecchymosis, both considered non-serious and rated grade 1. The medical report stated that the tolerance to BOSULIF was overall very good, except diarrheas less than once a month, described as "violent" and occurring rather at night "without warning". The subject took few, if any at all loperamide, presence of some ecchymosis and dermabrasions following a fall during a running was noted.
Bosutinib dose was not changed in response to these two events. The event diarrheas had not recovered. The event ecchymosis was recovering. The investigator considered that diarrheas was related to bosutinib and unrelated to a concomitant drug and that ecchymosis was unrelated to bosutinib or to a concomitant drug.
On 29Apr2020, the subject experienced hepatic cytolysis considered non-serious and rated grade 1. Bosutinib dose was not changed in response to the event. On 05Mar2020, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were normal. On 29Apr2020, ALT was 51. On 13May2020, ALT was 73, AST was 40. On 27May2020, ALT was 105, AST was 55. On 09Jun2020, ALT was 144, AST was 56. On 22Jun2020, ALT was 144, AST was 62, hepatitis C serology was negative, hepatitis A serology and serology EBV revealed old immunization. The event hepatic cytolysis was recovering. The investigator considered that hepatic cytolysis was related to bosutinib and unrelated to a concomitant drug.
The subject received bosutinib at 400 mg, daily from 19Feb2020 to 31Mar2020 then at 500 mg, daily from 01Apr2020 and ongoing.
Event dry skin recovered on 23Mar2020.

Follow-up (14Aug2020): New information was received from the investigational site via the CRO reporting the patient recovered from dry skin on 22Jun2020 and that the event was minimal.

Follow-up (29Oct2020): New information received from the investigational site via the CRO includes: Hepatic cytolysis was grade 2 on 06Jul2020. The hepatic cytolysis was a new event. The subject did not develop symptom related to the cytolysis. Concomitant medications included sodium alginate, sodium bicarbonate (GAVISCON) and loperamide (manufacturer unknown) as needed. Before the beginning of study treatment, the subject had effort tachycardia, and simple banal minimal mitral insufficiency. It was unknown if the subject had familial history of liver disease. During the year before the beginning of the study treatment, liver function tests were performed : on 20Mar2019, AST was 16, ALT was 21, on 20May2019, AST was 19, ALT was 13, on 29Jul2019, AST was 19, ALT was 13, on 28Oct2019, AST was 37, ALT was 22. At the beginning of the study treatment, liver function test was performed : on 19Dec2019, AST was 16 and ALT was 13. During the treatment, liver function test disclosed the following : on 29Apr2020, AST was 30, ALT was 51, GGT was 14, total bilirubin was 6.8, on 06Jul2020, AST was 63, ALT was 154 (grade 2) ,GGT was 23, total bilirubin was 9.2, on 06Aug2020, AST was 80, ALT was 135, GGT was 26, bilirubin total was 7.9, on 07Sep2020, AST was 61, ALT was 108, GGT was 26, and total bilirubin was 8.2, on 05Oct2020, AST was 117, ALT was 60, GGT was 29, and total bilirubin was 16 mmol/l.

Follow-up (29Apr2021) New information received from the investigational site via the CRO includes: on 25Mar2021 ALT was 48, grade 1 and AST was 32. The event diarrhea resolved on 12Jan2021 and the event ecchymosis resolved on 05Oct2020.

Follow-up (13Dec2021 and 14Dec2021): New information from the investigational site via the CRO includes medical history added (chronic myeloid leukemia), reaction data (recovery date of the event diarrhea was updated to 11Jan2021, outcome of event hepatic cytolysis was updated to recovered on 02Nov2020) and new event (Folliculitis) added.
Additionnal information: On 05Oct2020, the subject experienced folliculitis considered non-serious and rated grade 1, no action taken in response to this event, unrelated to study drug and concomitant medication. The outcome of the event folliculitis was resolved in Oct2020, the outcome of the event diarrhea resolved on 11Jan2021, the outcome of the event hepatic cytolysis was recovered on 02Nov2020.

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 hepatic cytolysis are related to bosutinib administration cannot be excluded. Conversely, the reported dry skin, ecchymosis and Folliculitis are unlikely related to bosutinib administration.
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	20-MAR-2019	Alanine aminotransferase	21	
2	20-MAY-2019	Alanine aminotransferase	13	
3	29-JUL-2019	Alanine aminotransferase	13	
4	28-OCT-2019	Alanine aminotransferase	22	
5	19-DEC-2019	Alanine aminotransferase	13	
6	05-MAR-2020	Alanine aminotransferase	normal	
7	29-APR-2020	Alanine aminotransferase	51	
8	13-MAY-2020	Alanine aminotransferase	73	
9	27-MAY-2020	Alanine aminotransferase	105	
10	09-JUN-2020	Alanine aminotransferase	144	
11	22-JUN-2020	Alanine aminotransferase	144	
12	06-JUL-2020	Alanine aminotransferase grade 2	154	
13	06-AUG-2020	Alanine aminotransferase	135	
14	07-SEP-2020	Alanine aminotransferase	108	
15	05-OCT-2020	Alanine aminotransferase	60	
16	25-MAR-2021	Alanine aminotransferase grade 1	48	
17	20-MAR-2019	Aspartate aminotransferase	16	
18	20-MAY-2019	Aspartate aminotransferase	19	
19	29-JUL-2019	Aspartate aminotransferase	19	
20	28-OCT-2019	Aspartate aminotransferase	37	
21	19-DEC-2019	Aspartate aminotransferase	16	
22	05-MAR-2020	Aspartate aminotransferase	normal	
23	29-APR-2020	Aspartate aminotransferase	30	
24	13-MAY-2020	Aspartate aminotransferase	40	
25	27-MAY-2020	Aspartate aminotransferase	55	

Mfr. Control Number: 2020238927

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
26	09-JUN-2020	Aspartate aminotransferase	56	
27	22-JUN-2020	Aspartate aminotransferase	62	
28	06-JUL-2020	Aspartate aminotransferase	63	
29	06-AUG-2020	Aspartate aminotransferase	80	
30	07-SEP-2020	Aspartate aminotransferase	61	
31	05-OCT-2020	Aspartate aminotransferase	117	
32	25-MAR-2021	Aspartate aminotransferase	32	
33	29-APR-2020	Blood bilirubin	6.8 mmol/L	
34	06-JUL-2020	Blood bilirubin	9.2 mmol/L	
35	06-AUG-2020	Blood bilirubin	7.9 mmol/L	
36	07-SEP-2020	Blood bilirubin	8.2 mmol/L	
37	05-OCT-2020	Blood bilirubin	16 mmol/L	
38	22-JUN-2020	Epstein-Barr virus test	old immunization	
39	29-APR-2020	Gamma-glutamyltransferase	14	
40	06-JUL-2020	Gamma-glutamyltransferase	23	
41	06-AUG-2020	Gamma-glutamyltransferase	26	
42	07-SEP-2020	Gamma-glutamyltransferase	26	
43	05-OCT-2020	Gamma-glutamyltransferase	29	
44	22-JUN-2020	Hepatitis A virus test	old immunization	
45	22-JUN-2020	Hepatitis C virus test Negative	NEGATIVE	

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-JAN-2020 / 18-FEB-2020; 1 month 11 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	400 mg, daily; Unknown	Unknown	19-FEB-2020 / 31-MAR-2020;

Mfr. Control Number: 2020238927

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 month 13 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	500 mg, daily; Unknown	Unknown	01-APR-2020 / Ongoing; Unknown

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

#1) GAVISCON [SODIUM ALGINATE;SODIUM BICARBONATE] (SODIUM ALGINATE, SODIUM BICARBONATE) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Mitral insufficiency (Mitral valve incompetence);
Unknown	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		PRIVACY		35 Years	Male	122.00 kg	16	SEP	2019

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

Increase of AST [Aspartate aminotransferase increased]
Increase of ALT [Alanine aminotransferase increased]

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

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

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) 12-DEC-2018 / 17-JUN-2020

19. THERAPY DURATION
#1) 1 year 6 months 6 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) HYPERIUM (RILMENIDINE PHOSPHATE) ; Unknown
#2) LERCAN (LERCANIDIPINE HYDROCHLORIDE) ; Unknown
#3) TEMERITDUO (HYDROCHLOROTHIAZIDE, NEBIVOLOL 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
2015 to Unknown	Relevant Med History	Hepatic function abnormal (Hepatic function abnormal)
Unknown	Relevant Med History	Metabolic disorder (Metabolic 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.
2020260943

24c. DATE RECEIVED BY MANUFACTURER
20-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.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A contactable physician reported that a 35-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 12Dec2018 to 17Jun2020 at 300 mg, daily for chronic myeloid leukaemia. Medical history was not reported. The subject is taking unspecified concomitant treatment. The subject experienced increase of Alanine aminotransferase (ALT) and increase of Aspartate aminotransferase (AST) on 16Sep2019. The events started on 10Mar2020, but the investigator was aware of these events on 17Jun2020 and stopped bosutinib. The events increase of ALT and increase of AST were rated grade 3 and non-serious. Lab values were as follows: ALT: 308 IU/l on 10Mar2020 and 420 IU/l on 17Jun2020 (normal range: 0 to 42 IU/l); and AST: 275 IU/l on 17Jun2020 (normal range: 0 to 38 IU/l). ALT at 157 IU/L on 16Sep2019. The action taken in response to the events for bosutinib was permanently withdrawn on 17Jun2020. The outcome of the events was resolved on 23Feb2022.

According to the investigator, events were related to study treatment and unrelated to concomitant treatment.

Follow-up (06Oct2020): This is a follow-up to a non-interventional clinical study case reporting non-serious events only. The events increase of Alanine aminotransferase (ALT) and increase of Aspartate aminotransferase (AST) started in Nov2019 (previously reported as 10Mar2020).

Follow-up (28Apr2021): New information received includes:
The event (increase of ALT, AST) was a new event. Hepatic function test was done in year preceding start of treatment on 12Dec2018, at the start of treatment, during treatment and after the treatment. The subject received concomitant treatments for cardiac disease or arterial pression: rilmenidine phosphate (HYPERIUM) and lercanidipine hydrochloride (LERCAN). Following events were present before the start of treatment: hepatic function test elevated in 2015, metabolic disease, hypertension, hypertriglyceridemia, left nephritic colic in Jul2011, overweight since 5 years. Subject had family history of hepatic neoplasia in father. Lab test were: ALT (N <42) 84 on IU/L on 24Jan2018, 120 IU/L on 25Jul2018, 102 IU/L on 12Sep2018, 93 IU/L on 26Sep2018, 98 IU/L on 09Dec2019, 308IU/L on 10Mar2020, 350IU/L on 09Jun2020, 420 IU/L on 17Jun2020, 160 IU/l on 07Jul2020, 153 IU/L on 08Sep2020, 265 IU/L on 07Dec2020, 240 IU/L on 11Dec2020, 172 IU/L on 26Jan2021; AST (N<38) 111 IU/l on 24Jan2018, 202 IU/L on 25Jul2018, 136 IU/L on 12Sep2018, 135 IU/L on 26Sep2018, 115 IU/L on 09Dec2019, 286 IU/L on 10Mar2020, 291 IU/L on 09Jun2020, 275 IU/L on 17Jun2020, 153 IU/l on 07Jul2020, 168 IU/L on 08Sep2020, 278 IU/L on 07Dec2020, 275 IU/L on 11Dec2020, 169 IU/l on 26Jan2021.
Consultation report of 10Jul2020: subject was seen in consultation for perturbation of hepatic function. Subject had medical history of hypertension arterial, overweight since 5 years, chronic myeloid leukemia discovered in 2015 (treated successively by Tasigna, Dasatinib, Bosulif. Concomitant treatment included hydrochlorothiazide/nebivolol hydrochloride (TEMERITDUO), Lercan and Hyperium. Subject was not smoking, did not drink alcohol and had no allergy. Had family history of cancer in father. Hepatic function test was perturbated from around 2015 with recent aggravation. Indeed, subject had blood test showing ALT at 400 IU/L and AST at 275 IU/l. Bosulif was interrupted 2 weeks and work up seemed to improve clearly with ALT at 153 IU/l and AST at 160 IU/L. There was no other favoring element. Weight was 119 kg. Abdomen was supple, with hepatomegaly. Cardio-pulmonary auscultation was without particularity. Blood pressure was elevated at that day at 170/80 mmHg. No sign of hepatopathy decompensation was noted. Two elements could favor hepatic perturbations: possible toxicity of Bosulif and probably background problem related to steatopathy.
Consultation report of 17Dec2020: the subject was seen again on 17Dec2020. There were two elements that were taken in account: a steatosis favored by weight gain in last 5 years and discovery of chronic myeloid leukemia and drug toxicity of Bosulif that was mentioned. Latest was modified with start of Asciminib. Hepatic function test was perturbated with AST at 240 IU/L. There was also perturbation of work-up with moderated hypertriglyceridemia and low cholesterol HDL. Ferritin and martial work-up were without particularity. IgG was discretely increased. Weight was increasing at 124 kg. No signs of advanced hepatopathy. Abdomen was supple and painless, without palpable masse. Cardio-pulmonary auscultation was without particularity.
Liver biopsy (27Jan2021): conclusion: biopsy showed intense lesions of steatopathy. From etiologic point of view these morphologic aspects corresponded to metabolic syndrome (NASH) or toxic etiology. More rarely drug toxicity could be responsible of steatopathy (to be confronted to clinical data). Score NASH : 7 (steatosis 3, lobular inflammation 2, balloonization: 2); fibrosis 3.

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.

Follow-up (07Jun2023): This is a Non-Interventional study follow up report from the investigational site via the CRO.
Updated information included: lab data, reaction date (onset date, outcome).

Follow-up (20Jul2023): 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: study drug information (start date).

Case Comment: The events increase of ALT and increase of AST is considered related to bosutinib, considering the temporal association and the known safety profile.
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		Alanine aminotransferase	400 IU/l	42
2	24-JAN-2018	Alanine aminotransferase	84 IU/l	42
3	25-JUL-2018	Alanine aminotransferase	120 IU/l	42
4	12-SEP-2018	Alanine aminotransferase	102 IU/l	42
5	26-SEP-2018	Alanine aminotransferase	93 IU/l	42
6	16-SEP-2019	Alanine aminotransferase	157 IU/l	42
7	09-DEC-2019	Alanine aminotransferase	98 IU/l	42
8	10-MAR-2020	Alanine aminotransferase	308 IU/l	42
9	09-JUN-2020	Alanine aminotransferase	350 IU/l	42
10	17-JUN-2020	Alanine aminotransferase	420 IU/l	42
11	07-JUL-2020	Alanine aminotransferase	160 IU/l	42
12	08-SEP-2020	Alanine aminotransferase	153 IU/l	42
13	07-DEC-2020	Alanine aminotransferase	265 IU/l	42
14	11-DEC-2020	Alanine aminotransferase	240 IU/l	42
15	26-JAN-2021	Alanine aminotransferase	172 IU/l	42
16		Aspartate aminotransferase	160 IU/l	38
17	24-JAN-2018	Aspartate aminotransferase	111 IU/l	38
18	25-JUL-2018	Aspartate aminotransferase	202 IU/l	38
19	12-SEP-2018	Aspartate aminotransferase	136 IU/l	38
20	26-SEP-2018	Aspartate aminotransferase	135 IU/l	38
21	09-DEC-2019	Aspartate aminotransferase	115 IU/l	38
22	10-MAR-2020	Aspartate aminotransferase	286 IU/l	38
23	09-JUN-2020	Aspartate aminotransferase	291 IU/l	38
24	17-JUN-2020	Aspartate aminotransferase	275 IU/l	38
25	07-JUL-2020	Aspartate aminotransferase	153 IU/l	38
26	08-SEP-2020	Aspartate aminotransferase	168 IU/l	38
27	07-DEC-2020	Aspartate aminotransferase	278 IU/l	38

Mfr. Control Number: 2020260943

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
28	11-DEC-2020	Aspartate aminotransferase	275 IU/l	38
29	17-DEC-2020	Aspartate aminotransferase	240 IU/l	38
30	26-JAN-2021	Aspartate aminotransferase	169 IU/l	38
31	10-JUL-2020	Auscultation	without particularity	
32	17-DEC-2020	Auscultation	without particularity	
33	27-JAN-2021	Biopsy liver	intense lesions of steatopathy	
34	17-DEC-2020	Blood immunoglobulin G	discretely increased	
35	17-DEC-2020	Blood iron	without particularity	
36	10-JUL-2020	Blood pressure measurement	170/80 mmHg	
37	17-DEC-2020	Investigation	moderated hypertriglyceridemia and low cholesterol	
38	10-JUL-2020	Physical examination	Abdomen was supple, with hepatomegaly	
39	17-DEC-2020	Physical examination	Abdomen was supple and painless	
40	10-JUL-2020	Weight	119 kg	
41	17-DEC-2020	Weight	124 kg	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Hypertension (Hypertension);
Unknown	Relevant Med History	Hypertriglyceridemia (Hypertriglyceridaemia);
JUL-2011 to Unknown	Relevant Med History	Colic renal (Renal colic);
Unknown	Relevant Med History in father	Hepatic neoplasia (Hepatic neoplasm);
Unknown	Relevant Med History since 5 years	Overweight (Overweight);
2015 to Unknown	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia);
Unknown	Past Drug Event	Tasigna (TASIGNA); Drug Indication: Chronic myeloid leukemia (Chronic myeloid leukaemia)
Unknown	Past Drug Event	Dasatinib (DASATINIB); Drug Indication: 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		PRIVACY		77 Years	Male	83.00 kg	17	JUL	2020

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 urinary retention [Urinary retention]
Severe masculin E. Coli urinary infection (grade 4) [Escherichia urinary tract infection]
Lower limb oedema during episode of acute urinary retention [Oedema peripheral]

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) 01-APR-2019 / 14-APR-2019	#1) 14 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) VESICARE (SOLIFENACIN SUCCINATE) ; Unknown
#2) EUPANTOL (PANTOPRAZOLE SODIUM SESQUIHYDRATE) ; Unknown
#3) GLUCOPHAGE (METFORMIN HYDROCHLORIDE) ; Unknown
#4) TRULICITY (DULAGLUTIDE) ; Unknown
#5) LANTUS (INSULIN GLARGINE) ; Unknown
#6) ELISOR (PRAVASTATIN SODIUM) Tablet ; 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
11-SEP-2017 to Ongoing	Relevant Med History	Chronic myeloid leukemia (Chronic myeloid leukaemia) in chronic phase in major molecular response in Sep2020
2017 to Unknown	Relevant Med History	complicated with diabetic retinopathy and muscular infarct of the right thigh (2017), 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.
2020309064

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

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 contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

A 77-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 01Apr2019 to 14Apr2019 at 100 mg, daily; from 15Apr2019 to 02Jul2019 at 200 mg, daily; from 03Jul2019 at 300 mg, daily; and from 02Oct2019, 30Dec2019, 30Mar2020, 24Jun2020, 16Sep2020, 07Dec2020 to an unspecified date at 300 mg, 1x/day; from 08Mar2021 to 06Sep2021 and ongoing from 02Jun2021 at 200 mg, 1x/day for an unspecified indication.
Medical history included benign prostate hypertrophy which was ongoing, chronic myeloid leukemia (CML) from 11Sep2017 to ongoing (in chronic phase in major molecular response in Sep2020), insulin-dependent diabetes mellitus from 2017 to ongoing (complicated with diabetic retinopathy and muscular infarct of the right thigh (2017), under treatment), arterial hypertension from 2000 to ongoing, metastatic prostate adenocarcinoma in the bones from 03Sep2000 to ongoing (currently treated with abiraterone + degarelix acetate (FIRMAGON) with good response), hypercholesterolemia, notion of ulcer confirmed by gastroscopy in 2019, renal lithiasis, benign prostate hypertrophy, sigmoid diverticule, operated bilateral cataract and bilateral deafness with device. Concomitant medications included solifenacin succinate (VESICARE), pantoprazole sodium sesquihydrate (EUPANTOL), metformin hydrochloride (GLUCOPHAGE), dulaglutide (TRULICITY), insulin glargine (LANTUS), ravastatin sodium (ELISOR), amlodipine besilate (AMLOR), irbesartan, manidipine, colecalciferol (ZYMAD), paracetamol (DOLIPRANE), alfuzosin hydrochloride (XATRAL) and fesoterodine fumarate (TOVIAZ).
The reported serious adverse events were acute urinary retention (grade 3) with onset date on 17Jul2020 and severe masculin E. Coli urinary infection (grade 4) on 02Aug2021. Seriousness criteria of the events was reported as hospitalization. Lower limb oedema during episode of acute urinary retention was also reported as a non-serious event, rated grade 2 with onset date on 18Jul2020. Action taken in response to the events with bosutinib was dose not changed for lower limb oedema and temporarily withdrawn for the other events. The subject recovered from urine retention on 11Aug2020. The outcome of event urinary infection was recovered on 17Aug2021.
On 26Jun2020, consultation in urology for lower tract symptoms, emptying phase and clinical examination is in favour of prostate cancer. PSA done on 27Jun2020. On 18Jul2020, first episode of acute urinary retention with a trip to the emergency room (less than 24 hours) and placement of a urinary catheter. On 19Jul2020, removal of the urinary catheter. The patient has not urinated since 09Aug2020. On 10Aug2020, the subject went to emergency for urinary retention / no miction since 09Aug2020. A urinary catheter with 800 ml of urine was inserted. The subject was transferred on 10Aug2020 in urology unit for history taking. Anamnesis: on 26Jun2020, urology consultation for lower system symptom, draining phase was performed. Clinical examination was in favour of prostate cancer. On 27Jun2020, Prostate Specific Antigen (PSA) was 7.6 (>4 suspicion cancer prostate). On 18Jul2020, first episode of acute urinary retention was noted with admission to emergency(< 24h) and insertion of an urinary probe removed on 19Jul2020. On 20Jul2020, consultation in urology unit with reinsertion of urine probe, removed on 03Aug2020: failure because of difficult miction and no more mictions since 09Aug2020. On 11Aug2020 the urology report stated that an urine probe has resolved the problem and the subject, after 48 hours of surveillance, can return home. The subject thus returned home with a urinary catheter in place / urology consultation scheduled for 04Sep2020. It was reported in the emergency report that subject follow-up in urology for prostate cancer who should be operated on 23Sep2020. The subject was seen as an emergency by the urologist on 03Aug2021 for recurring dysuria and a burning sensation upon urinating with pollakiuria. dilation of the urethra in a consultation on 03Aug2021, which revealed two urethral stenoses. The subject went to the emergency room on 04Aug2021 following hyperthermia and non-radiating pains in the right lumbar fossa for the last 48 hours, a burning sensation upon urinating and asthenia. Subject was hospitalized from 05Aug2021 to 17Aug2021 for a serious urinary infection with e coli complicated with bacteremia (antibiotic therapy) and renal failure requiring hyperhydration as well as an uncontrolled blood pressure (reajustment of the arterial hypertension treatment) and diabetic (readjustment of the treatment) he remained bedridden for a long time and he underwent a follow-up with physical therapy; further examinations were performed: urine cytology, blood culture, renal ultrasound, CT scan, blood and biochemistry test, COV SARS. Blood culture and cytobacteriological examination of urine were performed on 04Aug2021 and revealed E Coli infection. Kidney ultrasound and abdominal scan were performed on 05Aug2021. Bosutinib was discontinued from 06Aug2021 to 12Aug2021 then re-initiated. The patient was seen by the haematologist in a medical consultation on 09Sep2021 and here was his report: "stable weight at 77kg, good appetite, PS 0/1, no recent fever, cardiopulmonary auscultation normal, abdomen supple and painless, no palpable organomegaly". Bosulif was decreased on 09Sep2021 to 100 mg/day alternating with 200 mg/day following acute renal failure, metformin hydrochloride (GLUCOPHAGE) and irbesartan were discontinued following an acute renal infection since hospitalization.
Hospitalization report (from 05Aug2021 to 17Aug2021):
COVID status: Not given. The subject was hospitalized for male urinary tract infection.
The medical context was characterized by: Was seen by the physician on 03Aug2021 and 2 blind dilatations were performed which revealed 2 urethral stenoses. For the last 2 days, asthenia, cannot get up anymore. Consultation in the Emergency Room for hyperthermia combined with non-radiating pains in the right lumbar fossa. Describes a burning sensation upon urinating
In the Emergency Room on 04Aug2021: Clinically: Good general state, Regular heart sounds, no murmur, no signs of right- or left-sided heart failure, Bilateral and symmetrical vesicular breath sounds, no focal area, Abdomen supple, sensitive in the right lumbar fossa with no guarding. Overall, context more suggestive of right-sided pyelonephritis. Laboratory tests revealed CRP at 142, hyperleukocytosis, degradation of the renal function with BUN at 10 and creatinine at 200, hyperleukocytosis at 19 G/L, positive urine culture. Therefore, the patient with a history of adenocarcinoma with a bone metastasis in the prostate undergoing treatment with abiraterone and degarelix (FIRMAGON) and CML under bosutinib, hospitalized for a male urinary tract infection in the post-emergency medicine unit.
Treatment upon admission included bosutinib 100 mg: 2 tablets per day in the evening in one dose during a meal, solifenacin

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

succinate (VESICARE) 5 mg: 1 tablet in the evening, pantoprazole sodium sesquihydrate (EUPANTOL) 40 mg: 1 tablet in the morning, metformin hydrochloride (GLUCOPHAGE) 1000 mg in the morning and evening, dulaglutide (TRULICITY) 1.5 1 injection per week, insulin glargine (LANTUS) 10 IU in the morning, pravastatin sodium (ELISOR) 20 mg 1 tablet in the evening, zoledronic acid (ALMUR) 5 mg 1 capsule in the morning, irbesartan 300 1 tablet in the morning, manidipine 20 1 in the morning, colecalciferol (ZYMAD) 50,000 1 vial per month, paracetamol (DOLIPRANE) 1 g in the morning and evening, alfuzosin hydrochloride (XATRAL XL) 10 mg: 1 tablet in the evening, fesoterodine fumarate (TOVIAZ) 8 mg: 1 tablet in the evening.
The information collected during his hospitalization were: Severe male urinary tract infection with E Coli complicated with bacteraemia and renal failure. The renal ultrasound performed to look for an obstacle or a complication was normal. An abdomen pelvis PET scan with no contrast medium was also performed due to the appearance of guarding on the right and revealed an infiltration in the right renal cavity, no dilation of the pyelocaliceal cavities. Initially treated by ceftriaxone sodium (ROCEPHINE), then switched to piperacillin sodium/ tazobactam sodium (TAZOCILLIN) due to severe sepsis. The switch to CIFLOX 500 mg/24 hours by oral route is performed on 11Aug2021 for a total duration of 14 days so until 19Aug2021 included an indwelling urinary catheter had been implanted during severe sepsis, changed on 10Aug2021, then removed on 12Aug2021 after 48 tamsulosin. The subject then presented during his hospitalization with a decrease in his pains in the right iliac fossa and an improvement of his general state.
Acute renal failure due to chronic renal failure due to acute tubular necrosis. Initial presence of oliguria, requiring hyperhydration. The basal serum creatinine was 160 umol/l (laboratory report from July according to his general practitioner). The peak of his serum creatinine during the hospitalisation was 397 umol/L, with recovery under IV hydration and a suspension of the nephrotoxic treatments. Proteinuria <0.3 g/l, to be tested again a while after the acute episode. The urinary blood electrolytes revealed a profile of organic acute renal failure, compatible with the diagnosis of acute tubular necrosis. The recovery was fast but incomplete with serum creatinine at 229 umol/l at the time when he was discharged. We therefore scheduled a nephrology consultation on Wednesday 10Nov2021 at 2:30 pm.
Arterial hypertension: Presence during hospitalization of high blood pressure, in a patient under three long-term hypertension therapies (amlodipine besilate (AMLOR), irbesartan and manidipine). With regard to the renal function, it was decided to suspend ARA 2 and to continue a calcium treatment and to introduce a central hypertension treatment on 11Aug2021 with an increase on 12Aug2021. ARA 2 will be re-initiated when the renal function returns to normal values.
Insulin-requiring diabetes: HbA1c 8% which reflects a satisfactory usual blood sugar follow-up. The treatment with metformin is suspended due to the context of severe sepsis and acute renal failure which did not return during the hospitalization. Dulaglutide (TRULICITY) was re-initiated on 13Aug2021. As the blood sugar levels were high, the dosage of insulin glargine (LANTUS) was increased and we reinforced the bolus before the meals and corrections. the patient met the diabetology team on 17Aug2021 and will be seen again in a consultation to re-initiate treatment with ADO if possible. Insulin glargine 16 IU in the morning. Humalog insulin: 8 IU in the morning, 8IU at midday and 6 IU in the evening. And we would add more depending on the pre-meal blood sugar levels in the morning, noon and evening: 0 IU if between 1 and 2 g, 2 IU if 2< G <2.5 g/L, 4 IU if 2.5< G <3 g/L, 6 IU if over 3.0 g/L.
WITH REGARD TO THERAPY: The cancer treatments (bosutinib and abiraterone) were suspended then re-initiated on 11Aug2021. An injection of degarelix acetate (FIRMAGON) was given on 12Aug2021 (normally should have been given on 04Aug2021, not administered due to severe sepsis).
WITH REGARD TO MOTOR ABILITIES: the patient has been very much affected by this severe infection and remained bedridden for a long time. His physical therapy combined with a very strong will helped him to progress very quickly. At the end of the hospitalization he was moving around with no technical help and was even walking up several flights of stairs. We recommend that he continues his physical therapy at the end of his hospitalization.
Further test(s) performed: Renal ultrasound on 05Aug2021: Both kidneys are a normal size (right kidney measured 110 mm at its widest point and the left kidney 120 mm at its widest point), both carrying several cortical cysts (inferior pole of the right kidney and three poles on the left), and the appearance was superimposable with the CT scan of 28Dec2020. No images of renal abscesses. There is no urethral pyelocaliceal dilation. Small bladder capacity, walls could not be analyzed. No intraperitoneal effusion. Overall: No argument for a complication of the urinary tract infection.
Abdominal pelvic PET scan without contrast injection on 05Aug2021: Intraperitoneal effusion of a mild abondance in the rectouterine pouch with a significant infiltration of the right renal cavity overflowing into the peritoneal linings in the right paracolic gutter. No dilation of the pyelocaliceal cavities. Distention of the gall bladder without thickening of the walls with some images of lithiasis, no dilation of the intra or extrahepatic biliary tracts. Subject to the absence of contrast medium injection, no obvious anomalies on the rest of the abdomen, distention of the whole of the large colon with no argument for occlusion. Vesicular catheter in place. Small effusion of the pulmonary bases with pulmonary collapse upon contact. CONCLUSION: Infiltration of the right-sided renal cavity, no dilation of the pyelocaliceal cavities.
In conclusion they retain: A male urinary tract infection, complicated: by acute renal failure with tubular necrosis, by severe sepsis, by uncontrolled blood pressure, by uncontrolled diabetes.
The propositions upon discharge were as follows: PHYSICAL THERAPY Consultation in nephrology with follow-up lab test on Wednesday 10Nov2021 at 2:30 pm; Consultation in diabetology on 01Sep2021 at 10 am. Treatment upon discharge included Usual treatment: Bosulif 100 mg: 2 tablets per day in the evening in one dose during a meal, solifenacin succinate (VESICARE) 5 mg: 1 tablet in the evening, pantoprazole sodium sesquihydrate (EUPANTOL) 40 mg: 1 tablet in the morning, dulaglutide (TRULICITY) 1.5 1 injection per week, ravastatin sodium (ELISOR) 20 mg 1 tablet in the evening, colecalciferol (ZYMAD) 50,000 1 vial per month, paracetamol (DOLIPRANE) 1 g in the morning and evening, alfuzosin hydrochloride (XATRAL) L 10 mg: 1 tablet in the evening, fesoterodine fumarate (TOVIAZ) 8 mg: 1 tablet in the evening, prednisone (CORTANCYL) 10 mg in the morning.
Modified treatments included AMLODIPINE (AMLOR) 10 mg Capsule: 1 capsule in the evening, RILMENIDINE-HYPERIUM 1 mg Tablet: 1 tablet in the evening, URAPIDIL (EUPRESSYL) 30 mg Prolonged release capsule: 2 capsules in the morning, 2 capsules in the evening, ciprofloxacine (CIFLOX) 500 mg Film-coated tablet: 1 tablet in the evening until 19Aug2021 included, paracetamol-DAFALGAN 500 mg Effervescent tablet 2 tablets after a refractory period of 6 hours - maximum of 6 tablets per day -.
DO NOT TAKE: metformin hydrochloride (GLUCOPHAGE) 1000 mg in the morning and evening due to renal failure and irbesartan 300 1 tablet in the morning due to renal failure.
No risk linked to care during hospitalization.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Treatments received for the adverse event included ceftriaxone sodium (ROCEPHINE) 1g/24h from 04Aug2021 to 05Aug2021, from 09Aug2021 to 11Aug2021; piperacillin sodium/ tazobactam sodium (TAZOCILLINE) 4g x3/24h from 05Aug2021 to 09Aug2021; ciprofloxacin (CIPROFLOXACINE) 500 mg/24h from 11Aug2021 to 19Aug2021; tamsulosin (TAMSULOSINE) 0.4 mg/24h from 11Aug2021 to 17Aug2021; prednisone (CORTANCYL) 10 mg/24h from 12Aug2021; rilmenidine/ hyperium 1 mg/24h from 16Aug2021; heparin calcium (CALCIPARINE) 200 IU SC/24h from 11Aug2021 to 17Aug2021; furosemide (LASIX) 80 mg x3/24h IV from 07Aug2021 to 09Aug2021; macrogol (FORLAX) 10 g from 05Aug2021 to 13Aug2021; NORMACOL 1 enema from 11Aug2021 to 12Aug2021; nefopam 120 mg/24h (PSE) from 08Aug2021 to 09Aug2021; potassium chloride (DIFFUS K) 1800 mg x3/24h from 09Aug2021 to 13Aug2021; DIFFUS K 1800 mg x3/24h from 15Aug2021 to 17Aug2021; urapidil (EURESSYL) 60 mg/24h from 11Aug2021 to 18Aug2021; EURESSYL 30 mg x3/24h from 13Aug2021 to 13Aug2021; EURESSYL 60 mg x2/24h from 14Aug2021; racecadotril (TIORFAN) 100 mg x3/24h from 14Aug2021 to 17Aug2021; oxycodone 5 to 10 mg/4h if needed from 05Aug2021 to 08Aug2021 and from 10Aug2021 to 18Aug2021. Treatments discontinued during the hospitalization (and resumed) included abiraterone 1000 mg/24h (stop date: 05Aug2021, resumption date: 12Aug2021); metformin hydrochloride (GLUCOPHAGE) 1000 mg x2/24h (stop date: 05Aug2021); irbesartan 300 mg/24h (stop date: 06Aug2021); amlodipine besilate (AMLOR) 5 mg/24h (stop date: 07Aug2021); AMLOR 10 mg/24h (from 10Aug2021); alfuzosin hydrochloride (XATRAL) 10 mg/24h (stop date: 06Aug2021, resumption date: 17Aug2021); fesoterodine fumarate (TOVIAZ) 8 mg/24h (stop date: 06Aug2021, resumption date: 17Aug2021).
Examination performed on 05Aug2021: renal ultrasound Indication: male urinary tract infection with acute renal failure. Search for complications. Results: Both kidneys are a normal size (right kidney measured 110 mm at its widest point and the left kidney 120 mm at its widest point), both carrying several cortical cysts (inferior pole of the right kidney and three poles on the left), and the appearance was superimposable with the CT scan of 28Dec2020. No images of renal abscesses. There is no urethral pyelocaliceal dilation. Small bladder capacity, walls could not be analysed. No intraperitoneal effusion. Overall: No argument for a complication of the urinary tract infection.
Examination performed on 05Aug2021: abdominal CT scan Indication: Septic shock and guarding on the right side in a context of a urological intervention. Results: Intraperitoneal effusion of a mild abondance in the rectouterine pouch with a significant infiltration of the right renal cavity overflowing into the peritoneal linings in the right paracolic gutter. No dilation of the pyelocaliceal cavities. Distention of the gall bladder without thickening of the walls with some images of lithiasis, no dilation of the intra or extrahepatic biliary tracts. Subject to the absence of contrast medium injection, no obvious anomalies on the rest of the abdomen, distention of the whole of the large colon with no argument for occlusion. Vesicular catheter in place. Small effusion of the pulmonary bases with pulmonary collapse upon contact. conclusion: Infiltration of the right-sided renal cavity, no dilation of the pyelocaliceal cavities.

The investigator considered there was not a reasonable possibility that the events were related to the study drug or to any concomitant drug. The lower limb oedema was related to the urinary retention event.

Follow-up (17Aug2020): New information received includes updated event outcome.

Follow-up (27Oct2021): New information received from the investigator via the CRO includes: medical history, concomitant therapy, lab data, new dosage of bosutinib, new event (severe masculin E. Coli urinary infection), updated action taken (withdrawn), clinical course and hospitalization report.

Follow-up (15Dec2021): This is a report from a Non-Interventional Study source for Protocol B1871047. Updated information included: additional event Lower limb oedema; medical history; amended onset date of Acute urinary retention; clinical course.

Follow-up (31May2023): This is a non-interventional study follow-up report received from the CRO for protocol B1871047. Updated information included: change of date for PSA test, correction of start date of acute urinary retention.

Follow-up (29Jun2023): This is a non-interventional study follow-up report received from the CRO for protocol B1871047. Updated information included: event data (outcome for E.coli urinary infection updated to Recovered, end date added).

Case Comment: The events, acute urinary retention and severe masculin E. Coli urinary infection, are assessed as unrelated to bosutinib. the event Lower limb oedema was related to urinary retention and unrelated to bosutinib. The subject's significant medical history included benign prostate hypertrophy and prostate cancer.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	05-AUG-2021	Abdomen scan	Infiltration of the right-sided renal cavity, no d	
		Infiltration of the right-sided renal cavity, no dilation of the pyelocaliceal cavities		
2	04-AUG-2021	Antimicrobial susceptibility test	E Coli development	
3		Blood creatinine	160 umol/l	
		basal		

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
4		Blood creatinine recovery was fast but incomplete	229 umol/l	
5		Blood creatinine peak	397 umol/l	
6	04-AUG-2021	Blood creatinine	200	
7	04-AUG-2021	Blood creatinine	196	96 55
8	08-AUG-2021	Blood creatinine	362	96 55
9	09-AUG-2021	Blood creatinine	345	96 55
10	11-AUG-2021	Blood creatinine	265	96 55
11	09-SEP-2021	Blood creatinine	198	96 55
12	04-AUG-2021	Blood culture	E Coli	
13		Blood glucose	high	
14	04-AUG-2021	Blood urea	10	
15	04-AUG-2021	Blood urea	10.8 mmol/L	8.3 3.3
16	08-AUG-2021	Blood urea	20.3 mmol/L	8.3 3.3
17	09-AUG-2021	Blood urea	19.2 mmol/L	8.3 3.3
18	11-AUG-2021	Blood urea	15 mmol/L	8.3 3.3
19	04-AUG-2021	C-reactive protein	142	
20	04-AUG-2021	Chronic kidney disease	27 ml/min	
21	08-AUG-2021	Chronic kidney disease	13 ml/min	
22	09-AUG-2021	Chronic kidney disease	14 ml/min	
23	11-AUG-2021	Chronic kidney disease	19 ml/min	
24	09-SEP-2021	Chronic kidney disease	27 ml/min	
25	07-AUG-2021	Creatinine urine	4.6 mmol/L	
26	04-AUG-2021	Culture urine Positive	positive	
27	04-AUG-2021	Hyperleukocytosis	19 g/l	
28		Positron emission tomogram	no dilation of the	

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
			pyelocaliceal cavities	
29	05-AUG-2021	Positron emission tomogram Infiltration of the right-sided renal cavity, no dilation of the pyelocaliceal cavities	Infiltration of the right-sided renal cavity, no d	
30	27-JUN-2020	Prostatic specific antigen >4 suspiscion cancer prostate	7.6 ug	
31	04-AUG-2021	Protein total	67 g/l	82 57
32		Proteinuria	less than 0.3 g/l	
33		Ultrasound kidney	normal	
34	05-AUG-2021	Ultrasound kidney No argument in favour of urinary infection complication	No argument in favour	
35	07-AUG-2021	Urea urine	128 mmol/L	420 165
36	04-AUG-2021	Urine cytology	E Coli	
37	07-AUG-2021	Urine potassium	47 mmol/L	
38	07-AUG-2021	Urine sodium	37 mmol/L	
39	09-SEP-2021	Weight	77 kg	
40	04-AUG-2021	White blood cell count	19.5 g/l	10.0 3.8
41	09-SEP-2021	White blood cell count	10.4 g/l	10.0 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	200 mg, daily; Unknown	Unknown	15-APR-2019 / 02-JUL-2019; 2 months 18 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	Unknown	03-JUL-2019 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	300 mg, 1x/day; Unknown	Unknown	30-DEC-2019 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5	300 mg, 1x/day; Unknown	Unknown	30-MAR-2020 / Unknown;

Mfr. Control Number: 2020309064

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 #6	300 mg, 1x/day; Unknown	Unknown	24-JUN-2020 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7	300 mg, 1x/day; Unknown	Unknown	16-SEP-2020 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #8	300 mg, 1x/day; Unknown	Unknown	07-DEC-2020 / Unknown; Unknown
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #9	200 mg, 1x/day; Unknown	Unknown	08-MAR-2021 / 06-SEP-2021; 5 months 30 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #10	200 mg, 1x/day; Unknown	Unknown	02-JUN-2021 / Unknown; Unknown

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

#7) AMLOR (AMLODIPINE BESILATE) Capsule ; Unknown

#8) IRBESARTAN (IRBESARTAN) Tablet ; Unknown

#9) MANIDIPINE (MANIDIPINE) ; Unknown

#10) ZYMAD (COLECALCIFEROL) ; Unknown

#11) DOLIPRANE (PARACETAMOL) ; Unknown

#12) XATRAL (ALFUZOSIN HYDROCHLORIDE) Tablet ; Unknown

#13) TOVIAZ (FESOTERODINE FUMARATE) Tablet ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2017 to Unknown	Relevant Med History	Insulin-dependent diabetes mellitus (Type 1 diabetes mellitus); complicated with diabetic retinopathy and muscular infarct of the right thigh (2017), treated
2017 to Unknown	Relevant Med History	Diabetic retinopathy (Diabetic retinopathy);
2017 to Unknown	Relevant Med History	Muscle necrosis (Muscle necrosis);
2000 to Ongoing	Relevant Med History	Arterial hypertension (Hypertension); treated
03-SEP-2020 to Ongoing	Relevant Med History	Adenocarcinoma of prostate (Prostate cancer); treated with abiraterone + FIRMAGON with good response

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
03-SEP-2020 to Ongoing	Relevant Med History	Bone metastases (Metastases to bone); treated with abiraterone + FIRMAGON with good response
Unknown	Relevant Med History	Hypercholesterolemia (Hypercholesterolaemia);
2019 to Unknown	Relevant Med History	Ulcer (Ulcer); confirmed by gastroscopy
2019 to Unknown	Relevant Med History	Gastroscopy (Endoscopy upper gastrointestinal tract);
Unknown	Relevant Med History	Nephrolithiasis (Nephrolithiasis);
Unknown to Ongoing	Relevant Med History	Prostatic hypertrophy (benign) (Benign prostatic hyperplasia);
Unknown	Relevant Med History	Sigmoid diverticulosis (Diverticulum intestinal);
Unknown	Relevant Med History	Bilateral cataracts (Cataract);
Unknown	Relevant Med History	Deafness bilateral (Deafness bilateral);

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		PRIVACY		31 Years	Female	68.00 kg		FEB	2020

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

Cold [Nasopharyngitis]
Vaginal infection [Vaginal 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 received from 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) UNK

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

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

18. THERAPY DATES(from/to)
#1) 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

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.
2020314746

24c. DATE RECEIVED BY MANUFACTURER
09-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.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 31-year-old female patient received bosutinib (BOSULIF), (ongoing). The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: NASOPHARYNGITIS (non-serious) with onset Feb2020, outcome "recovered" (Feb2020), described as "Cold"; VAGINAL INFECTION (non-serious) with onset 05Jun2020, outcome "recovered" (18Nov2020). The action taken for bosutinib was dosage not changed.

The reporter considered "cold" and "vaginal infection" not related to bosutinib.

Additional information: Event cold reported with grade 1, non-serious, unrelated to study drug, in response to the event bosutinib dose was not changed. For cold, in the medical consultation of 11May2020: "simply reports a cold in february as well as her spouse". Event vaginal infection reported with grade 2, non-serious, unrelated to study drug, in response to the event bosutinib dose was not changed

Follow-up (09Feb2023): This is a follow-up Non-Interventional Study received from investigational site via CRO.
Information update: stop date and outcome of Vaginal infection.

Case Comment: Based on the information currently available, the reported 'cold' and 'vaginal infection' are assessed as unrelated to study drug bosutinib, and most likely represent intercurrent medical conditions.

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		PRIVACY		72 Years	Female	73.00 kg	05	NOV	2019

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

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 report 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

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) 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) 26-JUN-2019 / Ongoing

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) THYROXIN (LEVOTHYROXINE SODIUM) ; Ongoing
#2) COVERSYL [PERINDOPRIL ERBUMINE] (PERINDOPRIL ERBUMINE) ; Ongoing
#3) 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 to Ongoing	Relevant Med History	Renal failure (Renal failure)
Unknown to Ongoing	Relevant Med History	Arterial 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.
2020331161

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

24c. DATE RECEIVED BY MANUFACTURER
25-AUG-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020331161

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional clinical study case reporting non-serious event only.
A contactable physician reported that a 72-year-old female subject started to receive bosutinib (BOSULIF) oral from 26Jun2019 and ongoing at 300 mg, once a day for chronic myeloid leukaemia. Medical history included renal failure, arterial hypertension, hypothyroidism, and hypercholesterolemia; all were ongoing. Concomitant medications included levothyroxine sodium (THYROXIN) for hypothyroidism, perindopril erbumine (COVERSYL) for arterial hypertension, and rosuvastatin calcium (CRESTOR) for hypercholesterolemia. The subject experienced hyperthyroidism on 05Nov2019 with outcome of recovered on 06Feb2020. The action taken in response to the event for bosutinib was dose not changed. The event hyperthyroidism was rated grade 1 and assessed as non-serious. The investigator considered the event as unrelated to study drug and unrelated to concomitant drugs.

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

Case Comment: In concurrence with the reporting investigator, the Company considers the reported hyperthyroidism Grade 1 unrelated to bosutinib. The subject had a medical history of hyperthyroidism.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism);
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		PRIVACY		49 Years	Female	57.00 kg		SEP	2019

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) 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.
2020333047

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 49-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: DIARRHOEA (non-serious) with onset Sep2019, outcome "recovered" (12Sep2019), described as "Diarrhea". The action taken for bosutinib was dosage not changed.
Additional information: Diarrhea was rated grade 1.

According to the investigator event was related to study drug.

Amendment: This follow-up report is being submitted to amend previously reported information: supplement grade of diarrhea and update patient's initials.

Case Comment: The event diarrhea is considered related to bosutinib, based on temporal association and the known safety profile.

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		PRIVACY		72 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)

pelvic pain [Pelvic pain]
Scapula pain [Musculoskeletal 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) 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) UNK

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

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

18. THERAPY DATES(from/to)
#1) 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

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.
2020345998

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-year-old male subject received bosutinib (BOSULIF) at an unspecified dose from an unspecified date for an unspecified indication. The subject's medical history and concomitant medications were not reported. The subject experienced scapula pain on 08Mar2019 and pelvic pain on 14Oct2019. Both events were reported as non-serious and rated grade 1. The action taken in response to the event for bosutinib was dose not changed. The outcome of event pelvic pain was resolved on 23Apr2020, of event scapula pain was resolved on 20Jan2020.

According to the reporter, the events were unrelated to study drug and concomitant drug.

Follow-up (21Sep2020): New information reported includes new event (scapula pain), seriousness, outcome and assessment.

Follow-up (28Oct2021): This is a follow-up non-interventional study report (Post Authorization Safety Study) for protocol B1871047 from the investigator via the CRO. Updated information: stop date of event pelvic pain updated.

Case Comment: Based on the information available and in concurrence with the investigator, the reported pelvic pain and scapula pain are assessed as unrelated to the study drug, bosutinib. The events are not consistent with the known drug safety profile and most likely intercurrent condtions.

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		PRIVACY		73 Years	Male	96.00 kg	31	MAY	2020

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

itchy skin eruption [Rash pruritic]

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 case reporting non-serious event only 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) 300 mg, daily

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) 19-NOV-2019 / 09-SEP-2020

19. THERAPY DURATION
#1) 9 months 22 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
18-DEC-2017 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.
2020378631

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

24c. DATE RECEIVED BY MANUFACTURER
17-JAN-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 73-year-old male subject started to receive bosutinib (BOSULIF) on 19Nov2019 at 300 mg daily for chronic myeloid leukemia. Relevant medical history included chronic myeloid leukemia ongoing since 18Dec2017. Relevant concomitant medication was not provided. On 31May2020 the subject experienced itchy skin eruption, rated grade 2 and not serious. As corrective measures, the subject received fexofenadine (TELFAST), hydroxyzine (ATARAX), ebastine (KESTIN), and desloratadine (AERIUS), all by oral route and ongoing from 31May2020. Ferocious pruritus with skin rash +++ which persisted despite withdrawal of bosutinib during 42 days (starting from 09Sep2020). The event was not recovered.

According to the investigator, the event was unrelated to study drug bosutinib.

Follow-up (17Jan2022): This is a follow-up report for a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL) received from the investigational site. Updated information included: the patient's height updated, updated event term (''Pruritus'' changed to "itchy skin eruption''), days of withdrawal of bosutinib updated.

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

Case Comment: The non-serious event itchy skin eruption is assessed as not related to bosutinib in agreement with the Investigator. Although there is a known association with the drug, the prolonged exposure to the drug for more than 6 months prior to the event and persistence of symptoms for more than 2 weeks after interruption make causality unlikely.

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		PRIVACY		77 Years	Male	Unk	19	AUG	2020

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

Unbalance of diabetes [Diabetes mellitus inadequate control]
vomiting [Vomiting]

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

15. DAILY DOSE(S)
#1) 400 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-NOV-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

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.
2020380454

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.

Mfr. Control Number: 2020380454

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 77-year-old male patient received bosutinib (BOSULIF), since 28Nov2018 (ongoing) at 400 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported. The subject presented with unbalance of diabetes rated as grade 3 and vomiting rated as grade 2 on 19Aug2020. Hospitalization from 19Aug2020 to 24Aug2020 for acute pancreatitis flare in context of diabetes. No action was taken for bosutinib in response of the events. Both events were recovered on 24Aug2020.
According to the investigator, the event unbalance of diabetes was considered as not related to study drug while the event vomiting was considered as related to study drug.

Follow-up (21Feb2023): This is a follow up received from the investigator via the CRO.
Updated information included: Patient's initials, patient's gender updated to male (previously female).

Case Comment: The event unbalance of diabetes was considered as not related to study drug bosutinib. The reported vomiting was considered as related to study drug bosutinib based on known drug profile. Case will be reassessed if additional information is provided.

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		PRIVACY		61 Years	Male	Unk	03	SEP	2020

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

Arterial hypertension [Hypertension]

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. 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

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

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

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

18. THERAPY DATES(from/to)
#1) 30-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) LOXEN L P (NICARDIPINE HYDROCHLORIDE) ; 03-SEP-2020 / 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

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.
2020380587

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

24c. DATE RECEIVED BY MANUFACTURER
29-SEP-2020

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020380587

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 61-year-old male subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 30Jan2019 at 300 (unknow units), daily for an unspecified indication. Medical history was not reported. It was reported concomitant medications included nicardipine hydrochloride (LOXEN LP) since 03Sep2020 for arterial hypertension. The subject experienced arterial hypertension on 03Sep2020. Blood pressure measurement was 162/88 mmhg on 03Sep2020. The event arterial hypertension was assessed as non-serious. The action taken in response to the event for bosutinib and concomitant Loxen LP was dose reduced. The event was resolving.

The investigator considered the event as related to bosutinib and not related to concomitant Loxen LP. Following comment was provided: arterial hypertension in recent weeks attributed to bosutinib.

Case Comment: Assuming a plausible drug-event temporal association and considering the consistency of the reported event with the known safety profile of the suspect product, the company, in agreement with the investigator, considered the event arterial hypertension related to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	03-SEP-2020	Blood pressure measurement	162/88 mmHg	
		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		PRIVACY		74 Years	Male	76.00 kg	14	OCT	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
Gastroduodenal ulcer [Gastroduodenal ulcer]
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)

(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) Unknown

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

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

From/To Dates	Type of History / Notes	Description
MAR-2010 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.
2020390386

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:

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.

A 74-year-old male patient received bosutinib (BOSULIF), since 01Oct2019 (ongoing) at 300 mg 1x/day. The patient's relevant medical history included: "Chronic myeloid leukemia", start date: Mar2010 (ongoing). The patient's concomitant medications were not reported.
The following information was reported: ASTHENIA (non-serious) with onset 14Oct2019, outcome "recovered" (09Dec2019); GASTRODUODENAL ULCER (medically significant) with onset 31Jul2020, outcome "not recovered". The event asthenia was rated grade 2 event reported as non-serious. The event gastroduodenal ulcer was rated grade 1 event reported as serious. The action taken for bosutinib was dosage not changed.

The reporter considered "gastroduodenal ulcer" and "asthenia" not related to bosutinib.
Follow-up attempts are completed. No further information is expected.

Follow-up (16May2023): This is a follow-up report received from the CRO.
Updated information included: medical history added (Chronic myeloid leukemia), indication for Bosulif removed, event description changed, updated grade of events.

Case Comment: The Company considers there is not a reasonable possibility that the reported gastorduodenal ulcer grade 2 is related to the study drug, bosutinib, event is more likely an intercurrent disease. Similarly, asthenia is deemed unrelated to bosutinib, as well.
The follow up information 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		PRIVACY		77 Years	Female	Unk		FEB	2020

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

Vertiginous Syndrome [Vertigo]
Diarrhea episode [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. This is a non-interventional clinical study case reporting non-serious events 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) 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-MAY-2019 / 01-AUG-2019	#1) 2 months 30 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) LIPANTHYL (FENOFIBRATE) ; Ongoing
#2) EUPRESSYL [URAPIDIL HYDROCHLORIDE] (URAPIDIL HYDROCH
#3) ESIDREX (HYDROCHLOROTHIAZIDE) ; Ongoing
#4) APROVEL (IRBESARTAN) ; OCT-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
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.
2020448367

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-FEB-2022

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020448367

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 77-year-old female subject started to receive bosutinib (BOSULIF) from 03May2019 to 01Aug2019 at 200 mg daily, from 02Aug2019 to 22Oct2020 at 300 mg daily and from 23Oct2020 and ongoing at 200 mg daily for an unspecified indication. Relevant medical history was not reported. Concomitant medications included fenofibrate (LIPANTHYL), urapidil hydrochloride (EUPRESSYL), hydrochlorothiazide (ESIDREX) and irbesartan (APROVEL) since Oct2018, all taken orally and ongoing for hypertension arterial. The subject experienced vertiginous syndrome in Feb2020 and diarrhea in Oct2020. Vertiginous syndrome was assessed as non-serious and rated grade 2, diarrhea was assessed as non-serious and rated grade 3. Persistence of vertiginous symptomatology with no etiology identified, brain MRI performed at the end of Oct2020 did not disclose significant anomaly. The patient pursued vestibular rehabilitation but with no benefit for now. In response to the event vertiginous syndrome, bosutinib was temporarily withdrawn. Action taken in response to diarrhea was not applicable. Last action taken of bosutinib was dose reduced. The event diarrhea episode resolved on 21Dec2020, vertiginous syndrome was not resolved at the time of report.

The investigator assessed the events vertiginous syndrome as related to study drug bosutinib and diarrhea as not related to study drug bosutinib.

Follow-up (16Nov2020): New information received from the investigational site includes start date of bosutinib (at 200 mg from 23Oct2020).

Follow-up (07May2021 and 11May2021): New information received from the investigational site via the CRO included: causality assessment, action taken detail, dosage regimen, lab data, clinical course, event outcome, treatment.

No follow-up attempt performed. no further information expected.

Follow-up (03Feb2022): This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician) for protocol B1871047.

Updated information: Onset date of vertiginous syndrome, action taken in response of diarrhea, causality assessment of diarrhea was updated as not related to study drug.

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

Case Comment: In concurrence with the investigator, the company considers that the events vertiginous syndrome as related to study drug bosutinib and diarrhea as not related to study drug bosutinib. This case we will re-assessed should additional information become available.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	OCT-2020	Magnetic resonance imaging head	unremarkable	

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	02-AUG-2019 / 22-OCT-2020; 1 year 2 months 21 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	23-OCT-2020 / Ongoing; Unknown

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

#2) EUPRESSYL [URAPIDIL HYDROCHLORIDE] (URAPIDIL HYDROCHLORIDE) ; 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		PRIVACY		42 Years	Female	59.00 kg	18	AUG	2020

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

left subscapular pain [Musculoskeletal pain]
Agravation of joint pain [Arthralgia]
Aggravation of chronic 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 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

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) 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	Relevant Med History	Systemic lupus erythematosus (Systemic lupus erythematosus)
Unknown to Ongoing	Relevant Med History	Asthenia (Asthenia)

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.
2020474174

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:

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.

A 42-year-old female patient received bosutinib (BOSULIF), from 04Dec2017 to 17Jan2018 at 400 mg 1x/day. The patient's relevant medical history included: "asthenia" (ongoing); "diffuse pain at wake-up" (ongoing); "joint pain" (ongoing). The patient's family history included: "LUPUS" (unspecified if ongoing). The patient's concomitant medications were not reported.
The following information was reported: FATIGUE (non-serious) with onset 18Aug2020, outcome "not recovered", described as "Aggravation of chronic fatigue"; ARTHRALGIA (non-serious) with onset 18Aug2020, outcome "not recovered", described as "Agravation of joint pain"; MUSCULOSKELETAL PAIN (non-serious) with onset 18Aug2020, outcome "not recovered", described as "left subscapular pain". Therapeutic measures were taken as a result of fatigue.

The reporter considered "left subscapular pain", "agravation of joint pain" and "aggravation of chronic fatigue" not related to bosutinib.

Additional information: The patient received bosutinib (BOSULIF), at 400 mg once a day from 04Dec2017 to permanent withdrawal on 17Jan2018. The events were rated grade 1 and reported as non-serious. Last action taken in response to the events Left Subscapular pain and joint pain for bosutinib was dose not changed (reported as not applicable in response to Chronic fatigue). According to the reporter the events were unrelated to bosutinib and to concomitant drugs.
Sender comment (Left Subscapular pain and joint pain): clinically: little weight gain; little bloated abdomen; left subscapular pain; joint pain. She presented multiple symptoms and need to see her physician. Check-up was prescribed.
Sender comment (Chronic fatigue): clinically, as at the last consultation, the subject chronically complained of asthenia with diffuse pain at wake-up and attenuation in the late morning. She received vitamin cures and suffered from thyroid disorders which were resolving. The subject presented with these symptoms for several years. Family medical history of lupus. Complementary exams revealed no significant anomaly.

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

Follow-up (03Mar2023): New information received from investigational site via CRO which included the investigator's initial awareness date.

Follow-up (18Sep2023): 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 updated from "Joint pain" to "aggravation of joint pain" and from "chronic fatigue" to "aggravation of chronic fatigue".

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

Follow-up (22Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from clinical team for protocol B1871047.
Updated information: bosutinib dosage and action taken.

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

Case Comment: Based on available information, the company concurs with the investigator that reported "left subscapular pain", "agravation of joint pain" and "aggravation of chronic fatigue" are unrelated to bosutinib but more likely intercurrent medical conditions.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Diffuse pain (Pain);
Unknown to Ongoing	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
PRIVACY	FRANCE		PRIVACY		42 Years	Female	59.00 kg	07	APR	2020

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

Cephalgia [Headache]
Myalgia [Myalgia]

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

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.
2020474501

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 42-year-old female patient received bosutinib (BOSULIF), from 04Dec2017 to 17Jan2018 at 400 mg. The patient's relevant medical history and concomitant medications were not reported. The patient reported that for 10 days she had cephalgia without fever, several myalgia and impression of sore throat. Both events occurred on 07Apr2020. Events were grade 1, non-serious. She contacted her physician one week ago who reassured her. Patient was advised to contact her physician again. She had no fever. This patient was group 1 COVID (no particular risk). The action taken in response to the events for bosutinib was not applicable. The outcome of the event Cephalgia was recovered on 18Aug2020, for event myalgia was not recovered.

The reporter considered "cephalgia" and "myalgia" not related to bosutinib.

Follow-up (05Nov2021): This is a non-interventional follow-up study report (Post Authorization Safety Study) for protocol B1871047. Updated information included: New event (asthenia grade 1), Bosutinib treatment date and dosage, action taken updated (to not applicable), outcome of the event cephalgia was updated to resolving;

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

Follow-up (03Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the CRO for protocol B1871047.
Updated information: for event headache outcome updated to recovered on 18Aug2020.

Follow-up (18Sep2023): 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: Asthenia grade 1 (2020) was removed.

Follow-up (22Sep2023): 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 dose (400 mg daily), start date (04Dec2017) and stop date (17Jan2018) removed.

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. Updated information includes: bosulif daily dose and therapy dates.

Case Comment: Based on available information, the company concurs with the investigator that reported cephalgia and myalgia are unrelated to bosutinib but more likely intercurrent medical conditions. The onset of the events was post therapy.

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		PRIVACY		66 Years	Male	63.00 kg	28	OCT	2020

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

Caroli disease [Dilatation intrahepatic duct congenital]

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.

A 66-year-old male subject started to receive bosutinib (BOSULIF),

(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) 08-AUG-2019 / 22-AUG-2019	#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
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
21-JUN-2017 to Ongoing	Relevant Med History	CML (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.
2020478405

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
08-JUN-2022

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2020478405

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

from 08Aug2019 to 22Aug2019 at 100 mg, daily; then from 23Aug2019 to 19Aug2020 at 200 mg to 400 mg daily, then from 20Aug2020 and ongoing at 500 mg, daily via an unspecified route of administration for an unspecified indication. The subject had a relevant history of ongoing arterial hypertension, ongong CML (Chronic myeloid leukaemia) from 21Jun2017, Cholecystitis from 25Jul2020 to 29Jul2020, Cholecystectomy on 28Jul2020. The concomitants were not reported. It was reported following a per operative cholangiography (during a cholecystectomy on 28Jul2020), a unifocal cystic dilation of the biliary tract of the left lobe was highlighted. the surgeon requested a Bile ducts MRI which revealed: "MRI evoking a Caroli's disease lowly expressed with a single communicating cystic lesion, stage 5 of the Todani classification". The hematologist and the surgeon discussed for a hepatectomy to be done, without emergencies, because of an increased risk of adenocarcinoma. The reported adverse event was Caroli's disease with onset date 28Oct2020. Event was rated as grade 1. Disease was stable. Monitoring only, asymptomatic. Following discussion with hematologist, this event was not considered as medically significant. This event was non-serious. The subject underwent lab tests and procedures which included Bile ducts MRI on 28Oct2020 and showed Caroli disease; operative cholangiography: a unifocal cystic dilation of the biliary tract of the left lobe was highlighted. The product bosutinib dose was not changed as a result of event. The outcome of the event at the time of the report was not resolved.

The investigator considered that the event was unrelated to the study drug or to any concomitant drug.

Follow-up (29Nov2021): This is a Non-Interventional Study follow-up report for Protocol B1871047, Study alias BOSEVAL from the study site via CRO upon the query. New information includes: grade of event added, and clinical course added.

Follow-up (08Jun2022). This follow-up is received from the investigational site. Updated information included: downgrade of seriousness (from serious to non-serious).

Case Comment: In concurrence with the reporting investigator, the Company deems there is not a reasonable possibility that the reported Caroli's disease is related to the study drug, bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Cholangiogram the left lobe was highlighted	a unifocal cystic dilation of the biliary tract of	
2	28-OCT-2020	Magnetic resonance imaging	Caroli disease	

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 to 400 mg daily; Unknown	Unknown	23-AUG-2019 / 19-AUG-2020; 11 months 28 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	500 mg, daily; Unknown	Unknown	20-AUG-2020 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
25-JUL-2020 to 29-JUL-2020	Relevant Med History cholecystectomy on 28Jul2020	Cholecystitis (Cholecystitis);
28-JUL-2020 to 28-JUL-2020	Relevant Med History	Cholecystectomy (Cholecystectomy);

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		PRIVACY		76 Years	Female	Unk	22	OCT	2019

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

Majoration of dyspnea [Dyspnoea]
myalgia aggravation [Myalgia]
HYPERTENSION AGGRAVATION [Hypertension]

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) 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) 03-MAY-2019 / 01-AUG-2019	#1) 2 months 30 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.
2020487400

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

for protocol B1871047.
A 76-years old female subject started to receive bosutinib (BOSULIF) from an unspecified date, at an unknown dose for an unspecified indication. Relevant medical history and concomitant medications were not reported. On 01Aug2020 the subject was found to have a lack of efficacy and bosutinib dose was increased in response to the event. On 22Oct2019 the subject experienced myalgia aggravation and hypertension aggravation. Action taken in response to the events was dose not changed. The subject recovered from hypertension aggravation on 22Oct2020, from Myalgia aggravation on 16Jan2020. The subject had not yet recovered from lack of efficacy.

The investigator considered the events Hypertension aggravation and myalgia aggravation as not related to bosutinib, while the event lack of efficacy was considered related to bosutinib therapy.

Follow-up (06May2021 and 07May2021): New information received from the investigational site via the CRO includes: the subject took bosutinib at 200 mg per day from 03May2019 to 01Aug2019, 300 mg daily taken from 02Aug2019 was stopped on 22OCt2020 and restarted at 200 mg daily on 23Oct2020, still ongoing. On 01Aug2019, PCR BCR-ABL was 2.59% and on 22Oct2019 was 0.92%. The event lack of efficacy was considered as related to study drug bosutinib. The subject developed lack of efficacy on 01Aug2019, assessed as not serious and resolved on 16Jan2020. the investigator assessed this event lack of efficacy as related to study drug bosutinib and unrelated to concomitant medication. As result of the event lack of efficacy, bosutinib dose was increased. In Dec2020, the subject developed majoration of dyspnea, considered not serious and rated grade 2. The event did not resolve. In response to this event, bosutinib was stopped.

The investigator assessed the event majoration of dyspnea as related to study drug bosutinib and unrelated to concomitant drug.

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

Follow-up (03Feb2022): This is a follow-up to a non-interventional clinical study case: Additional information: Lack of effiacy was rated as grade 2.

Follow-up (20Jan2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from CRO for protocol B1871047.
Updated information includes: ongoing status of bosutinib dosage from 23Oct2020.

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

Case Comment: The company concurs with the investigator that the reported hypertension aggravation and myalgia aggravation are not related to bosutinib. The events are likely associated to the subject's concurrent medical condition. The worsened dyspnea is related to bosutinib due to plausible temporal association. The follow-up information received does not alter the previous company clinical evaluation. This case will be reassessed when further information is provided.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	01-AUG-2019	Cytogenetic analysis	2.59 %	
2	22-OCT-2019	Cytogenetic analysis	0.92 %	

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	02-AUG-2019 / 22-OCT-2020; 1 year 2 months 21 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	23-OCT-2020 / 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		PRIVACY		51 Years	Female	97.50 kg	24	JUN	2019

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

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.

(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

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) 24-JUN-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)

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.
2020493204

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:

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

A 51-year-old female subject started to receive bosutinib, at 300 mg daily ongoing since 24Jun2019 for an unspecified indication. The patient medical history and concomitant medications were not reported. The patient experienced asthenia on 24Jun2019, event was reported as non-serious. Asthenia was rated grade 1. It was reported that no action was taken with bosutinib in response to the event asthenia. Asthenia resolved on 04Jul2019.

Asthenia was considered unrelated to study drug per the PI.

Follow-up (07Jan2021): New information reported includes an update about subject's demography, therapy with bosutinib, grading, seriousness, outcome and causality assessment for asthenia, action taken with bosutinib.

Follow-up (22Jan2021): New information received from CRO included: event abdominal pain removed (reported under AER 2021016158).

Follow-up (05Jul2022): New information received from the investigator via the CRO.
Updated information: stop date for asthenia updated to 2019 from 04Jul2019.

Follow-up (15May2023): This is a non-interventional study follow up report received from contactable reporter(s) (Physician) for protocol B1871047. Updated information includes: patient's weight updated to 97.5 kg (previously reported as 98 kg).

Follow-up attempts are not needed. No further information is expected.

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 includes: new reporter and event details (onset date and stop date updated).

Case Comment: Based on the reasonable temporal association and considering the known safety profile of bosutinib, the Company cannot completely exclude the possible causality between the reported asthenia and the administration of the suspect. 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		PRIVACY		52 Years	Female	60.70 kg		JAN	2020

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

Diarrhea [Diarrhoea]
Hepatic cytolysis [Hepatic cytolysis]
Hypersialorrhea [Salivary hypersecretion]

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

(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) chronic myeloid leukemia (Chronic myeloid leukaemia)

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

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 29-DEC-2019 / 06-JAN-2020	#1) 9 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.
2020493241

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
05-JUL-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

This is a Non-Interventional Study report with non-serious events only.

A 52-years-old female patient was enrolled in above mentioned study and started to receive bosutinib (BOSULIF), via an unspecified route of administration from an unspecified date to an unspecified date at unknown dose for chronic myeloid leukemia. Medical history and concomitant treatments were not reported. The subject experienced diarrhea from Jan2020 to 23Apr2020, hypersialorrhea from Jan2020 to 15Mar2020 and hepatic toxicity from 06Apr2020 to 24Apr2020. Bosutinib was discontinued due to hepatic toxicity then dose was decreased.

The reporter's assessment of the causal relationship of the events 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 (07Jan2021): New information received from the study site.
The patient started to received bosutinib (BOSULIF) at 400 mg daily on 23Jan2019. Event term was updated from hepatic toxicity to hepatic cytolysis: The patient presented with hepatic cytolysis on 30Mar2020 (to be clarified), resolved on 24Apr2020. Diarrhea and hypersialorrhea were rated grade 1. No action was taken for bosutinib in response to diarrhea and hypersialorrhea. Dose reduced due to hepatic cytolysis.

According to the investigator, hepatic cytolysis and diarrhea were related to bosutinib, and hypersialorrhea was unrelated to bosutinib

Follow-up (21Jan2021): This is a follow-up to a non-interventional clinical study case reporting non-serious events only.
The subject received bosutinib at 100 mg daily from 29Dec2019 to 06Jan2020, at 200 mg daily from 07Jan2020 to 13Jan2020, 300 mg daily from 14Jan2020 to 22Jan2020 and 400 mg from 23Jan2020 to 29Mar2020.
Hepatic cytolysis started on 06Apr2020 and resolved on 28Apr2020.
The event hepatic cytolysis was a new event and not an exacerbation of underlying disease or a recurrence of event. It was unknown if the patient had family history of hepatic disease.
Before the treatment, on 18Nov2019, ASAT was 26 IU/L and ALAT was 20 IU/L.
At the beginning of treatment, on 06Jan2020, (Day 1 = 29Dec2019), ASAT was 23 IU/L and ALAT was 24 IU/L.
On 06Apr2020, ASAT was 99 IU/L (normal less than 32), ALAT was 268 IU/L (normal less than 33), GGT was 79 IU/L (normal between 5 and 36), total bilirubin was 10 umol/L (normal less than 21) and alkaline phosphatase was 112 IU/L (normal between 35 and 105).
After the treatment, on 20Apr2020: ASAT was 41 IU/L and ALAT was 85 IU/L, on 28Apr2020 (on reintroduction of bosutinib): ASAT was 35 IU/L and ALAT was 49 IU/L.

Follow-up(05JUL2022): New information received from investigational site via CRO included: hepatic cytolysis grade 2, dose not changed due to hepatic cytolysis

Case Comment: Considering a plausible drug-event temporal association and the consistency of the events with the known safety profile, there is a reasonable possibility that the reported diarrhea and hepatic cytolysis are related to bosutinib. Lacking alternative explanation, a reasonable possibility that the reported hypersialorrhea is related to bosutinib cannot be completely excluded.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	18-NOV-2019	Alanine aminotransferase	20 IU/l	
2	06-JAN-2020	Alanine aminotransferase	24 IU/l	
3	06-APR-2020	Alanine aminotransferase	268 IU/l	33
4	20-APR-2020	Alanine aminotransferase	85 IU/l	
5	28-APR-2020	Alanine aminotransferase	49 IU/l	
6	18-NOV-2019	Aspartate aminotransferase	26 IU/l	
7	06-JAN-2020	Aspartate aminotransferase	23 IU/l	
8	06-APR-2020	Aspartate aminotransferase	99 IU/l	32
9	20-APR-2020	Aspartate aminotransferase	41 IU/l	

Mfr. Control Number: 2020493241

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
10	28-APR-2020	Aspartate aminotransferase	35 IU/l	
11	06-APR-2020	Blood alkaline phosphatase	112 IU/l	105 35
12	06-APR-2020	Blood bilirubin	10 umol/l	21
13	06-APR-2020	Gamma-glutamyltransferase	79 IU/l	36 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	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	07-JAN-2020 / 13-JAN-2020; 7 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	300 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	14-JAN-2020 / 22-JAN-2020; 9 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	400 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	23-JAN-2020 / 29-MAR-2020; 2 months 6 days 23 hrs 60 min

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		PRIVACY		75 Years	Female	52.10 kg	26	DEC	2019

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

digestive disorders of diarrhea type [Diarrhoea]
Aggravation disorders digestive diarrhea type [Condition aggravated]
to cervical arthrosic and joints pain resurgence [Osteoarthritis]
Irvine-Gass syndrome [Cystoid macular oedema]
Scalp itching [Pruritus]

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) 16-DEC-2019 / 25-DEC-2019

19. THERAPY DURATION
#1) 10 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) SECTRAL (ACEBUTOLOL HYDROCHLORIDE) ; 1990 / Ongoing
#2) CYMBALTA (DULOXETINE HYDROCHLORIDE) ; 2009 / Ongoing
#3) CEBUTID (FLURBIPROFEN) ; 2018 / Ongoing
#4) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; 2007 / Ongoing

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

From/To Dates	Type of History / Notes	Description
2003 to Ongoing	Relevant Med History Right	Cervicobrachialgia (Cervicobrachial syndrome)
1990 to Ongoing	Relevant Med History	Arterial 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.
2020493488

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

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

A 75-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB), first regimen from 16Dec2019 to 25Dec2019 at 100 mg daily, second regimen from 26Dec2019 to 05Jan2020 at 200 mg daily, third regimen from 06Jan2020 to 16Jan2020 at 300 mg daily, fourth regimen since 17Jan2020 (ongoing) at 200 mg daily and fifth regimen since 27Mar2020 (ongoing) at 300 mg daily. The patient's relevant medical history included: "right cervicobrachial neuralgia", start date: 2003 (ongoing), notes: Right; "arterial hypertension", start date: 1990 (ongoing); "chronic venous insufficiency", start date: 2013 (ongoing); "hypothyroidism", start date: 2007 (ongoing); "chronic diarrhea" (unspecified if ongoing). Concomitant medication(s) included: SECTRAL oral taken for hypertension, start date: 1990 (ongoing); CYMBALTA oral taken for neuralgia, start date: 2009 (ongoing); CEBUTID oral taken for pain, start date: 2018 (ongoing); LEVOTHYROX oral taken for hypothyroidism, start date: 2007 (ongoing). Past drug history included: Imatinib, start date: 03Apr2018, stop date: 12Dec2019.
The following information was reported: CONDITION AGGRAVATED (non-serious) with onset 26Dec2019, outcome "recovered" (17Jan2020), described as "Aggravation disorders digestive diarrhea type"; DIARRHOEA (non-serious) with onset 26Dec2019, outcome "recovered" (17Jan2020), described as "digestive disorders of diarrhea type"; OSTEOARTHRITIS (non-serious) with onset 26Dec2019, outcome "not recovered", described as "to cervical arthrosic and joints pain resurgence"; CYSTOID MACULAR OEDEMA (non-serious) with onset 01Jun2020, outcome "not recovered", described as "Irvine-Gass syndrome"; PRURITUS (non-serious) with onset Jun2020, outcome "recovered" (2021), described as "Scalp itching". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of pruritus.
Clinical course: Digestive disorders of the diarrhea type grade 2, after reduction of bosutinib to 200mg/day, change to grade 1. Known chronic diarrhea preexisted at the start of bosutinib, and became more frequent, especially at the dose of 300 mg. Osteoarthritis pain has increased since stopping imatinib, and is probably not an adverse event due to bosutinib. On 01Jun2020, the subject experienced Irvine-Gass syndrome. It was confirmed that no hospitalization or other seriousness criteria were reported for the events Irvine-Gass syndrome. In Jun2020, scalp itching developed: localized pruritus on the scalp associated with cutaneous xerosis and intermittent and moderate pruritus (improvement by changing shampoos), on 17Dec2020 patient reports growths (seborrheic keratoses). On clinical examination: no suspicious lesion of the scalp. Moderate cutaneous xerosis. Bosutinib dose was reduced due to digestive disorders of diarrhea type, while the action taken with the study drug in response to the other events was dose not changed. On 17Jan2020: End date of diarrhea grade 2, then transition to grade 1, which is not to be put as adverse event because grade 1 and already present before the start of Bosulif. The event Condition aggravated was rated grade 2, reported as non-serious.

The reporter considered "digestive disorders of diarrhea type" and "scalp itching" related to bosutinib. The reporter considered "to cervical arthrosic and joints pain resurgence" and "irvine-gass syndrome" not related to bosutinib. The investigator considered that the event Condition aggravated was related to Bosulif and not related to any concomitant drug.

Follow-up (22Jan2021): New information received from the CRO includes an update about subject's demography, relevant medical history, concomitant medications, events (macular degeneration added), clinical course and causality assessment.

Follow-up (18Mar2021): New information received from the clinical team includes: Imatinib was taken from 03Apr2018 to 12Dec2019, before beginning of study and study drug.

Follow-up (14Feb2022): This is a non-interventional clinical study follow-up report. Updated information: Confirmation the events macular degeneration and Irvine-Gass syndrome are non-serious.

Follow-up (02Jun2022): new information received from CRO is as follows: The event term macular degeneration or Irvine-Gass syndrome was changed for Irvine-Gass syndrome. This event was unrelated to study drug.

Follow-up (05Jul2022): new information received from the investigator via the CRO. Event digestive disorders of diarrhea type: stop date added (Mar2020), outcome updated to recovered.

Follow-up (06Sep2022): This is a non-interventional study report (Post Authorization Safety Study) received from the CRO for protocol B1871047. Updated information: start date and outcome of pruritus, treatment received, and clinical course.

Follow-up (10May2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable Physician and Other HCP for protocol B1871047. Updated information included: onset date and outcome of the event digestive disorders of diarrhea, event cervical arthrosic and joints pain changed to cervical arthrosic and joints pain resurgence and onset date was updated.

Follow-up (18Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable Physician and Other HCP for protocol B1871047. Updated information included: Event cervical arthrosic and joints pain was deleted (previously replaced by cervical arthrosic and joints pain resurgence).

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

Follow-up (28Jul2023): New information received from clinical team following a clarification request regarding the event diarrhea

Mfr. Control Number: 2020493488

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

included: relevant medical history details, event details (End date of diarrhea grade 2) and clinical course updated.

Follow-up (07Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable Physician and Other HCP for protocol B1871047.
Updated information: primary reporter details (first name), patient details (weight), suspect drug Bosutinib details (stop date removed, ongoing checked for 200 mg on 17Jan2020), concomitant drug Cebutid details (indication), event Diarrhoea details, new event of Condition aggravated.

Case Comment: Based on very limited available information and the temporal relationship, the reasonable possibility of an association between increase of diarrhea, increase of cervical and arthrosis pain, scalp itching, Irvine-Gass syndrome and suspect drug bosutinib cannot be ruled out.
A contributory role of bosutinib to the reported "aggravation disorders digestive diarrhea type" is considered a reasonable possibility based on the consistency with the known safety profile and information 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) Bosutinib (BOSUTINIB) Unknown; Regimen #2	200 mg, daily; Unknown	Unknown	26-DEC-2019 / 05-JAN-2020; 11 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #3	300 mg, daily; Unknown	Unknown	06-JAN-2020 / 16-JAN-2020; 11 days
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #4	200 mg, daily; Unknown	Unknown	17-JAN-2020 / Ongoing; Unknown
#1) Bosutinib (BOSUTINIB) Unknown; Regimen #5	300 mg, daily; Unknown	Unknown	27-MAR-2020 / Ongoing; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
2013 to Ongoing	Relevant Med History	Chronic venous insufficiency (Peripheral venous disease);
2007 to Ongoing	Relevant Med History	Hypothyroidism (Hypothyroidism);
03-APR-2018 to 12-DEC-2019	Past Drug Event	Imatinib (IMATINIB);
Unknown	Relevant Med History	Chronic diarrhea (Diarrhoea);

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		PRIVACY		81 Years	Female	64.00 kg		SEP	2019

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

Ungueal fragility [Onychoclasis]

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 events 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) 400 mg, daily

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

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

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

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.
2020493614

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

24c. DATE RECEIVED BY MANUFACTURER
07-JAN-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

An 81 years old female subject started to receive bosutinib (BOSULIF), via an unspecified route of administration ongoing since 19Apr2019 at 400 mg daily for an unspecified indication. The subject's medical history and concomitant medications were not reported. The subject experienced ungueal fragility in Sep2019, this event was rated grade 1 and considered not serious. No action was taken on bosutinib in response to this event. The outcome of the event was recovered in Nov2019.

The investigator assessed this event as unrelated to study drug bosutinib and unrelated to concomitant medication.

Follow-up (15Dec2020): This is a Non-Interventional Study report with non-serious events only. New information received from clinical team included update of patient ID, center ID, patient gender (female) and patient date of birth with age (81).

Follow-up (07Jan2021): New information reported includes subject's info (weight, height), details on bosutinib administration, clinical course with event (previous AE nail toxicity was corrected to ungueal fragility), action taken with bosutinib (no action) and reporter's assessment (event unrelated to study drug bosutinib).

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported event Onychoclasis .

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		PRIVACY		73 Years	Male	90.00 kg			2020

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

Pericarditis effusion [Pericarditis]

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) 500 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) 27-NOV-2017 / 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
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.
2021004628

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

NAME AND ADDRESS WITHHELD.

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

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 2021004628

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 73-year-old male patient received bosutinib (BOSULIF), first regimen since 27Nov2017 at 500 mg daily and second regimen since 28Jan2020 (ongoing) at 500 mg 1x/day. The patient had no relevant medical history. The patient's concomitant medications were not reported.
The following information was reported: PERICARDITIS (non-serious) with onset 2020, outcome "not recovered", described as "Pericarditis effusion". The action taken for bosutinib was dosage not changed.

According to the investigator, the event was related to study drug but not related to any concomitant medication.

Follow-up (28Feb2023): new information received from the investigator via the CRO.
Updated information included: second regimen of Bosulif

Case Comment: Due to a plausible drug-event temporal association, the known drug safety profile and the investigator's opinion, the company deems there is a reasonable possibility that the reported pericarditis effusion is 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	500 mg, 1x/day; Unknown	Unknown	28-JAN-2020 / 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		PRIVACY		73 Years	Male	90.00 kg	24	NOV	2020

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

Dyspnea [Dyspnoea]

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) 400 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) 27-NOV-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) JANUMET [METFORMIN HYDROCHLORIDE;SITAGLIPTIN] (METFO
#2) DIPROSONE [BETAMETHASONE DIPROPIONATE] (BETAMETHASO
#3) LAMISIL [TERBINAFINE] (TERBINAFINE) ; JUL-2019 / Ongoing
#4) ARKOLEVURE (INULIN, SACCHAROMYCES BOULARDII) ; SEP-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
2007 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.
2021004830

24c. DATE RECEIVED BY MANUFACTURER
18-JAN-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.

Mfr. Control Number: 2021004830

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 73-year-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 27Nov2017 and ongoing at 400 mg, daily for an unspecified indication. Medical history included diabetes from 2007 and ongoing, ongoing psoriasis, ongoing chronic sinusitis and mycosis started in Jul2019. Ongoing concomitant medications included metformin hydrochloride/sitagliptin (JANUMET) via oral route started in 2007 for diabetes, betamethasone dipropionate (DIPROSONE, cream) from an unknown date for psoriasis, terbinafine (LAMISIL) via oral route started in Jul2019 for mycosis, inulin/saccharomyces boulardii (ARKOLEVURE) via oral route started in Sep2019 for constipation. The subject experienced dyspnea on 24Nov2020, dyspnea was rated as grade 1. The action taken in response to the event dyspnea for bosutinib was dose not changed. Dyspnea was still ongoing at the end of study. The subject loss of response and was rated as grade 2. It was reported that dose increased for loss of response.

According to the investigator, the event dyspnea was related to study drug but not related to concomitant medication.

Follow-up (18Jan2021): New information received included: medical history and concomitant medications.

Case Comment: Assuming a plausible drug-event temporal association and considering the known safety profile of the suspect drug, the company concurs with the causality assessment expressed by the investigator, considering there is a reasonable possibility that dyspnea is related to the suspect drug bosutinib.

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

#1) JANUMET [METFORMIN HYDROCHLORIDE;SITAGLIPTIN] (METFORMIN HYDROCHLORIDE, SITAGLIPTIN) ; 2007 / Ongoing

#2) DIPROSONE [BETAMETHASONE DIPROPIONATE] (BETAMETHASONE DIPROPIONATE) Cream ; Ongoing

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Chronic sinusitis (Chronic sinusitis);
JUL-2019 to Unknown	Relevant Med History	Mycosis (Fungal infection);

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		PRIVACY		73 Years	Male	75.00 kg	16	JUN	2021

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

Dyspnea (grade 2) [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.

(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)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 mg, 1x/day	#1) Unknown
#2) 100 mg, 1x/day	#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) 27-SEP-2019 / 29-OCT-2019	#1) 1 month 3 days
#2) 29-OCT-2019 / Ongoing	#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) AMLOR (AMLODIPINE BESILATE) ; 2003 / Ongoing
#2) TACROLIMUS (TACROLIMUS) ; 2003 / Ongoing

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

From/To Dates	Type of History / Notes	Description
2003 to Ongoing	Relevant Med History	Liver transplant (Liver transplant)
2003 to 2003	Relevant Med History	Hepatitis C (Hepatitis C)

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.
202100996816

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 73-year-old male patient received bosutinib (BOSULIF), from 27Sep2019 to 29Oct2019 at 200 mg 1x/day; dasatinib monohydrate (SPRYCEL), since 29Oct2019 (ongoing) (Batch/Lot number: unknown) at 100 mg 1x/day, oral for chronic myeloid leukaemia. The patient's relevant medical history included: "Liver transplant", start date: 2003 (ongoing); "Hepatitis C", start date: 2003, stop date: 2003. Concomitant medication(s) included: AMLOR oral taken for hypertension, start date: 2003 (ongoing); TACROLIMUS oral taken for prophylaxis against transplant rejection, start date: 2003 (ongoing).
The following information was reported: DYSPNOEA (non-serious) with onset 16Jun2021, outcome "recovering", described as "Dyspnea (grade 2)". The action taken for bosutinib was unknown; for dasatinib monohydrate was dosage not changed.

The reporter considered "dyspnea (grade 2)" not related to bosutinib and related to co-suspect drug dasatinib monohydrate.

Follow-up (07Nov2022): This is a follow-up report received from the CRO.

Updated information included: start dose of bosulif, route of administartion for sprycel, product indication for sprycel.

Case Comment: Reported dyspnea, occurred more than a year after reported date of last dose of bosutinib, is considered unrelated to bosutinib. Co-suspect product dasatinib monohydrate may provide an alternative explanation to reported event.

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		PRIVACY		66 Years	Male	67.00 kg	05	JUL	2021

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

Anasarca [Generalised oedema]
Bilateral pleural effusion [Pleural effusion]

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) 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) 06-NOV-2019 / 08-JUL-2021

19. THERAPY DURATION
#1) 1 year 8 months 3 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) CANDESARTAN (CANDESARTAN) ; 1996 / Unknown
#2) BISOPROLOL (BISOPROLOL) ; 1998 / Ongoing
#3) EZETROL (EZETIMIBE) ; Ongoing

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

From/To Dates	Type of History / Notes	Description
1996 to Ongoing	Relevant Med History	Hypertension arterial (Hypertension)
Unknown to Ongoing	Relevant Med History Chronic	

(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.
202101075091

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

24c. DATE RECEIVED BY MANUFACTURER
06-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 66-year-old male patient received bosutinib (BOSULIF), from 06Nov2019 to 08Jul2021 at 300 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: "Hypertension arterial", start date: 1996 (ongoing); "Pulmonary arterial hypertension" (ongoing), notes: Chronic; "Hypercholesterolemia" (ongoing); "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: CANDESARTAN oral taken for hypertension, start date: 1996; BISOPROLOL oral taken for hypertension, start date: Jun1998 (ongoing); EZETROL oral taken for hypercholesterolaemia (ongoing).
The following information was reported: GENERALISED OEDEMA (hospitalization) with onset 05Jul2021, outcome "recovered" (10Aug2021), described as "Anasarca"; PLEURAL EFFUSION (hospitalization) with onset 05Jul2021, outcome "not recovered", described as "Bilateral pleural effusion". The patient was hospitalized for generalised oedema, pleural effusion (start date: 05Jul2021, discharge date: 20Jul2021, hospitalization duration: 15 day(s)). The patient was hospitalized in the emergency department on 05Jul2021 for anasarca with bilateral pleural effusion, ascites, edemas of the lower limbs and weight gain of 7kg. Pleural punctures were performed (2 on the right side and one on the left), during which exudative fluid with protein level of 37 G/L was obtained. Diuretic treatment with furosemide (unspecified trade name) 40 mg twice a day was started and allowed disappearance of the lower limb edemas and weight loss (the patient returned to his normal weight of 63kg). Imaging by computed tomographic angiography and by computed tomography of chest, abdomen and pelvis performed on 07Jul2021 and on 20Jul2021, respectively, did not disclose evidence of pulmonary embolism, mediastinal or parenchymal abnormality apart of bilateral atelectasis related to pleural effusion. The patient was discharged from the hospital on 20Jul2021, with prescription of furosemide 40mg twice a day and oxygen therapy, as the blood gas test performed on room air on 19Jul2021 showed PaO2 at 48 mmHg. When re-interviewed, the patient admitted that he had suffered from insidious dyspnea at least 2 months before hospitalization, followed by appearance of edema and weight gain. At the consultation performed on 10Aug2021, there was a hypoventilation over the left lung base with decrease of breath sounds (vesicular murmur) related to pleural effusion, which was still present. Blood gas parameters were unremarkable. It was planned to decrease dose of furosemide to 40 mg/day from 11Aug2021, and to stop oxygen therapy. A follow-up consultation of a pulmonologist in order to discuss the need of pleural puncture was scheduled on 17Aug2021. Pleural punctions are in favor of a chylothorax. Refusal of the patient to be followed in hospitalization for drainage. Setting up a fat-free diet. Favorable development. But no full resolution of the pleural effusions at the date of 20Dec2021. Event was rated grade 2. At the end of the follow-up (09Mar2023), persistence of left pleural effusion related to known chylothorax. No worsening with initiation of imatinib treatment. Event Anasarca was rated as grade 2. The patient underwent the following laboratory tests and procedures: Angiogram: (07Jul2021) did not disclose evidence of pulmonary embolism; Blood gases: (10Aug2021) unremarkable; Computerised tomogram: (20Jul2021) did not disclose evidence of pulmonary embolism; PO2: (19Jul2021) 48 mmHg; Protein total: (unspecified date) 37 g/l. The action taken for bosutinib was dosage permanently withdrawn on 08Jul2021. Bosulif action taken was discontinued, then dose was reduced. Therapeutic measures were taken as a result of generalised oedema.

According to the investigator events was related to study drug and unrelated to concomitant treatments.

Follow-up (21Dec2021): This is a Non-Interventional Study follow-up report received from investigational site via CRO. Additional information: anasarca recovered on 10Aug2021, new serious event pleural effusion grade 2 requiring hospitalization, action taken in response to this event - permanently withdrawn, related to bosutinib, unrelated to concomitant, clinical course.

Follow-up (09Mar2023): This is a Non-Interventional Study follow-up report received from CRO. Updated information included: clinical course.

Follow-up (03Oct2023): New information received from CRO is as follows:
Updated information includes: Relevant medical history was updated. Bosutinib indication provided and start date updated. Concomitant drugs bisoprolol start date updated.

Follow-up (06Dec2023): This is a Non-Interventional Study follow-up report received from the investigator via the CRO.
Updated information: medical history and clniical course.

Case Comment: Based on the temporal association and known product safety profile, the events Anasarca and Bilateral pleural effusion are assessed as related to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	07-JUL-2021	Angiogram	did not disclose evidence of pulmonary embolism	
2	10-AUG-2021	Blood gases	unremarkable	
3	20-JUL-2021	Computerised tomogram	did not disclose evidence of pulmonary embolism	
4	19-JUL-2021	PO2	48 mmHg	

Mfr. Control Number: 202101075091

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
5		Protein total	37 g/l	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History Chronic	Pulmonary arterial hypertension (Pulmonary arterial hypertension);
Unknown 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		PRIVACY		70 Years	Male	82.00 kg	18	JUN	2021

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

Pneumonia (grade 5) [Pneumonia]

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. A 70-years-old male subject started to receive bosutinib (BOSULIF) via an unspecified route of administration from 30Jan2019 and 17Sep2019 400mg once a day for an unspecified indication.

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☒ PATIENT DIED Date: 27-JUN-2021
- ☐ 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) 30-JAN-2019 / 17-SEP-2019

19. THERAPY DURATION
#1) 7 months 19 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) ICLUSIG (PONATINIB HYDROCHLORIDE) ; 18-SEP-2019 / Ongoing
#2) HYDREA (HYDROXYCARBAMIDE) ; Ongoing
#3) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Ongoing
#4) ATORVASTATINE [ATORVASTATIN] (ATORVASTATINE [ATORVAS
#5) VIMPAT (LACOSAMIDE) ; Ongoing
#6) DISCOTRINE (GLYCERYL TRINITRATE) ; 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	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.
202101215618

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

24c. DATE RECEIVED BY MANUFACTURER
15-SEP-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

Medical history was none. Concomitant medications included ponatinib hydrochloride (ICLUSIG) orally from 18Sep2019 and ongoing for chronic myeloid leukemia (CML), hydroxycarbamide (HYDREA) orally ongoing for CML, acetylsalicylateysine (KARDEGIC) orally ongoing, atorvastatine orally ongoing, lacosamide (VIMPAT) orally ongoing, glyceryl trinitrate (DISCOTRINE) orally ongoing, pantoprazole orally ongoing, and vortioxetine hydrobromide (BRINTELLIX) orally ongoing. The subject experienced pneumonia on 18Jun2021 was reported as serious with fatal outcome with grade 5. Dose was not changed for bosulif. The patient died on 27Jun2021. It was unknown if an autopsy was performed.

According to the investigator, the event was related to study drug bosulif and unrelated to concomitant drugs.

This is a final report for initial notification of a fatal event.

Case Comment: Fatal Pneumonia is unlisted in the SRSD for Bosutinib and unrelated per Company assessment.

Based on the time from last dose of Bosutinib to onset of fatal Pneumonia (1 year 9 months 1 day), the Company did not consider a reasonable possibility that the event may be related to the suspect study drug. The underlying malignancy may provide the most plausible alternative cause towards the event.

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 appropriate.

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

#4) ATORVASTATINE [ATORVASTATIN] (ATORVASTATINE [ATORVASTATIN]) ; Ongoing

#7) PANTOPRAZOLE (PANTOPRAZOLE) ; Ongoing

#8) BRINTELLIX (VORTIOXETINE HYDROBROMIDE) ; Ongoing

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		PRIVACY		51 Years	Female	97.50 kg	20	FEB	2020

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

ABDOMINAL PAINS [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 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

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) 24-JUN-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)

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.
2021012234

24c. DATE RECEIVED BY MANUFACTURER
15-MAY-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 51-year-old female subject received bosutinib (BOSULIF), since 24Jun2019 (ongoing) at 300 mg daily. The subject medical history and concomitant medications were not reported. The subject experienced abdominal pains on 20Feb2020. The event was considered non serious and rated grade 2. The action taken in response to the event for bosutinib was dose not changed. The event was resolved on 28Feb2020.

According to the investigator, the event abdominal pains was related to study drug but not related to concomitant medication.

Follow-up (15May2023): 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: start date of study drug bosutinib was updated to 24Jun2019 (instead of 29Jun2019).

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

Case Comment: In concurrence with the investigator, a causal association between bosutinib and the reported abdominal pains cannot be excluded based on the known drug safety profile and temporal relationship.

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		PRIVACY		74 Years	Male	76.00 kg	31	AUG	2020

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
Left temple carcinoma excision - Bowen's disease [Second primary malignancy]
Left temple carcinoma excision - Bowen's disease [Bowen's disease]
Rheumatic right knee pain [Arthralgia]
right knee pain aggravation [Arthralgia]

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) 300 mg, daily

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

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

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

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 myelogenous 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.
202101338160

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:

25b. NAME AND ADDRESS OF REPORTER
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 74-year-old male patient received bosutinib (BOSULIF), oral from 01Oct2019 and ongoing, at 300 mg daily for chronic myelogenous leukemia. The patient's medical history included ongoing chronic myelogenous leukemia. Concomitant medications were not reported. The patient experienced rheumatic right knee pain on 31Aug2020 with outcome of not recovered. The patient had a consultation of 20May2021. The patient experienced left temple carcinoma excision - bowen's disease on 20May2021 with outcome of recovered on 26May2021. Excision of the left temporal lesion performed on 26May2021. The patient experienced right knee pain aggravation on 06Sep2021 with outcome not recovered. Lab data included anatomopathomorphology test on 02Jun2021 confirming the disease with complete excision. Event left temple carcinoma excision - Bowen's disease reported as grade 3, serious for medically significant. Event rheumatic right knee pain reported as grade 1, non-serious. Event right knee pain aggravation was reported as non-serious, grade 2. The action taken in response to the events for bosutinib was dose not changed. Treatment was received for the event (left temple carcinoma excision - Bowen's disease).

All events were reported as unrelated to the study drug or concomitant medications.

Follow-up (16May2023): 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: lab data added, medical history added (CML), suspect drug data (dosing frequency), event data (onset date and seriousness updated for Bowen's disease), and new event added ("right knee pain aggravation"). This case is now serious.

Case Comment: In concurrence with the reporter, the Company deems the reported rheumatic right knee pain, second primary malignancy of Bowen's disease and right knee pain aggravation are unrelated to the suspect, bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	02-JUN-2021	Histology	confirming the disease with complete excision	

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		PRIVACY		78 Years	Male	Unk	02	APR	2019

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

CERVICALGIA [Neck pain]
HEAVY HEAD SENSATION [Head discomfort]

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

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)

18. THERAPY DATES(from/to)
#1) 14-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)

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.
202101339747

24c. DATE RECEIVED BY MANUFACTURER
19-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.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 78-year-old male patient received bosutinib (BOSULIF), via an unspecified route of administration from 14Aug2018 and ongoing, at 400 mg, once daily for chronic myeloid leukaemia. The patient medical history and concomitant medications were not reported. The patient experienced secondary pancreatitis with lithiasic migration on Mar2021 with outcome of recovered on 22Jun2021. The subject presented with secondary pancreatitis with lithiasic migration rated as grade 3 and considered as non-serious. It was further reported that the patient underwent an endoscopy ultrasound for assessment of pancreatitis rated grade 2 on 22Jun2021 which was reported as medically significant and resolved on 22Jun2021. On an 02Apr2019 (as reported) patient experienced CERVICALGIA grade 1, reported as non-serious and recovered in May2019. On an unspecified date patient experienced heavy dead sensation coded as head discomfort reported as non-serious and not recovered. The action taken in response to the events for bosutinib was dose not changed.

The reporter considered "secondary pancreatitis with lithiasic migration" and "cervicalgia" not related to bosutinib or concomitant medication. The reporter considered "heavy head sensation" related to bosutinib and unrelated to any concomitant medication.

Follow-up (25Jan2022): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047 (study alias BOSEVAL).
Updated information: The subject underwent an endoscopy ultrasound for assessment of pancreatitis rated grade 2 on 22Jun2021 which was reported as medically significant and resolved on 22Jun2021. According to the reporter, the event was unrelated to bosutinib.

Follow-up(13Oct2022): New information received from investigational site via CRO included:
Updated information included: Reaction data (events head discomfort and neck pain added).

Amendment: This follow-up report is being submitted to amend previous information: Event Pancreatitis was removed.
Updated information included: product onset date corrected to 14Aug2018.

Case Comment: The reported cervicalgia and heavy head sensation are considered unrelated to bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	22-JUN-2021	Endoscopic ultrasound	unknown result	

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		PRIVACY		60 Years	Female	118.00 kg		MAR	2021

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

1 episode of rectorrhagia [Rectal haemorrhage]
Hot flushes [Hot flush]

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)

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) 25-SEP-2018 / 07-DEC-2020

19. THERAPY DURATION
#1) 2 years 2 months 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)

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 myelogenous 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.
202101444735

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.

Mfr. Control Number: 202101444735

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 60-year-old female patient received bosutinib (BOSULIF), first regimen from 25Sep2018 to 07Dec2020 at 200 mg daily, second regimen from 08Dec2020 to 30Mar2021 at 300 mg daily and third regimen since 31Mar2021 (ongoing) at 200 mg daily. The patient's relevant medical history included: "Chronic myelogenous leukemia" (ongoing). The patient's concomitant medications were not reported.
The following information was reported: HOT FLUSH (non-serious) with onset Mar2021, outcome "not recovered", described as "Hot flushes"; RECTAL HAEMORRHAGE (non-serious) with onset Jul2021, outcome "recovered" (Jul2021), described as "1 episode of rectorrhagia". The action taken for bosutinib was dosage not changed.

The reporter considered "1 episode of rectorrhagia" and "hot flushes" not related to bosutinib.

Additional information: In the report of 12Oct2021: since last consultation: hot flushes and episode of rectorrhagia in Jul2021 without recidive. The events were both rated grade 1 and considered not serious.

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

Follow-up (12Jul2023): This follow-up is received from the investigational site CRO to a non-interventional clinical study case. Updated information include: second reporter name and surname.

Follow-up (24Jul2023): This is a follow-up to a non-interventional study for protocol B1871047 received from investigator site. Updated information included: bosutinib dosage regimens updated.

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

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: medical history (changed to ongoing Chronic myelogenous leukemia); dosage regimen of bosutinib.

Case Comment: Events Rectorrhagia X1 and Hot flushes are most likely related to intercurrent or underlying conditions and unrelated to suspect drug BOSUTINIB.
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	300 mg, daily; Unknown	Unknown	08-DEC-2020 / 30-MAR-2021; 3 months 23 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	31-MAR-2021 / 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		PRIVACY		59 Years	Female	118.00 kg		MAR	2021

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

Right iliac fossa pain episode [Abdominal pain lower]
decreased/ weak appetite [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.

(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)

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)

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.
202101447729

25b. NAME AND ADDRESS OF REPORTER
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:

Mfr. Control Number: 202101447729

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 59-year-old female patient received bosutinib (BOSULIF), first regimen from 25Sep2018 to 07Dec2020 at 200 mg daily, second regimen from 08Dec2020 to 30Mar2021 at 300 mg daily and third regimen since 31Mar2021 (ongoing) at 200 mg daily. The patient's relevant medical history included: "chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported. The following information was reported: ABDOMINAL PAIN LOWER (non-serious) with onset Mar2021, outcome "not recovered", described as "Right iliac fossa pain episode"; DECREASED APPETITE (non-serious) with onset Mar2021, outcome "not recovered", described as "decreased/ weak appetite". The action taken for bosutinib was dosage not changed.

The reporter considered "right iliac fossa pain episode" and "decreased/ weak appetite" not related to bosutinib.

Additional information: The event right iliac fossa pain episode and decreased appetite were rated grade (CTCAE) 1. In the report of 12Oct2021: right iliac fossa pain episode, abdominal ultrasound to be done, weak appetite, no transit disorders, difficult psychological context.

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

Follow-up(23May2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from contactable reporter(s) from investigational site via CRO for protocol B1871047. Updated information: reporter causality for events "right iliac pain" and "decreased/ weak appetite" (unrelated to bosutinib).

Follow-up (12Jul2023): This is a non-interventional study follow up report (Post Authorization Safety Study) from the investigational site via the CRO. Updated information included: other HCP considered as contactable.

Follow-up (24Jul2023): This is a non-interventional study follow up report (Post Authorization Safety Study) from the CRO. Updated information included: bosutinib dosage regimens.

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

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: medical history details, dosage regimen of bosutinib, event term (event term right iliac pain was changed to right iliac fossa pain episode).

Case Comment: The causal relationship of the "right iliac fossa pain episode" with the suspect product bosutinib is unlikely. 'Decreased appetite' may be due to the use of the suspect drug. Underlying malignancy and medical history positive for "Colic diverticulitis" may provide alternative explanations.

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 / 30-MAR-2021; 3 months 23 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	Unknown	31-MAR-2021 / 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		PRIVACY		73 Years	Female	73.00 kg	22	JUN	2020

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

Weight increased [Weight increased]
Tachycardia [Tachycardia]

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) 300 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) 26-JUN-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)

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.
202101462898

25b. NAME AND ADDRESS OF REPORTER
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:

Mfr. Control Number: 202101462898

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 73-year-old female patient received bosutinib (BOSULIF), since 26Jun2019 (ongoing) at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: WEIGHT INCREASED (non-serious) with onset 22Jun2020, outcome "not recovered"; TACHYCARDIA (non-serious) with onset Dec2020, outcome "recovered" (10Mar2021). The action taken for bosutinib was dosage not changed.
Additional information: Weight increased was rated Grade 2 and tachycardia was rated Grade 1.

Events were assessed as non-serious by reporter.

The investigator considered there was not a reasonable possibility that the events "weight increased" and "tachycardia" were related to bosutinib or concomitant medication.

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

Follow-up (19Sep2023): This is a non-interventional study follow-up report received from investigational site via CRO.
Updated information included: product and patient details, and additional information.

Follow-up (04Oct2023): 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: suspect drug data (dosage regimen).
Follow-up attempts are completed. No further information is expected.

Case Comment: Based on the available information, there was not a reasonable possibility that the events "weight increased" and "tachycardia" were related to bosutinib or concomitant medication. 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		PRIVACY		65 Years	Male	62.00 kg	08	JUN	2017

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

Edematous syndrome [Oedema]
Hyperparathyroidism [Hyperparathyroidism]
Cramps [Muscle spasms]
Foot infection [Localised infection]
Hyperkalemia [Hyperkalaemia]

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) 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) 500 mg, daily	#1) Unknown
#2) UNK	#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)	19. THERAPY DURATION
#1) 26-JUL-2016 / 12-MAY-2017	#1) 9 months 17 days
#2) 13-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)

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)

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.
202101463974

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

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

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

A 65-year-old male patient received bosutinib (BOSULIF), via an unspecified route of administration from 26Jul2016 (Batch/Lot number was not reported) to 12May2017, at 500 mg, daily for an unspecified indication; imatinib mesilate (GLIVEC), oral from 13May2017 (Batch/Lot number was not reported) and ongoing, at unspecified dose for chronic myeloid leukemia; trandolapril, verapamil hydrochloride (TARKA), via an unspecified route of administration from an unspecified date at an unspecified dose as antihypertensive agent. The patient's relevant medical history included: "chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported. The patient experienced edematous syndrome on 08Jun2017 with outcome of recovered on 20Feb2019, hyperparathyroidism in Jan2018 with outcome of not recovered, cramps in Oct2018 with outcome of recovered in Jan2019, foot infection in Jul2018 with outcome of recovered in Jul2018, hyperkalemia in Jun2017 with outcome of recovered on 14Jun2017. The patient stopped bosutinib on 12May2017 and was since under imatinib (GLIVEC). The event cramps was rated grade 1 and can be explained by vascular problems. Edematous syndrome grade 2 following introduction of imatinib (GLIVEC) and hyperkalemia grade 2 following treatment with an antihypertensive agent trandolapril, verapamil hydrochloride (TARKA). The patient underwent lab tests and procedures which included blood potassium: hyperkalemia in Jun2017. The action taken in response to the events for bosutinib was post-therapy. The last action taken in response to the events for imatinib mesilate was no modifications, for trandolapril, verapamil hydrochloride was stop (temporary or permanent, or delayed administration).

The investigator considered that cramps was considered unrelated to study drug or to any concomitant drug. Edematous syndrome was considered as unrelated to bosutinib and related to concomitant drug imatinib (GLIVEC), hyperkalemia was considered as unrelated to bosutinib and related to concomitant drug trandolapril, verapamil hydrochloride (TARKA). Hyperparathyroidism was grade 2, secondary to renal failure of vascular origin and considered as unrelated to bosutinib or to any concomitant drugs. Foot infection was grade 1, following trauma, and considered as unrelated to bosutinib or to any concomitant drugs.

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

Follow-up (06Jul2023): This is a Non-Interventional follow-up report received from CRO.
Updated information included: the event "breast pain" removed.

Follow-up (19Sep2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician) for protocol B1871047.
Updated information included: reporter details, medical history, action taken for Glivec and Tarka added.

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

Case Comment: The Company deems the reported events including cramps, edematous syndrome, hyperkalemia, hyperparathyroidism and foot infection following trauma are unrelated to the study drug, bosutinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	JUN-2017	Blood potassium	hyperkalemia	

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) TARKA (TRANDOLAPRIL, VERAPAMIL HYDROCHLORIDE) ; Regimen #1	; Unknown	antihypertensive agent (Hypertension)	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		PRIVACY		74 Years	Female	Unk	29	MAR	2021

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

hyperparathyroidism secondary to renal insufficiency [Hyperparathyroidism secondary]

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

This is a non-interventional study report for protocol B1871047.

A 74 year-old female patient received bosutinib (BOSULIF) (Batch/Lot

(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) UNK

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

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

18. THERAPY DATES(from/to)
#1) 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)

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.
202101465454

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

24c. DATE RECEIVED BY MANUFACTURER
27-OCT-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

number: unknown). The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: HYPERPARATHYROIDISM SECONDARY (non-serious) with onset 29Mar2021, outcome "not recovered", described as "hyperparathyroidism secondary to renal insufficiency". The action taken for bosutinib was dosage not changed.

The investigator considered there was not a reasonable possibility that the event "hyperparathyroidism secondary to renal insufficiency" was related to bosutinib.

Additional information: Event assessed as non-serious; no action taken in response to event. According to the reporter, the event not related to study drug bosutinib or concomitant medication.

Case Comment: Based on available information and in agreement with the Investigator, the event hyperparathyroidism secondary to renal insufficiency is most likely related to intercurrent or underlying conditions and unrelated to suspect drug BOSUTINIB.

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		PRIVACY		73 Years	Male	87.00 kg		NOV	2020

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) for protocol B1871047.

A 73 year-old male patient received bosutinib (BOSULIF), first regimen

(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) METFORMINE [METFORMIN] (METFORMINE [METFORMIN])
(Continued on Additional Information Page)

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 400 mg, daily	#1) Unknown
#2)	#2) Unknown

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

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 19-OCT-2018 / 26-MAY-2021	#1) 2 years 7 months 8 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)

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.
202101473921

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 202101473921

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

from 19Oct2018 (Batch/Lot number: unknown) to 26May2021 at 400 mg daily and second regimen since 27May2021 (ongoing) (Batch/Lot number: unknown) at 300 mg daily; metformine [metformin] (METFORMINE [METFORMIN]) (Batch/Lot number: unknown). The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: DIARRHOEA (non-serious) with onset Nov2020, outcome "not recovered", described as "diarrhea". The action taken for bosutinib was dosage reduced; for metformine [metformin] was unknown.
Additional information: The event was reported as non-serious and rated grade 2.

The investigator considered the event was related to bosutinib and to concomitant drug metformin.

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

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported event diarrhea.

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-MAY-2021 / 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		PRIVACY		73 Years	Male	87.00 kg	19	NOV	2020

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

Erythematous spots [Erythema]
skin and mucous membrane pallor [Pallor]

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

This is a non-interventional study report for protocol B1871047.

A 73-year-old male patient received bosutinib (BOSULIF), first regimen

(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) 19-OCT-2018 / 26-MAY-2021	#1) 2 years 7 months 8 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.
202101473923

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 202101473923

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

from 19Oct2018 (Batch/Lot number: unknown) to 26May2021 at 400 mg daily and second regimen since 27May2021 (ongoing) (Batch/Lot number: unknown) at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: ERYTHEMA (non-serious) with onset 2021, outcome "recovered" (06Sep2021), described as "Erythematous spots"; PALLOR (non-serious) with onset 19Nov2020, outcome "recovered" (06Sep2021), described as "skin and mucous membrane pallor". The action taken for bosutinib was dosage not changed.

Additional information: Both events rated grade 1 and not serious

The investigator considered there was not a reasonable possibility that the events "erythematous spots" and "skin and mucous membrane pallor" were related to bosutinib.

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

Amendment (29Jun2023): This follow-up report is being submitted to amend previous information: Patient's gender updated to male.

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

Case Comment: The reported events "erythematous spots" and "skin and mucous membrane pallor" were unrelated to suspect drug, bosutinib, (BOSULIF) and assessed as non serious. This case will be reassessed when further information is 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	27-MAY-2021 / 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		PRIVACY		53 Years	Male	115.00 kg	14	MAR	2019

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

intermittent hepatic cytolysis [Hepatic cytolysis]

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) 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) 05-MAR-2018 / 02-MAR-2020	#1) 1 year 11 months 27 days

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) SITAGLIPTINE (SITAGLIPTINE) ; 2019 / Ongoing
#2) GLIMEPIRIDE (GLIMEPIRIDE) ; 2019 / Ongoing
#3) EPROSARTAN (EPROSARTAN) ; 2019 / Ongoing
#4) FENOFIBRATE (FENOFIBRATE) ; 2019 / 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

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.
202101479539

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:

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

NAME AND ADDRESS WITHHELD.

Mfr. Control Number: 202101479539

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 53-year-old male patient received bosutinib (BOSULIF), first regimen from 05Mar2018 to 02Mar2020 at 300 mg 1x/day and second regimen since 03Mar2020 (ongoing) at 200 mg 1x/day. Medical history was not reported. Concomitant medications included sitagliptine taken for diabetes from 2019 and ongoing; glimepiride taken for diabetes from 2019 and ongoing; eprosartan taken for arterial hypertension from 2019 and ongoing; fenofibrate taken for dyslipidaemia from 2019 and ongoing. The subject experienced intermittent hepatic cytolysis on 14Mar2019. The action taken in response to the event for bosutinib was dose not changed. The outcome of the event was not resolved. Event hepatic cytolysis reported as non-serious.

The investigator considered event hepatic cytolysis was related to bosutinib and unrelated to concomitant drug.

Follow-up (15Nov2021): New information received from the investigational site via the CRO includes: the event term was updated to intermittent hepatic cytolysis. The recovery date was updated to unknown. No action was taken on bosutinib in response to the event. The investigator considered the event as related to bosutinib and unrelated to concomitant drug.

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

Follow-up (22Dec2021): New information from the investigator via CRO included: outcome of the event intermittent hepatic cytolysis was updated to not resolved (previously resolved).

Follow-up (13Apr2023): New information received from investigational site via CRO.
Updated information included: first regimen for Bosulif updated
Follow-up attempts are completed. No further information is expected.

Case Comment: In concurrence with the investigator, the reported hepatic cytolysis is unrelated to the study drug, bosutinib. Event is most likely an intercurrent condition.

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	03-MAR-2020 / 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		PRIVACY		72 Years	Male	Unk	21	JUL	2021

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

Pleural effusion [Pleural effusion]

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

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) 15-OCT-2019 / 26-AUG-2021

19. THERAPY DURATION
#1) 1 year 10 months 12 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
FEB-2014 to OCT-2014	Relevant Med History	Gastritis (Gastritis)
MAR-2014 to MAR-2014	Relevant Med History	Coronary angioplasty (Coronary angioplasty)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Stella Pietrafesa
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Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
202101495315

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

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:

Mfr. Control Number: 202101495315

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-years-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 15Oct2019 to 26Aug2021, at 300 mg, once daily for an unspecified indication. Medical history included superficial antritis from Feb2014 to Oct2014, coronary angioplasty from Mar2014 to Mar2014, pleural effusions from Jun2019 to Jun2019, pleural effusion from Apr2014 to May2014. The subject's concomitant medications were not reported. The subject experienced pleural effusion on 21Jul2021, grade was 2. The subject was hospitalized for pleural effusion from 21Jul2021 to 23Jul2021. The subject was hospitalized in pneumology for dyspnea from 21Jul2021 to 23Jul2021. Clinical examination: dyspnea rated 1 on the MMRC scale. No febrile syndrome, saturation was 96% in ambient air. Examinations: pleural echography found low output abundance pleural effusion. To be reminded subject was under Plavix. It was punctured only 30 cc of a citrine liquid. The radiological control found complete disappearance of pleural effusion, no pneumothorax. Action taken for bosutinib was permanently withdrawn. The outcome of the event was recovered on 31Aug2021.

According to the investigator event was related to study drug and unrelated to concomitant treatments.

Follow-up (19Sep2023): This is a report from a Non-Interventional Study from the investigational site via the CRO. Updated information includes: relevant medical history and recovery date of the event.

Follow-up (22Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporters (Physician and Other HCP) for protocol B1871047. Updated information included: Bosutinib was stopped on 26Aug2021 (previously reported on 30Aug2021).

Case Comment: Based on the known drug safety profile and temporal relationship, a causal association between bosutinib and the reported pleural effusion cannot be excluded.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Investigation	dyspnea rated 1	
2		Oxygen saturation in ambient air	96 %	
3		Ultrasound chest	low output abundance pleural effusion	
4		X-ray no pneumothorax	complete disappearance of pleural effusion	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
JUN-2019 to JUN-2019	Relevant Med History	Pleural effusion (Pleural effusion);
APR-2014 to MAY-2014	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		PRIVACY		69 Years	Male	114.00 kg		JUL	2020

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

Articular pain increase [Arthralgia]
DYSPNEA ON EFFORT [Dyspnoea exertional]

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 Regulatory Authority 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
#2) DASATINIB (DASATINIB)
(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
#2) UNK	#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)	19. THERAPY DURATION
#1) 15-JUL-2020 / 03-SEP-2020	#1) 1 month 20 days
#2) 03-SEP-2020 / 05-NOV-2020	#2) 2 months 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		

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.
202101503411

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.

Mfr. Control Number: 202101503411

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 69-year-old male patient received bosutinib (BOSULIF), first regimen from 15Jul2020 to 03Sep2020 at 200 mg daily and second regimen since 12Nov2020 (ongoing) at 300 mg 1x/day; dasatinib (DASATINIB), from 03Sep2020 to 05Nov2020, oral for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: ARTHRALGIA (non-serious) with onset Jul2020, outcome "not recovered", described as "Articular pain increase"; DYSPNOEA EXERTIONAL (non-serious) with onset Oct2020, outcome "recovered" (Nov2020), described as "DYSPNEA ON EFFORT". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was temporarily withdrawn; for dasatinib was dosage permanently withdrawn on 05Nov2020.
Additional information: The event articular pain increase was reported as non-serious, grade2. According to the investigator, the event was related to study drug bosutinib and unrelated to concomitant drugs. "Exertional dyspnea" with cough occurred when changing positions. Pulmonary auscultation showed a right basal mastitis. And on radiological examination, it showed no effusion. Dasatinib stopped and bosulif restarted. Acknowledgement by the doctor on 05Nov2020. The event exertional dyspnea was reported as non-serious, rated grade 1.

The investigator considered there was a reasonable possibility that the event "articular pain increase" was related to bosutinib. The investigator considered the event "dyspnea on effort" was related to concomitant dasatinib, while unrelated to bosutinib.

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

Follow-up(15Sep2022): New information received from investigational site via CRO.
Updated information includes: labs (auscultation and X-ray), new dosage of bosutinib, additional suspect drug (dasatinib), new event (dyspnea on effort), updated action taken of bosutinib (temporarily withdrawn), and clinical course.

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) from Regulatory Authority for protocol B1871047. Updated information: suspect durg data.

Case Comment: A causal association between administration of bosutinib and the onset of Articular pain increase cannot be excluded, considering the temporal association and the known adverse event profile of the suspect product.
Conversely in agreement with the reporter, dyspnoea exertional is considered unrelated to bosutinib and likely due to dasatinib.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Auscultation	a right basal mastitis	
2		X-ray	no effusion	

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	12-NOV-2020 / 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		PRIVACY		70 Years	Male	114.00 kg		OCT	2020

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

Cough [Cough]
Oedema [Oedema]

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
#2) DASATINIB (DASATINIB)
(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
#2) UNK	#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)	19. THERAPY DURATION
#1) 11-JUL-2020 / 03-SEP-2020	#1) 1 month 24 days
#2) 03-NOV-2020 / 18-NOV-2020	#2) 16 days

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-JAN-2019 / Ongoing
#2) KETOPROFEN (KETOPROFEN) ; 03-AUG-2020 / 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		

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.
202101509280

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:

Mfr. Control Number: 202101509280

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 70-year-old male patient received bosutinib (BOSULIF), first regimen from 11Jul2020 to 03Sep2020 at 200 mg daily and second regimen since 12Nov2020 (ongoing) at 300 mg daily; dasatinib (DASATINIB), from 03Nov2020 (Batch/Lot number: unknown) to 18Nov2020, oral for chronic myeloid leukaemia; indapamide, perindopril arginine (BIPRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE]), since Apr2017 (Batch/Lot number: unknown), oral for hypertension. The patient's relevant medical history was not reported. Concomitant medication(s) included: ASPEGIC oral taken for arthralgia, start date: 10Jan2019 (ongoing); KETOPROFEN oral taken for arthralgia, start date: 03Aug2020 (ongoing).
The following information was reported: COUGH (non-serious) with onset Oct2020, 1 year 9 months 16 days after the suspect product(s) administration, outcome "recovered" (Nov2020); OEDEMA (non-serious) with onset Feb2021, outcome "recovered" (Mar2021). The action taken for bosutinib was dosage not changed. The action taken for dasatinib was dosage permanently withdrawn on 18Nov2020; for indapamide, perindopril arginine was dosage permanently withdrawn.

The investigator considered there was not a reasonable possibility that the events "cough" and "oedema" were related to bosutinib.

Additional information: Cough and oedema was rated grade 1. The investigator assessed the event cough as related to concomitant dasatinib and the event oedema as related to concomitant BIPRETERAX.

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

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 included: Details of suspect drug Bosulif (start/stop date and dose of 200 mg).

Case Comment: There was not a reasonable possibility that the events "cough" and "oedema" were related to bosutinib, (BOSULIF). This case will be reassessed when further information becomes 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; Regimen #2	300 mg, daily; Unknown	Unknown	12-NOV-2020 / Ongoing; Unknown
#3) BIPRETERAX [INDAPAMIDE;PERINDOPRIL ARGININE] (INDAPAMIDE, PERINDOPRIL ARGININE) ; Regimen #1	UNK; Oral	Arterial hypertension (Hypertension)	APR-2017 / 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		PRIVACY		75 Years	Male	97.00 kg		DEC	2020

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

Joints pains left knee, left wrist and right knee [Arthralgia]
Joints pains left knee, left wrist and right knee [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.

(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) UNK

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

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

18. THERAPY DATES(from/to)
#1) 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	Chondrocalcinosis (Chondrocalcinosis)

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.
202101511233

24c. DATE RECEIVED BY MANUFACTURER
09-MAR-2022

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 75-year-old male patient received bosutinib (BOSULIF), (ongoing). The patient's relevant medical history included: "Joint chondrocalcinosis" (ongoing). There were no concomitant medications.
The following information was reported: ARTHRALGIA (non-serious), ARTHRALGIA (non-serious) all with onset Dec2020, outcome "recovered" (08Nov2021) and all described as "Joints pains left knee, left wrist and right knee". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of arthralgia, arthralgia.

The reporter considered "joints pains left knee, left wrist and right knee" not related to bosutinib.

Follow-up (09Mar2022 and 20Apr2022): 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 verbatim was updated to 'joints pains left knee, left wrist and right knee', event outcome.

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

Case Comment: There is not a reasonable possibility that the event of Arthralgia (both episodes) were related to bosutinib. The event was most likely attributed to intercurrent medical condition in this 75-year-old patient.

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		PRIVACY		61 Years	Male	Unk	19	OCT	2021

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
Pericarditis [Pericarditis]

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

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) 01-OCT-2018 / 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) ENTECAVIR (ENTECAVIR) ; 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-2005 to Ongoing	Relevant Med History	Hepatitis B (Hepatitis B)
Unknown	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.
202101516314

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

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 61-year-old male patient received bosutinib (BOSULIF), since 01Oct2018 at 400 mg 1x/day. The patient's relevant medical history included: "Hepatitis B", start date: Jul2005 (ongoing); "Renal insufficiency" (unspecified if ongoing). Concomitant medication(s) included: ENTECAVIR. On 19Oct2021, the subject experienced pericarditis. The event pericarditis was rated grade 2 and assessed as medically significant. Consultation on 22Jun2021: "Reason for consultation: I am seeing the patient again today as part of routine follow-up for his CML in 4th line treatment with BOSUTINIB + ENTECAVIR for pre-existing hepatitis B serology. Physical and additional examinations Patient WHO 0. Weight stable at 106 kg. No hepatosplenomegaly. Since the last consultation, the patient presented with increased chest pain on inspiration suggesting pericarditis. He therefore consulted a Cardiologist and the ultrasound on 14Jun2021 revealed slightly abundant pericardial effusion which, in principle, was treated with COLCHICINE for pericarditis and led to an improvement in symptomatology. From a biological perspective, the last Bcr-Abl test on 16Feb2021 found a decrease in level between the MMR and MMR4. For COVID, the patient received a first injection of the vaccine and is expected to have their second injection on Saturday at 2 pm. Conclusions: Chronic myeloid leukaemia treated with BOSULIF 400 mg in combination with ENTECAVIR. I am renewing the treatment despite the adverse effects because the pleural effusion is of very low abundance and the other molecules available have much more side effects. Follow-up blood tests performed today; I will see the patient again in 4 months." Consultation on 19Oct2021:"Reason for consultation I am seeing the patient today as part of routine follow-up for his CML in 4th line treatment with BOSUTINIB + ENTECAVIR for pre-existing positive hepatitis B serology. Physical and additional examinations Clinical symptoms: Patient WHO 0. Weight up to 109 kg versus 106 kg in June; No hepatosplenomegaly; Cardiopulmonary auscultation unremarkable. There was no recurrence of pericarditis, however, it should be noted that the patient only stopped COLCHICINE around ten days ago. From a biological perspective, the last Bcr-Abl test from June found a stable transcript rate below the threshold of 0.1% to 0.023%, i.e., a major molecular response. Regarding COVID, the patient has had his 2 injections. Conclusions: Chronic Myeloid Leukaemia treated with BOSULIF combined with ENTECAVIR, in major molecular response. I am renewing the BOSULIF treatment and have asked the patient to inform me as soon as possible if pericarditis recurs. Follow-up laboratory workup today and I will see the patient again in 6 months." As of 19Sep2023 it was reported Pericarditis after stopping colchicine. The action taken in response to the event for bosutinib was temporarily withdrawn, ongoing at the report time (22Sep2023). The patient recovered from the event on 18Oct2022.
According to the investigator, the event pericarditis was related to bosutinib and unrelated to concomitant drug, Entecavir was not suspected in the appearance of pericarditis.

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

Follow-up (09Jan2023): 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: updated event onset date (from 27Oct2021 to 19Oct2021), updated event outcome (from recovering to recovered) and recovery date.

Follow-up (13Feb2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site for protocol B1871047. Updated information included: bosutinib details, medical history and clinical course.

Follow-up (06Mar2023 and 06Mar2023): This is a follow-up report received from a Clinical Research Associate.
Updated information includes: lab data added and clinical details(Summary of the consultation on 22Jun2021 and 19Oct2021 added).

Follow-up (17Mar2023): This is a follow-up report received from a Clinical Research Associate. Updated information includes: Entecavir added as concomitant treatments and was not suspected in the appearance of pericarditis.

Follow-up (19Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from the investigational site for protocol B1871047.
Updated information included: Investigator Initial Aware Date, new dosage regimen for Bosulif and additional information regarding event description.

Follow-up (22Sep2023): This follow-up is received from the investigational site via CRO.

Updated information included: dosage regimen, action taken.

Case Comment: Based on a plausible temporal relationship and safety profile of the drug, causality for the onset of pericarditis secondary to Bosutinib cannot be ruled out. Of note, Bosutinib was permanently withdrawn due to the SAE and at the time of reporting, the event was resolving.
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	OCT-2021	Cardiac monitoring	Cardiopulmonary auscultation	
		Cardiopulmonary auscultation unremarkable		

Mfr. Control Number: 202101516314

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
2	16-FEB-2021	Cytogenetic analysis	found a decrease in level between the MMR and MMR4	
3	JUN-2021	Cytogenetic analysis	found a stable transcript rate below	
		The last Bcr-Abl test from June found a stable transcript rate below the threshold of 0.1% to 0.023%, i.e., a major molecular response		
4	14-JUN-2021	Ultrasound scan	revealed slightly abundant pericardial effusion	
5	JUN-2021	Weight	106 kg	
		Weight stable at 106 kg		
6	OCT-2021	Weight	109 kg	
		Weight up to 109 kg versus 106 kg in June		

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		PRIVACY		72 Years	Female	86.00 kg	23	JAN	2020

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]
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 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

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) 09-DEC-2019 / 23-JAN-2020

19. THERAPY DURATION
#1) 1 month 15 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) BISOPROLOL (BISOPROLOL) ; MAR-2014 / Ongoing
#2) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; DEC-1999 / Ongoing
#3) FLECAINE (FLECAINIDE ACETATE) ; MAR-2014 / Ongoing
#4) IMODIUM (LOPERAMIDE HYDROCHLORIDE) ; 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
Unknown to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
JUL-2013 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.
202101516611

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-year-old female patient received bosutinib (BOSULIF), from 09Dec2019 to 23Jan2020 at 300 mg daily. The patient's relevant medical history included: "Arterial hypertension" (ongoing); "Atrial fibrillation", start date: Jul2013 (ongoing); "Rectal carcinoma", start date: Apr2013, stop date: Apr2013; "Hypothyroidism", start date: Dec1999 (ongoing). Concomitant medication(s) included: BISOPROLOL oral taken for hypertension, start date: Mar2014 (ongoing); LEVOTHYROX oral taken for hypothyroidism, start date: Dec1999 (ongoing); FLECAINE oral taken for atrial fibrillation, start date: Mar2014 (ongoing); IMODIUM oral taken for diarrhoea, start date: Jan2016 (ongoing).
The following information was reported: HEPATIC CYTOLYSIS (non-serious) with onset 23Jan2020, outcome "recovered" (03Feb2020); FATIGUE (non-serious) with onset 2020, outcome "recovered" (10Jan2020). Action taken with bosutinib in response to hepatic cytolysis was reported as temporarily withdrawn.

According to the investigator the event hepatic cytolysis was related to study drug and unrelated to concomitant treatments.
According to the investigator the event fatigue was unrelated to study drug and unrelated to concomitant treatments.

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

Follow-up (07Sep2022): This is a Non-Interventional Study follow-up report received from the CRO. Updated information included: action taken for Bosutinib (from permanently withdrawn to dose reduced) and rechallenge for both events (as not applicable).

Follow-up (23Nov2023): This is a Non-Interventional Study follow-up report received from the CRO.
Updated information included: action taken for Bosutinib updated to temporarily withdrawn.

Case Comment: The Company cannot completely exclude the possible causality between the reported hepatic cytolysis, fatigue and the administration of the suspect, bosutinib, based on the reasonable temporal association. Fatigue and hepatoxicity are known adverse reactions for bosutinib.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
APR-2013 to APR-2013	Relevant Med History	Rectal carcinoma (Rectal cancer);
DEC-1999 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		PRIVACY		72 Years	Female	86.00 kg	12	MAR	2020

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]
Right shoulder rash [Rash]

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) 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) 09-DEC-2019 / 11-MAR-2020

19. THERAPY DURATION
#1) 3 months 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

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.
202101517932

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:

Mfr. Control Number: 202101517932

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 72-year-old female patient received bosutinib (BOSULIF), first regimen from 09Dec2019 to 11Mar2020 at 300 mg daily, second regimen from 12Mar2020 to 01Apr2020 at 200 mg daily, third regimen from 06Apr2020 to 13Apr2020 at 200 mg daily and fourth regimen since 14Apr2020 (ongoing) at 200 mg alternate day for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: HEPATIC CYTOLYSIS (non-serious) with onset 12Mar2020, outcome "recovered" (16Apr2020); RASH (non-serious) with onset Jun2020, outcome "recovered" (Jun2020), described as "Right shoulder rash". The action taken for bosutinib was temporarily withdrawn.

The reporter considered "hepatic cytolysis" related to bosutinib. The reporter considered "right shoulder rash" not related to bosutinib.

Additional information: The event cytolysis hepatic, grade 2, non-serious, related to the study drug, unrelated to concomitant medications; action taken with BOSULIF: drug temporarily withdrawn. The event right shoulder rash, grade 1, non-serious, unrelated to bosutinib and concomitant medications; action taken with BOSULIF: dose not changed. Investigator assessment regarding the study drug not reported.

Follow-up (14Feb2022 and 15Feb2022): This is a follow-up report from the investigator. Updated information: stop date of event "hepatic cytolysis" updated, action taken.
No follow-up attempts are needed. No further information is expected.

Amendment. This follow-up is submitted to confirm that previous follow-up information was received by the Company on 14Feb2022 and 15Feb2022 (erroneously reported as 14Mar2022 and 15Mar2022 in the case description).

Follow-up (17Jul2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from a contactable other HCP for protocol B1871047.
Updated information included: Patient's age was re-calculated as 72-year-old, causality assessment of "right shoulder rash" with bosutinib was provided as unrelated (previously not provided).

Follow-up (23Nov2023): This is a non-interventional study follow up report received from CRO. Updated information included: confirmed action taken with bosutinib in response to hepatic cytolysis was temporarily withdrawn.

Case Comment: Based on the temporal relationship and known drug safety profile, a causal association between bosutinib and the reported hepatic cytolysis and rash 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	chronic myeloid leukemia (Chronic myeloid leukaemia)	12-MAR-2020 / 01-APR-2020; 21 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3	200 mg, daily; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	06-APR-2020 / 13-APR-2020; 8 days
#1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4	200 mg, alternate day; Unknown	chronic myeloid leukemia (Chronic myeloid leukaemia)	14-APR-2020 / 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		PRIVACY		44 Years	Male	72.50 kg			2018

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

SCALP LESIONS [Skin lesion]

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, daily

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

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

18. THERAPY DATES(from/to)
#1) 01-SEP-2016 / 24-MAY-2018

19. THERAPY DURATION
#1) 1 year 8 months 24 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) PONATINIB (PONATINIB) ; 25-MAY-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.
202101522188

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:

Mfr. Control Number: 202101522188

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 44-year-old male patient received bosutinib (BOSULIF), from 01Sep2016 to 24May2018 at 500 mg daily. The patient had no relevant medical history. Concomitant medication(s) included: PONATINIB oral taken for chronic myeloid leukaemia, start date: 25May2018 (ongoing).
The following information was reported: SKIN LESION (non-serious) with onset 2018, outcome "recovered" (20Dec2018), described as "SCALP LESIONS".

The investigator considered there was not a reasonable possibility that the event "scalp lesions" was related to bosutinib.

Additional Information: The event was reported as non-serious and rated grade 1. In response to the event no action was taken with ponatinib.

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

Follow-up (07Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information included: stop date of the event.

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

Amendment: This follow-up report is being submitted to amend previous information: update patient's gender from "female" to "Male".

Case Comment: The Company, in agreement with the reporter, considers the possibility that the suspect drug bosutinib may have caused the reported non serious event skin lesion can be excluded. The event is most likely an intercurrent condition.

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		PRIVACY		40 Years	Female	59.00 kg	25	JUN	2018

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

tachycardia [Tachycardia]

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.

A 40-year-old female patient (unknown if pregnant) received bosutinib

(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) 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 to Ongoing	Relevant Med History	Hyperthyroidism (Hyperthyroidism)
Unknown to Ongoing	Relevant Med History	Pericarditis (Pericarditis)

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.
202101534372

25b. NAME AND ADDRESS OF REPORTER
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:

Mfr. Control Number: 202101534372

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

(BOSULIF), from 04Dec2017 to 17Jan2018 at 400 mg daily. The patient's relevant medical history included: "hyperthyroidism" (ongoing); "pericarditis" (ongoing); "superficial venous insufficiency" (ongoing). There were no concomitant medications.
The following information was reported: TACHYCARDIA (non-serious) with onset 25Jun2018, outcome "recovered" (24Sep2018).

Additional information: The event tachycardia was reported as non-serious and rated grade 2.

The investigator considered there was not a reasonable possibility that the events "tachycardia" was related to bosutinib.

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

Follow-up (18Sep2023): 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: patient age, event "joint pain" was deleted, outcome for event "tachycardia" with recovered date.

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

Case Comment: Both reported tachycardia and joint pain are deemed unrelated to the study drug, bosutinib. Event occurred more than 5 months after the last dose of the study drug.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Venous insufficiency (Peripheral venous disease);

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		PRIVACY		68 Years	Male	84.00 kg	23	OCT	2018

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

Febrile dyspnea [Dyspnoea]
Acute renal insufficiency on probable vascular origin [Acute kidney injury]

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 ID: 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) 300 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) Unknown / 19-MAY-2020

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) SPRYCEL (DASATINIB MONOHYDRATE) ; 20-MAY-2017 / 25-JUN-2017
#2) GLIVEC (IMATINIB MESILATE) ; 26-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
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.
202101535467

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

24c. DATE RECEIVED BY MANUFACTURER
05-NOV-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

A 68-year-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from an unspecified date (Batch/Lot number was not reported) to 19May2020, at 300 mg, daily for an unspecified indication. The subject's medical history was not reported. Concomitant medication included dasatinib monohydrate (SPRYCEL) taken for chronic myeloid leukaemia from 20May2017 to 25Jun2017; imatinib mesilate (GLIVEC) taken for chronic myeloid leukaemia from 26Jun2017 and ongoing.
The subject experienced febrile dyspnea which led to hospitalization or prolongation of hospitalization on 23Oct2018 with outcome of recovered on 27Oct2018, acute renal insufficiency on probable vascular origin which led to hospitalization or prolongation of hospitalization on 21Nov2018 with outcome of recovered on 07Dec2018. Event description: pulmonary embolism and cardiac decompensation. The action taken in response to the events for bosutinib was unknown.

The investigator considered there was not a reasonable possibility that the events could be related to the study drug bosutinib.

Case Comment: Both reported events, febrile dyspnea and acute renal insufficiency, onset before the initiation of the study drug, bosutinib, is deemed unrelated to the administration of the suspect.

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		PRIVACY		68 Years	Male	84.00 kg	05	JUL	2018

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

Unbalanced type 2 diabetes [Diabetes mellitus inadequate control]

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).

A 68-year-old male subject started to receive bosutinib (BOSULIF) from

(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) 02-MAY-2017 / 19-MAY-2017

19. THERAPY DURATION
#1) 18 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) SPRYCEL (DASATINIB MONOHYDRATE) ; 20-JUL-2017 / Unknown
#2) GLIVEC (IMATINIB MESILATE) ; 26-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
Unknown to Ongoing	Relevant Med History	
Unknown to Ongoing	Relevant Med History	Chronic renal insufficiency (Chronic kidney disease)

(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.
202101535616

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

24c. DATE RECEIVED BY MANUFACTURER
05-NOV-2021

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 202101535616

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

02May2017 to 19May2017 at 300 mg daily for unknown indication. Medical history included Chronic obstructive bronchopneumopathy, Chronic renal insufficiency, Type 2 diabetes mellitus, Arterial hypertension, all ongoing. Concomitant medications included dasatinib monohydrate (SPRYCEL) from 20Jul2017 to "25Jun2017" (as reported) for Chronic myeloid leukaemia, imatinib mesilate (GLIVEC) from 26Jun2017 and ongoing for Chronic myeloid leukaemia. On 05Jul2018, the subject presented with unbalance of type 2 diabetes rated as grade 3, inducing hospitalization. No action was taken in response of these events. The outcome of the event was resolved on 08Jul2018.

According to the investigator, the event unbalance of type 2 diabetes was considered as not related to study drug or concomitant medication.

Case Comment: The reported unbalance of type 2 diabetes occurred more than 13 months after the last dose of the suspect, is deemed unrelated to the administration of bosutinib.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Chronic obstructive bronchopneumopathy (Chronic obstructive pulmonary disease);
Unknown to Ongoing	Relevant Med History	Type 2 diabetes mellitus (Type 2 diabetes mellitus);
Unknown to Ongoing	Relevant Med History	Arterial hypertension (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		PRIVACY		60 Years	Male	Unk	08	JAN	2020

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

Blood pressure increased (grade 2) [Blood pressure increased]
Gout crisis (grade 2) [Gout]

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

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) 01-OCT-2018 / 03-NOV-2021

19. THERAPY DURATION
#1) 3 years 1 month 3 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.
202101539374

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:

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

NAME AND ADDRESS WITHHELD.

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 60-year-old male patient received bosutinib (BOSULIF), from 01Oct2018 to 03Nov2021 at 400 mg 1x/day. The patient's relevant medical history was not reported. There were no concomitant medications.
The following information was reported: BLOOD PRESSURE INCREASED (non-serious) with onset 08Jan2020, outcome "recovered" (15Apr2020), described as "Blood pressure increased (grade 2)"; GOUT (non-serious) with onset Feb2021, outcome "recovered" (Oct2021), described as "Gout crisis (grade 2)". The action taken for bosutinib was dosage not changed.

The reporter considered "blood pressure increased (grade 2)" and "gout crisis (grade 2)" not related to bosutinib.

Follow-up (09Jan2023): This is a follow-up non-interventional study report received from investigational site via CRO.
Updated information: outcome of event Gout crisis (grade 2).

Follow-up (19Sep2023): This is a report from a Non-Interventional Study from the investigational site via the CRO.
Updated information includes: dosage details of bosutinib, no concomitant drug, and updated stop dates of events blood pressure increased and gout crisis.

Case Comment: In concurrence with the reporting investigator, the Company considers the reported Blood pressure increased grade 2 and Gout crisis grade 2 unrelated to the study drug, bosutinib.

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		PRIVACY		70 Years	Female	64.00 kg		DEC	2018

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

Nausea [Nausea]
Face oedema [Face oedema]
Anorexia [Decreased appetite]
Transit disorder [Functional gastrointestinal 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

(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) IMATINIB (IMATINIB)

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) 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) 05-SEP-2018 / 12-OCT-2018	#1) 1 month 8 days
#2) 12-DEC-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 to Ongoing	Relevant Med History	Arterial hypertension (Hypertension)
Unknown to Ongoing	Relevant Med History	Osteoporosis (Osteoporosis)

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.
202101539504

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

NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
05-NOV-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

Study) for protocol B1871047.

A 70 year-old female patient received bosutinib (BOSUTINIB), from 05Sep2018 (Batch/Lot number: unknown) to 12Oct2018 at 300 mg daily for chronic myeloid leukaemia; imatinib (IMATINIB), oral since 12Dec2018 (Batch/Lot number: unknown) for chronic myeloid leukaemia. Relevant medical history included: "Arterial hypertension" (ongoing); "Osteoporosis" (ongoing); "Asthma" (ongoing); "Gastritis" (ongoing). The patient's concomitant medications were not reported. The following information was reported: NAUSEA (non-serious) with onset Dec2018, outcome "recovered" (2019), described as "Nausea"; FACE OEDEMA (non-serious) with onset Dec2018, outcome "recovered" (2019), described as "Face oedema"; DECREASED APPETITE (non-serious) with onset Dec2018, outcome "recovered" (2019), described as "Anorexia"; FUNCTIONAL GASTROINTESTINAL DISORDER (non-serious) with onset Dec2018, outcome "recovered" (2019), described as "Transit disorder". The action taken for bosutinib was unknown; for imatinib was dosage reduced.

The investigator considered there was not a reasonable possibility that the events "nausea", "face oedema", "anorexia" and "transit disorder" were related to bosutinib.

Additional information: All events were assessed as non-serious and rated as grade 1. According to the reporter, the events were not related to study drug bosutinib but related to imatinib.

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

Case Comment: In concurrence with the investigator, there was no reasonable possibility that the events nausea, face oedema, anorexia and transit disorder are related to the study drug bosutinib. Of note, the events occurred about 2 months after the last dose of bosutinib. The patient's other medication may provide an alternative explanation for the events.

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Asthma (Asthma);
Unknown to Ongoing	Relevant Med History	Gastritis (Gastritis);

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		PRIVACY		72 Years	Female	64.00 kg			2020

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
Post operative severe pain (left eye cataract surgery) [Procedural pain]
right eye cataract [Cataract]
left eye cataract [Cataract]

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) IMATINIB (IMATINIB)

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) chronic myeloid leukaemia (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) 05-SEP-2018 / 12-OCT-2018	#1) 1 month 8 days
#2) 12-DEC-2018 / Ongoing	#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.
202101542211

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 72-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 05Sep2018 to 12Oct2018 at 300 mg daily for chronic myeloid leukaemia; imatinib (IMATINIB), since 12Dec2018 (ongoing) (Batch/Lot number: unknown), oral for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: CATARACT (non-serious) with onset 2020, outcome "recovered" (07Dec2020), described as "left eye cataract"; CATARACT (non-serious) with onset 2020, outcome "recovered" (11Jan2021), described as "right eye cataract"; PROCEDURAL PAIN (medically significant) with onset 08Dec2020, outcome "recovered" (2021), described as "Post operative severe pain (left eye cataract surgery)". The action taken for bosutinib was unknown; for imatinib was dosage not changed.

Additional information: The subject experienced post operative severe pain (left eye cataract surgery) on 08Dec2020, CTCAE grade 3, assessed as medically significant. The subject had cataract right eye on 2020, rated grade 2 and considered not serious, and cataract left eye on 2020, rated grade 2 and considered not serious. The subject had cataract surgery of the right eye on 11Jan2021 and cataract surgery of the left eye on 07Dec2020.

The investigator considered there was not a reasonable possibility that the event post operative severe pain could be related to the study drug bosutinib. The investigator assessed "right eye cataract" and "left eye cataract" not related to bosutinib and unrelated to concomitant medications.

Follow-up (05Nov2021): New information received from the investigational site included reaction data (new events added: cataract surgery of the right eye and cataract surgery of the left eye).

Follow-up (16Nov2021): New information received from the investigational site via CRO included reaction data (onset date of the event Cataract surgery of right eye / right eye cataract and Cataract surgery of left eye / left eye cataract updated).

Follow-up (18Sep2023): 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: patient data, event verbatims and stop date updated.
Follow-up attempts are completed. No further information is expected.

Case Comment: There is not a reasonable possibility that the events "Procedural pain", "left eye cataract" and "right eye cataract" were related to the study drug bosutinib. The event "Procedural pain" was related to the left eye cataract surgery, which (cataract) is also unrelated to bosutinib. Events occurred more than two years after the last dose of the study drug.

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		PRIVACY		69 Years	Female	58.00 kg	17	NOV	2016

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

Cardiac decompensation [Cardiac 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 Study) for protocol B1871047.

A 69 year-old female patient received bosutinib (BOSULIF), from

(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) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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) HYDREA (HYDROXYCARBAMIDE) ; 02-MAR-2016 / Ongoing
#2) COLCHIMAX [COLCHICINE;PAPAVER SOMNIFERUM POWDER;TIE
#3) APROVEL (IRBESARTAN) ; Ongoing
#4) LODOZ (BISOPROLOL FUMARATE, HYDROCHLOROTHIAZIDE) ; Ongoing
#5) LANSOPRAZOLE (LANSOPRAZOLE) ; Unknown
#6) PLAVIX (CLOPIDOGREL BISULFATE) ; 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	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.
202101591701

24c. DATE RECEIVED BY MANUFACTURER
14-MAR-2022

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

24Feb2016 (Batch/Lot number: unknown) to 03Mar2016 at 300 mg daily. Relevant medical history included: "Arterial hypertension" (ongoing); "HYPOTHYROIDISM" (ongoing); "RIGHT CAROTIDAL STENOSIS" (unspecified if ongoing); "HIATAL HERNIA" (ongoing); "LUMBAR PAIN" (unspecified if ongoing); "TOTAL RIGHT HIP PROSTHESIS", start date: 2015 (unspecified if ongoing); "FEMUR NECK FRACTURE" (unspecified if ongoing); "COLIC TUMOR RESECTION", start date: 2003 (unspecified if ongoing); "DYSLIPIDEMIA" (unspecified if ongoing). Concomitant medications included: HYDREA taken for neoplasm progression, start date: 02Mar2016 (ongoing); COLCHIMAX [COLCHICINE;PAPAVER SOMNIFERUM POWDER;TIEMONIUM METHYLSULPHATE] taken for hyperuricaemia, start date: 09Mar2016 (ongoing); APROVEL taken for hypertension (ongoing); LODOZ taken for hypertension (ongoing); LANSOPRAZOLE; PLAVIX; KARDEGIC; CORDARONE taken for arrhythmia (ongoing); LEVOTHYROX.
The following information was reported: CARDIAC FAILURE (hospitalization) with onset 17Nov2016, outcome "not recovered", described as "Cardiac decompensation". The patient was hospitalized for cardiac failure (start date: 17Nov2016, discharge date: 24Nov2016, hospitalization duration: 7 day(s)).
The subject experienced cardiac decompensation, rated grade 2, considered serious. Investigator's comment: hospitalization from 17Nov2016 to 24Nov2016 for painful syndrome of the right lower limb and fainting with loss of consciousness. The cardiac consultation of 24Nov2021 found a mitral leak and objectived a cardiac decompensation. The patient underwent the following laboratory tests and procedures: auscultation: (24Nov2016) mitral valve leak, notes: cardiac decompensation. Occurrence of a bronchial superifection from 17Nov2016 to 26Nov2016 treated with Augmentin. The event occurred post therapy. The outcome of cardiac failure was not recovered, the bronchial superinfection was recovered on 26Nov2016.

The investigator considered there was not a reasonable possibility that the event "cardiac decompensation" was related to bosutinib or concomitant medication.

Follow-up (13Dec2021): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL. Updated information: bosutinib start date, stop date and daily dose updated, medical history, concomitant drugs, action taken.

Follow-up (20Dec2021 and 27Dec2021): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047, Study alias BOSEVAL.
Updated information: relevant medical history, bosutinib start date, stop date, dosage regimen of concomitant drug CORDARONE, seriousness criteria of the event bronchial superinfection (the event was considered serious).

Follow-up (14Mar2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047.
Updated information included: Event "Bronchial superinfection" was removed.

Case Comment: In concurrence with the Investigator, there is no reasonable possibility that the onset of Cardiac failure may be related to bosutinib therapy. Findings of a mitral valve leak on cardiac consultation may provide the most likely cause for the event.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1	24-NOV-2016	Auscultation	mitral valve leak	
		cardiac decompensation		

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

#2) COLCHIMAX [COLCHICINE;PAPAVER SOMNIFERUM POWDER;TIEMONIUM METHYLSULPHATE] (COLCHICINE, PAPAVER SOMNIFERUM POWDER, TIEMONIUM METHYLSULPHATE) ; 09-MAR-2016 / Ongoing

#7) KARDEGIC (ACETYLSALICYLATE LYSINE) ; Unknown

#8) CORDARONE (AMIODARONE HYDROCHLORIDE) ; Ongoing

#9) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Stenosis (Stenosis);

Mfr. Control Number: 202101591701

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown to Ongoing	Relevant Med History	Hiatal hernia (Hiatus hernia);
Unknown	Relevant Med History	Lumbar pain (Back pain);
2015 to Unknown	Relevant Med History	Hip prosthesis insertion (Hip arthroplasty);
Unknown	Relevant Med History	Fracture of neck of femur (Femoral neck fracture);
2003 to Unknown	Relevant Med History	Tumor resection (Tumour excision);
Unknown	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		PRIVACY		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)

Anemia [Anaemia]
Renal function degradation [Renal impairment]

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) 300 mg, 1x/day

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

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

18. THERAPY DATES(from/to)
#1) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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	Arterial 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.
202101592807

24c. DATE RECEIVED BY MANUFACTURER
31-JAN-2022

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 68-years-old female subject received bosutinib (BOSULIF; film-coated tablet), via an unspecified route of administration from 24Feb2016 to 03Mar2016 at 300 mg once daily for an unspecified indication. Medical history included ongoing arterial hypertension. The subject's concomitant medications were not reported. The subject experienced renal function degradation on 07Mar2016 with introduction of diuretics; anemia on 06Mar2016 requiring regular blood transfusions, at 4.1 g/dl before death. Renal function degradation was non-serious, with outcome of recovered on 29Mar2016. Anemia was grade 4, life threatening, with outcome of not recovered. Additional lab tests included blood uric acid: 121 /l on 07Mar2016, creatinine renal clearance: 29 ml/min on 07Mar2016, haemoglobin: 7.4 g/dl on 05Mar2016. On 27Dec2021. The action taken in response to the events for bosutinib was not applicable.

The investigator considered that the events unrelated to study drug or concomitant.

Follow-up (27Dec2021): This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: dose regimen of bosutinib updated, and event renal function degradation updated as serious (hospitalization).

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

Follow-up (31Jan2022). This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047 received from the investigational site via CRO. Updated information: event renal function degradation updated to non-serious and outcome updated as resolved and stop date added, and event anemia updated to serious (life threatening), treatment for anemia added, and lab date (hemoglobin) added.

Case Comment: Based on currently available information, the reported events, renal impairment and anemia, are deemed unrelated to the Pfizer drug, Bosutinib.
Causality will be re assessed when further information becomes available.

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	07-MAR-2016	Blood uric acid units: /L	121	57 24
2	07-MAR-2016	Creatinine renal clearance	29 ml/min	
3		Haemoglobin	4.1 g/dl	15 11.5
4	05-MAR-2016	Haemoglobin	7.4 g/dl	15 11.5

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		PRIVACY		53 Years	Male	115.00 kg		MAR	2019

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

GROIN FOLLICULITIS [Folliculitis]
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. 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
#2) METFORMIN (METFORMIN)

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
#2) UNK	#2) Oral

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

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

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 05-MAR-2018 / Ongoing	#1) Unknown
#2) 19-OCT-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) 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	Arterial hypertension (Hypertension)
27-OCT-2017 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.
202101594120

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

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:

Mfr. Control Number: 202101594120

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 53-years-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 05Mar2018 (Batch/Lot number was not reported) and ongoing at 300 mg, once daily for an unspecified indication; metformin, oral from 19Oct2018 (Batch/Lot number was not reported) and ongoing at unspecified dose for diabetes. Medical history included ongoing arterial hypertension, diabetes from 27Oct2017 and ongoing, dyslipidemia from an unknown date. Concomitant medications included eprosartan taken for arterial hypertension from an unspecified start date and ongoing; fenofibrate taken for dyslipidemia from an unspecified start date and ongoing. The subject experienced groin folliculitis in Mar2019, diarrhea in 2019. Groin folliculitis was grade 2 and diarrhea was grade 1. Events were considered non serious. Metformin was stopped in response to event diarrhea. The action taken in response to the events for bosutinib was dose not changed, for metformin was permanently withdrawn on an unspecified date. The outcome of the event groin folliculitis was recovered in Mar2019 and the outcome of the event diarrhea was recovered in 2019.

The investigator considered that the event groin folliculitis was unrelated to bosutinib or to any concomitnat drug and that diarrhea was unrelated to bosutinib and related to metformin.

Follow-up (13Apr2023): This is a report from a Non-Interventional Study from the investigational site via the CRO.
Updated information included: date of administration of Bosulif.

Case Comment: Events represent intercurrent medical conditions and unrelated to bosutinib .

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	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		PRIVACY		68 Years	Female	58.00 kg	05	APR	2016

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]
Heel skin necrosis [Skin necrosis]

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) 300 mg, daily

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

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

18. THERAPY DATES(from/to)
#1) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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	

(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.
202101595488

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

24c. DATE RECEIVED BY MANUFACTURER
27-DEC-2021

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

Mfr. Control Number: 202101595488

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 68 year-old female subject (unknown if pregnant) received bosutinib (BOSULIF), route of administration, start and stop date, batch/lot number and dose were not reported for an unspecified indication. The subject's medical history included obliterative arteriopathy of the lower limbs from an unspecified date. Concomitant medications were not reported. The subject experienced heel skin necrosis on 11Apr2016, bilateral pleural effusion on 05Apr2016. The events were considered as non-serious according to the investigator. The subject presented with bilateral pleural effusion rated as grade 2 and heel skin necrosis rated as grade 2.Event Bilateral pleural effusion was assessed as serious (hospitalization). The subject had heel pain with skin detachment and toe pain with necrosis point, related to obliterative arteriopathy of the lower limbs that the subject had, which was not anticoagulated, due to the presence of digestive lesions. The subject underwent lab tests and procedures which included Thorax X-ray: bilateral left-sided pleural effusion on an unspecified date. The action taken in response to the events for bosutinib was not applicable. The outcome of the event heel skin necrosis was not resolved and of the event bilateral pleural effusion was resolved on 19Apr2016.

The investigator considered the events bilateral pleural effusion and heel skin necrosis was considered as not related to study drug.

Follow-up (27Dec2021): This is a follow-up non-interventional study report (Post Authorization Safety Study) for protocol B1871047. New information received from the investigator via the CRO includes: dose regimen of suspect product, seriousness criteria of event bilateral pleural effusion.

Case Comment: In concurrence with the reporting investigator, the Company deems the reported heel skin necrosis grade 2 is unrelated to the study drug, bosutinib. The subject's medical history of obliterative arteriopathy of the lower limbs provided alternative explanation. Similarly, the Company deems the reported bilateral pleural effusion grade 2 unlikely related 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		Chest X-ray	bilateral left-sided pleural effusion	

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	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			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET		
		Day	Month	Year				Day	Month	Year
PRIVACY	FRANCE		PRIVACY		53 Years	Male	115.00 kg	19	MAR	2019

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

Intermittent arterial hypertension peak [Hypertension]
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 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

15. DAILY DOSE(S)
#1) UNK

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

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

18. THERAPY DATES(from/to)
#1) 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)

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.
202101595710

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:

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 patient received bosutinib (BOSULIF). The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: FATIGUE (non-serious) with onset 19Mar2019, outcome "recovered" (06Sep2019); HYPERTENSION (non-serious), outcome "not recovered", described as "Intermittent arterial hypertension peak". The action taken for bosutinib was dosage not changed.

The reporter considered "intermittent arterial hypertension peak" related to bosutinib. The reporter considered "fatigue" not related to bosutinib.

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

Follow-up(13Apr2023): This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.
Updated information: updated patient's DOB and patient's age.

Case Comment: Based on the reasonable temporal association and considering the known safety profile of bosutinib, the Company cannot completely exclude the possible causality between the reported "Intermittent arterial hypertension peak", "fatigue" and the administration of the suspect.

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		PRIVACY		68 Years	Female	58.00 kg	21	MAR	2016

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

Pancytopenia [Pancytopenia]
Acute lung oedema flare-up [Acute pulmonary oedema]

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. 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

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) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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
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66 Hudson Boulevard East
New York, NY 10001 UNITED STATES
Phone: 212 733 4045

26. REMARKS

24b. MFR CONTROL NO.
202101601816

24c. DATE RECEIVED BY MANUFACTURER
31-JAN-2022

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.

Mfr. Control Number: 202101601816

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 68-year-old female subject received bosutinib (BOSULIF), via unknown route of administration, from 24Feb2016 to 03Mar2016, (batch/lot number not reported) at 300 mg, daily. The subject medical history and concomitant medications were not reported. The patient experienced pancytopenia on 21Mar2016 and acute lung oedema flare-up on 01Apr2016. Events Acute lung oedema flare-up and Pancytopenia were considered serious due to hospitalization/ prolongation of hospitalization. The site described dyspnea with desaturation on the night of 01Ap42016, with probable Acute lung oedema flare-up and the patient was put under amiodarone hydrochloride (CORDARONE). The patient underwent lab tests and procedures which included haemoglobin: 9.7 g/dl on 21Mar2016, platelet count: 10000 10*6/l on 21Mar2016, white blood cell count: 630 10*6/l on 21Mar2016. The action taken in response to the event for bosutinib was not applicable. The outcome of Pancytopenia was resolved on 18Apr2016. The outcome of Acute lung oedema flare-up was resolved on 01Apr2016.

The investigator considered that the events were unrelated to the study drug or to any concomitant drug.

Follow-up (27Dec2021): This is a Non-Interventional Study follow-up report from the investigational site via the CRO. Updated information included: Bosutinib dose regimen, therapy dates and added seriousness criteria hospitalization for events acute lung oedema flare-up and pancytopenia. Case was upgraded to serious.

Follow-up (31Jan2022): This is a Non-Interventional Study follow-up report from the investigational site via the CRO.
Updated information: Stop date of the event Acute lung oedema flare-up was updated to 01Apr2016.

Case Comment: Based on the available information, the company is in agreement with the investigator's assessment that the events Acute lung oedema flare-up and Pancytopenia were unrelated to the study drug or to any concomitant drug. This case will be re-assessed should additional information becomes available. 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	21-MAR-2016	Haemoglobin	9.7 g/dl	15 11.5
2	21-MAR-2016	Platelet count	10000 10*6/L	445000 150000
3	21-MAR-2016	White blood cell count	630 10*6/L	11000 3800

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		PRIVACY		68 Years	Female	58.00 kg	20	MAR	2016

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

Epistaxis [Epistaxis]
Epigastric pain [Abdominal pain upper]

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

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) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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.
202101602292

24c. DATE RECEIVED BY MANUFACTURER
31-JAN-2022

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 68-year-old female patient received bosutinib (BOSULIF), from 24Feb2016 to 03Mar2016 at 300 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.
The following information was reported: EPISTAXIS (non-serious) with onset 20Mar2016, outcome "recovered" (23Mar2016); ABDOMINAL PAIN UPPER (non-serious) with onset 05Apr2016, outcome "not recovered", described as "Epigastric pain".
Therapeutic measures were taken as a result of epistaxis.
Additional information: Epistaxis with wick nose on 21Mar2016.

The investigator considered there was not a reasonable possibility that the events "epistaxis" and "epigastric pain" were related to bosutinib.

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

Follow-up (31Jan2022): This is a follow-up report received from the investigator. Updated information: updated event term (event "epigastric pain with candidiasis" was updated to "epigastric pain"), updated recovery date of event epistaxis. Patient's age at event onset was amended.

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

Case Comment: In concurrence with the reporting investigator, the Company considers that there was not a reasonable possibility that the events "epistaxis" and "epigastric pain" were related to bosutinib.

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		PRIVACY		71 Years	Male	84.00 kg		JUN	2018

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

Uncontrolled asthma (grade 2) [Asthma]

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.

A 71 year-old male patient received bosutinib (BOSUTINIB), first

(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) 300 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) 31-MAY-2016 / 12-JUN-2019

19. THERAPY DURATION
#1) 3 years 13 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
2013 to Ongoing	Relevant Med History	Cardiomyopathy (Cardiomyopathy)
2020 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.
202101602408

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

24c. DATE RECEIVED BY MANUFACTURER
11-MAY-2022

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

DATE OF THIS REPORT
27-FEB-2024

25a. REPORT TYPE
- ☒ INITIAL
- ☐ FOLLOWUP:

Mfr. Control Number: 202101602408

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

regimen from 31May2016 (Batch/Lot number: unknown) to 12Jun2019 at 300 mg 1x/day and second regimen since 13Jun2019 (Batch/Lot number: unknown) at 200 mg 1x/day. Relevant medical history included: "Cardiomyopathy", start date: 2013 (ongoing); "Diabetes", start date: 2020 (ongoing); "Pancreas cancer", start date: 04Aug2015 (ongoing); "Arterial hypertension", start date: 1986 (ongoing). The patient's concomitant medications were not reported.
The following information was reported: ASTHMA (non-serious) with onset Jun2018, outcome "recovered" (30Oct2018), described as "Uncontrolled asthma (grade 2)". The action taken for bosutinib was unknown.

The investigator considered there was not a reasonable possibility that the event "uncontrolled asthma (grade 2)" was related to bosutinib.

Additional information: The event uncontrolled asthma was reported as non-serious with grade 2.
According to the investigator, the event was unrelated to study drug bosutinib and unrelated to concomitant drugs.

Follow-up (11May2022): new information received from the investigator via the CRO.
Updated end date of event uncontrolled asthma from 30Aug2018 to 30Oct2018.

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

Case Comment: Event Uncontrolled asthma (grade 2) is most likely related to intercurrent or underlying conditions and 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) Bosutinib (BOSUTINIB) Unknown; Regimen #2	200 mg, 1x/day; Unknown	Unknown	13-JUN-2019 / Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
04-AUG-2015 to Ongoing	Relevant Med History	Pancreas cancer (Pancreatic carcinoma);
1986 to Ongoing	Relevant Med History	Arterial hypertension (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		PRIVACY		68 Years	Female	58.00 kg	26	FEB	2016

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

superficial femoral artery obliteration [Peripheral arterial occlusive disease]
Balance disorders [Balance 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)

(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

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

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

18. THERAPY DATES(from/to)
#1) 24-FEB-2016 / 03-MAR-2016

19. THERAPY DURATION
#1) 9 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) HYDREA (HYDROXYCARBAMIDE) ; 02-MAR-2016 / Ongoing
#2) APROVEL (IRBESARTAN) ; Ongoing
#3) LEVOTHYROX (LEVOTHYROXINE SODIUM) ; Ongoing
#4) DUROGESIC (FENTANYL) ; Ongoing
#5) INEXIUM [ESOMEPRAZOLE MAGNESIUM] (ESOMEPRAZOLE MAGNESIUM) ; Unknown
#6) LASILIX [FUROSEMIDE] (FUROSEMIDE) ; 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	Arterial 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.
202101602448

24c. DATE RECEIVED BY MANUFACTURER
09-MAR-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.

A 68-year-old female patient received bosutinib (BOSULIF), from 24Feb2016 to 03Mar2016 at 300 mg, oral. The patient's relevant medical history included: "arterial hypertension" (ongoing). Concomitant medication(s) included: HYDREA oral taken for chronic myeloid leukaemia, start date: 02Mar2016 (ongoing); APROVEL oral taken for hypertension (ongoing); LEVOTHYROX oral taken for hypothyroidism (ongoing); DUROGESIC oral taken for pain (ongoing); INEXIUM [ESOMEPRAZOLE MAGNESIUM]; LASILIX [FUROSEMIDE]; CORDARONE; ALPRAZOLAM; OXYNORMORO.
The subject experienced superficial femoral artery obliteration (hospitalization) on 26Feb2016 with outcome of recovered on 15May2016, balance disorders (non-serious) on 06Dec2016 with outcome of resolved in Dec2016. The subject was hospitalized from 29Apr2016 to 15May2016 for superficial femoral artery obliteration on severe leg artery and bypass surgery on 15May2016. The action taken in response to the events for bosutinib was not applicable.

Balance disorders, grade 1, non-serious, unrelated to the study drug or concomitant medications. Superficial femoral artery obliteration, grade 2, led to hospitalization, unrelated to the study drug or concomitant medications.

Follow-up (13Dec2021): This is a follow-up non-interventional study report for protocol B1871047. Updated information: medical history, concomitant medications, administration details and action taken for bosutinib.

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

Follow-up (27Dec2021): This is a follow-up for non-interventional study report for protocol B1871047. Updated information: BOSUTINIB start date updated to 24Feb2016 and stop date updated to 03Mar2016.

Follow-up (31Jan2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information included: onset date for event superficial femoral artery obliteration updated (from 29Apr2016 to 26Feb2016), outcome for event balance disorders updated (from not resolved to resolved in Dec2016).

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

Follow-up (09Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information: the action taken for bosutinib and investigator initial aware date.

Case Comment: In concurrence with the investigator, the reported superficial femoral artery obliteration and balance disorders are unrelated to the study drug, bosutinib. The events are most likely intercurrent conditions. The follow up information received does not alter the previous company clinical evaluation.

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

#7) CORDARONE (AMIODARONE HYDROCHLORIDE) ; Unknown

#8) ALPRAZOLAM (ALPRAZOLAM) ; Unknown

#9) OXYNORMORO (OXYCODONE HYDROCHLORIDE) ; Unknown