| | | | | | | | | | | | | | | CIO | 01 | /IS | FO | RN |
|---|---|--|------------------------|---|-----------------------------|---------|------|-------|-------|--------|-------|-------------|-----------------------------|----------------------------|---------|----------|----|----|
| | | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | | Τ | | | Ī | П | | | Τ | Т | Τ | Τ | Τ |
| | | | | | | | 1 | 1 | | | | | | | \perp | | | |
| | I | | | | MATION | | | | | | 1 | | | | _ | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | Day Month Year PRIVACY | 2a. AGE 61 Years | 3. SEX Male | 3a. WEIGHT Unk | Day 03 | N | Month | | Year | | | APP | CK ALL ROPRIA ERSE F | ATE | | N | |
| | CTION(S) (including relevant RRED TERM] (Related symp mia [Hypertriglyceri [Renal failure] | as) | | | | | | | | 1 | | INVO PRO | DLVED OLONGE | OR ED I | | ENT | | |
| | : OBSERVATIONAL IFE CONDITIONS (| ON OF EF | FICACY | AND SAFE | TY O | F B | osı | JLIF | | 1 | | OR S | OLVED SIGNIFI ABILITY | ICAI OR | NΤ | ENT | | |
| | | ional Study source for the non-serious events of | | 3187104 | 7 (Study alia | as BO | SE | VAL |). Th | nis i: | s , | | LIFE | APACIT | Υ | | | |
| | | | | (Conti | nued on Add | itional | Info | rmat | ion F | age |) L | | | EATEN | ING | | | |
| 44 QUODEOT DDUG(0) | (include acceptance) | II. SUSPEC | T DRUC | S(S) IN | FORMAT | ION | | | | | 100 | DID | DEA | CTION | _ | | | |
| , , | (Include generic name) JTINIB) Film-coated MLODIPINE BESILA | | | • | nued on Add | _ | Info | rmat | ion F | age | | ABA | | CTION AFTER S | | PPIN | 3 | |
| 15. DAILY DOSE(S) #1) 400 mg, 1x/da #2) | | | #1 | ROUTE(S) Unkno Unkno | | ATION | _ | | | | | | YES | S 🔯 N | Ю | <u> </u> | IA | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | RUSE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 16-DEC-2015 #2) Unknown | | | #1 | 19. THERAPY DURATION #1) 3 years 4 months 10 days #2) Unknown | | | | | | | | | | <u></u> | IA | | | |
| | | III. CONCOMIT | TANT DE | RUG(S |) AND HI | STO | RY | , | | | | | | | | | | |
| 22. CONCOMITANT DRU | UG(S) AND DATES OF ADM | MINISTRATION (exclude those us | ed to treat rea | ction) | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| From/To Dates 1999 to Ongoing JUN-2014 to Ong | | allergies, pregnancy with last mo Type of History / Notes Relevant Med His Relevant Med His | story l | Description nflamma | itory rheum ffusion (Ple | | | | | c dis | orde | er) | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 24a NAME AND ADDRE | ESS OF MANUFACTURER | ACTUR | ER INF | ORMATI | ION | | | | | | | | | _ | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | vard East 01 UNITED STATES | 3 | | ZO. NEW | , with | | | | | | | | | | | | | |
| | 24b, MFR CO 2021104 | | | | ME AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 01-FEB-2021 | ER 24d. REPORT STUDY HEALTH PROFES | LITERATURE | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 61-year-old male subject received bosutinib (BOSULIF) from 16Dec2015 to 25Apr2019 at 400 mg once daily and from 26Apr2019 at 300 mg once daily and amlodipine besilate / valsartan (EXFORGE) from an unknown date at unknown dose, both for an unknown indication.

Medical history included ongoing Inflammatory rheumatism from 1999, ongoing pleural effusion from Jun2014 and myocardial infarction in Nov2015.

Concomitant medications, if any, were not reported.

On 03Aug2018, the subject experienced hypertriglyceridemia, rated as grade 1. In response to this event, no action was taken with bosutinib.

On 11Apr2019, the subject experienced renal failure, rated as grade 1. In response to this event, the dose of bosutinib was reduced and amlodipine besilate / valsartan (EXFORGE) was discontinued. At the time of the report, the subject had not recovered from the event renal failure. The clinical outcome of the event hypertriglyceridemia was unknown.

According to the reporter, renal failure was not related to study drug but related to concomitant medication amlodipine besilate / valsartan. According to the investigator, the event hypertriglyceridemia was related to bosutinib but not related to concomitant medications.

Case Comment: The limited information provided precludes a full clinical assessment of the case. Significant in the assessment of causality would be concomitant medications, diagnosis, stage and extent of the underlying malignancy, and possible confounding factors like dietary habit and level of hydration, which were unknown at the time of the report. Based on available information and until further data is provided, the Company deems there is not a reasonable possibility that hypertriglyceridemia and renal failure are related to bosutinib regimen ongoing from more than five years.

13. Lab Data

| # | Date | Test / Assess | ment / Notes | Results | Normal High / Low |
|-------------------------------|-----------------------------|---------------|---|---------------------------|--|
| 1 | 11-APR-2019 | Blood crea | atinine | 171 umol/l | 104 59 |
| | 03-AUG-2018 | Blood trigl | ycerides | 2.49 mmol/L | 1.7 0.4 |
| 14. SUSPECT DRU | G(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 (E Regimen #2 | BOSUTINIB) Film-cc | ated tablet; | 300 mg, 1x/day; Unknow | n Unknown | 26-APR-2019 / Ongoing; Unknown |

| From/To Dates | Type of History / Notes | Description |
|----------------------|-------------------------|--|
| NOV-2015 to NOV-2015 | Relevant Med History | Myocardial infarction (Myocardial infarction); |

| | | | | | | | | | | | | | | | | | CIC | OMS | F | OF | ₹M |
|---|--|-----------------------------|---|-----------------|--------------------|--------------------------|--------------------------|--------|--------|-----------|-------|-------------------|--------------|----------------|---------------------------|---------------|----------|----------------|------|------|------------|
| | | | | | | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE | REAC | TION REF | POR | Т | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | T | Т | Τ | Τ | Τ | Τ | П | | П | |
| | | | | | | | | | | | | | | | | | | Ш | | Ш | |
| 1. PATIENT INITIALS | 1a. COUNTRY | T 2 | I. RE | | TION 2a. AGE | 3. SEX | MATION 3a, WEIGH | | 4.6 RF | ACTIO | 2N 0N | IQE | - 1 | 8-12 | | IECI | < ALL | | _ | | _ |
| PRIVACY | FRANCE | Day | | ear | 72 Years | Male | 90.00 kg | Da 24 | ay | Mon NO | th | | ar | 8-1∠ | AP | PPRC | DPRIA | TE TO EACTI | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Dyspnea [Dyspnoe | RED TERM] (Related sym | nt tests/lab iptoms if a | data) ny separated by col | ommas) | | | | | | | | | | 7 | 1 | | NT DIE | | | | |
| Case Description: | anti-cancer produ | eceipt o | of follow- | | | | | • | | is | | J PR HC | ROLC DSPI | ONGEI TALIS | D INPA ATION | l | | | | | |
| this case now conf | · | | | | | | | | | - | | | | | OR DIS | R SIG SABI | SNIFIC | OR | TEN | ۱T | |
| OBSERVATIONAL CONDITIONS OF | | ND SAF | ETY OF | BOSULIF | F UNI | DER | REA | AL-L | .IFE | • | | | | ACITY | | | | | | | |
| | | | | | | (Cont | inued on A | dditio | nal In | form | ation | Pa | ge) | |] LIF | E IREA | ATENIN | ΝG | | | |
| | | | II. SUSPE | ECT | DRU | G(S) IN | FORMA | ATIO | N | | | | | | | | | | | | |
| | 4. SUSPECT DRUG(S) (include generic name) 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | | | | | | | | | | | | | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | | | | | | | F | DID RE REAPF REINTI | PEAF | R AFTI | | | | |
| 18. THERAPY DATES(fror #1) 28-JAN-2020 / | · | | | | | 9. THERAPY 41) Unkno | | | | | | | | ſ | □ YE | ES [| NO | × 🗵 | NA | · · | |
| | | III | . CONCON | —— MITA | NT D | RUG(S |) AND H | HIST | OR | Υ | | | 1 | | | | | | | | |
| 22. CONCOMITANT DRUG #1) JANUMET (M | | MINISTRA | TION (exclude thos | se used | to treat rea | action) | , | | | - | | | | | | | | | | | |
| #2) DIPROSONE #3) LAMISIL [TEF #4) ARKOLEVUR | [BETAMETHASC RBINAFINE] (TER | ONE SC | DDIUM PHOS INE) ; JUL-2 | SPHAT 2019 / | TE] (BE / Ongoi | TAMETH | | 20 | | | | | | | | | | | | | |
| ## / AINIOLL VOIX | L (IIVOLIIV, GAGO | / I/AIAC | WITCEO DOG | JEMIN | , راال <i>ر</i> | JLI -20. | g / Origo | ıy | | | (Cc | ntii | nued | on A | ∆ddit | tion | al Inf | ormat | tior | n Pa | uë) |
| 23. OTHER RELEVANT H | ISTORY. (e.g. diagnostics | | | | | | | | | | ,00 | JI 16. | lucu | U | | | 21 11111 | J1111 | | | <i>3€,</i> |
| From/To Dates 2007 to Ongoing Unknown to Ongo | ing | R | ype of History / Note Relevant Med Relevant Med | l Histo | ory | | s (Diabete s (Psorias | | llitus | s) | | | | | | | | | | | |
| | | | | , | | | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | S OF MANUFACTURER | | IV. MAN | UFA | CIUR | 26. REN | | HOI | N_ | | | | | | | | | | | _ | _ |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATE | S | | | | | | | | | | | | | | | | | | | |
| | | | | | | <u> </u> | | -78 | | | _ | | | | | | | | | | |
| | 24b. MFR C0 | | | | | | ME AND ADD | | | | | Э. | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES 28-FEB-2023 | Malana | | E LITERATUR | IRE | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | TE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

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

A 72-year-old male patient received bosutinib (BOSULIF), since 28Jan2020 at 500 mg daily. The patient's relevant medical history included: "Diabetes", start date: 2007 (ongoing); "Psoriasis" (ongoing); "Chronic sinusitis" (ongoing); "Mycosis", start date: Jul2019 (unspecified if ongoing). Concomitant medication(s) included: JANUMET oral taken for diabetes mellitus, start date: 2007 (ongoing); DIPROSONE [BETAMETHASONE SODIUM PHOSPHATE] taken for psoriasis (ongoing); LAMISIL [TERBINAFINE] oral taken for fungal infection, start date: Jul2019 (ongoing); ARKOLEVURE oral taken for constipation, start date: Sep2019 (ongoing). The following information was reported: DYSPNOEA (non-serious) with onset 24Nov2020, outcome "not recovered", described as "Dyspnea". The action taken for bosutinib was dosage not changed.

Additional information: The event of dyspnea was rated grade 1, the action taken for bosutinib in response to the event dyspnea was reported as dose not changed. The dyspnea event was still in progress at the end of the study. It was also reported an additional event of "loss of response" with onset 30Dec2019, reported as non-serious rated grade 2, for which the action taken for bosutinib was dosage increased, the event resulted as resolved on 02Jun2020, according to the reporter, the event was related to bosutinib and unrelated to concomitant drugs.

The reporter considered "dyspnea" related to bosutinib and unrelated to concomitant drugs

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

Case Comment: The Company considers the reported event "dyspnea" is related to bosutinib and unrelated. This case will be reassessed should additional information become available.

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

#1) JANUMET (METFORMIN HYDROCHLORIDE, SITAGLIPTIN PHOSPHATE MONOHYDRATE); 2007 / Ongoing

#2) DIPROSONE [BETAMETHASONE SODIUM PHOSPHATE] (BETAMETHASONE SODIUM PHOSPHATE); Ongoing

| 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); |

| | | | | | | | | | | | | C | O | MS | FO | RN |
|---|------------------------------------|--|---------------------|---|----------------------|-----------|-------------|---------|--------------|-----------|----------|---|--------------|-------|-----|----|
| | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE R | EACTION REPO | DRT | | | | | | | | | | | | | |
| | | | | | | | И | | | | | | | | | |
| | | I DEA | ACTION II | | 4ATION | | | 1 | | | | 1 1 | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | | | 3a. WEIGHT | 4-6 RI | EACTIO | N ONS | ET | 8-1 | | HECK AI | | | | |
| PRIVACY | FRANCE | PRIVACY Year | 24 Years F | emale | | Day 30 | Mont SEI | | Year 2020 | | | PROPE | | | N | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR IRON DEFICIENC) | ED TERM] (Related sympt | tests/lab data) toms if any separated by comm | nas) | | | | | | |] | | TIENT (| O OR | | | |
| Case Description: 0 | | . STUDY - EVALUATI OF USE | ON OF EFF | FICACY | AND SAFET | Y OF | BOS | ULIF | : | | НС | ROLONO | LISAT | TION | | • |
| This is a non-interv reporter(s) (Physici | | ort (Post Authorization 1871047. | n Safety Stu | udy) rece | ived from a | conta | ctabl | е | | | OF DI | VOLVEI R SIGNII SABILIT CAPACI | FICA Y OF | NT | ENT | |
| | | | | (Contin | ued on Addition | onal Ir | nforma | ition F | Page | , [| ⊐ H | E IREATE | NINC | } | | |
| | | II. SUSPEC | CT DRUG | (S) INF | ORMATIC | ON | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (in #1) Bosulif (BOSUT | | | | | | | | | | 20. | | ACTION AFTER ? | | OPPIN | G | |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/day | | | | ROUTE(S) (| OF ADMINISTRAT VN | TON | | | | YES NO NA | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | SE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | |
| 18. THERAPY DATES(from #1) 14-NOV-2018 / | • | | | 19. THERAPY DURATION #1) Unknown YES \(\sum \no \) NA | | | | | | | | | | NA | | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | TOR | Υ | | | • | | | | | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADMI | NISTRATION (exclude those u | used to treat react | tion) | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | _ | | | |
| 23. OTHER RELEVANT HIS From/To Dates MAY-2009 to Ongo | | allergies, pregnancy with last m Type of History / Notes Relevant Med Hi | D | escription | nyeloid leuke | mia (| Chro | nic m | wol | oid Io | ukaa | mia) | | | | |
| WA1-2009 to Oligo | illig | Relevant Med I II | istory C | A II OI IIC II | iyelolu leuke | iiiia (| CIIIO | THE III | iyeit | Jiu ie | ukae | iiia) | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | S OF MANUFACTURER | | | 26. REMA | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevar New York, NY 1000 ^o Phone: 212 733 404 | I UNITED STATES | | | | | | | | | | | | | | | |
| | 24b. MFR COM | NTROL NO. | | 25b. NAM | E AND ADDRESS | S OF RI | EPORT | ER | | | | | | | | |
| | 20211525 | 516 | | NAME | AND ADDRE | SS W | /ITHH | ELD. | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT STUDY | SOURCE LITERATURE | | | | | | | | | | | | | | |
| 24-APR-2023 | HEALTH PROFESS | ш | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | TE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 25-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since 14Nov2018 (ongoing) at 300 mg 1x/day. The patient's relevant medical history included: "CHRONIC MYELOID LEUKEMIA", start date: May2009 (ongoing). The patient's concomitant medications were not reported. The following information was reported: IRON DEFICIENCY (non-serious) with onset 30Sep2020, outcome "not recovered". The event iron deficiency (abundant and painful periods) was rated grade 2. Treatment included ferritin dosage on 30Sep2020 was 28 ng/ml and ascorbic acid/ ferrous sulfate (TIMOFEROL). The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of iron deficiency.

The event was not related to bosutinib or to any concomitant drug.

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

Follow-up (10May2022): This is a non-interventional study follow-up report for protocol B1871047. Updated information: outcome of the event iron deficiency was updated to not resolved. Recovery date deleted.

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

Follow-up (24Apr2023): This is a non-interventional study follow-up report from the CRO for protocol B1871047. Updated information included: updated patient's DOB, event description.

Case Comment: In concurrence with the reporter, the Company deems the reported Iron deficiency (abundant menstruation) unrelated to bosutinib.

13. Lab Data

| # | Date | Test / Assessment / Notes | | 4 | Results | Normal High / Low |
|---|-------------|---------------------------|--|---|----------|-------------------|
| 1 | 30-SEP-2020 | Serum ferritin | | | 28 ng/ml | |

| | | | | | | | | | | | | | | CI | OM | SI | FOI | RM |
|---|-----------------------|---|-------------------|---|----------------------------|---------|--------|------|-------|------|---|-----------------------|--------------|-------------------------------------|---------------|------------|-----|----|
| | | | | | | | | | | | | | | | | | | |
| SUSPECT | ADVERSE | REACTION REPO |)RT | | | | | | | | | | | | | | | |
| | | | | | | | Τ | | | | П | \top | Т | \top | Τ | Τ | Τ | Τ |
| | | | | | | | 4 | | | | | | \perp | \perp | \perp | L | | |
| 1. PATIENT INITIALS | 10 COLINTRY | I. REA | CTION I | | MATION 3a. WEIGHT | 465 | REACT | 'ONL | ONICE | | I | 2 (| | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 59 Years | 3. SEX Female | 3a. WEIGHT 118.00 kg | Day | Mo | | | Year | 0 8-1 | Α | PPF | CK ALL ROPRI ERSE I | ATE T | | 1 | |
| 7 + 13 DESCRIBE REACTION Event Verbatim [PREFERRE gingivitis [Gingivitis] | ED TÉRM] (Related sym | nt tests/lab data) nptoms if any separated by comm | as) | | | | | | | | l I | | NVO | ENT DI | OR | | | |
| Case Description: C UNDER REAL-LIFE | | AL STUDY - EVALUATION OF USE | ON OF EFI | FICACY | AND SAFE | TY OF | F BO | SU | LIF | | | Н | HOSI | LONGE PITALI: | SATIC | ON | | |
| | | eport (Post Authorization CP) for protocol B18710 | | tudy) rece | eived from o | contac | ctable | е | | | | | OR S | OLVED BIGNIFI BILITY PACIT | ICANT ' OR | | :NI | |
| | | | | (Contin | nued on Addi | tional | Inforn | nati | on P | age | , [| 그 | IFE HRE | EATEN | IING | | | |
| | | II. SUSPEC | T DRUG | G(S) INI | FORMAT | ION | | | | | <u>^ 1 </u> | | | | | | | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI #2) SPIRAMYCINE | INIB) Film-coated | l tablet | | • | nued on Addi | | Inforn | nati | on P | age | | DID R ABAT DRUG | ГΕΑ | CTION FTER | | PING | } | |
| 15. DAILY DOSE(S) #1) 200 mg, daily #2) UNK | | | #1 | i. ROUTE(S) (1) Unknov 2) Unknov | | ATION | | | | | | | | | | X N | Α | |
| 17. INDICATION(S) FOR US #1) Unknown #2) Unknown | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(from/r #1) 25-SEP-2018 / 0 #2) Unknown | | | #1 | 19. THERAPY DURATION #1) 2 years 2 months 13 days #2) Unknown | | | | | | | | | | ⊠ № | Α | | | |
| | | III. CONCOMI | TANT DE | RUG(S) | AND HIS | STOI | RY | | | | | | _ | | | _ | | _ |
| 22. CONCOMITANT DRUG(| S) AND DATES OF ADM | MINISTRATION (exclude those us | sed to treat read | ction) | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | _ | | | | | |
| 23. OTHER RELEVANT HIS From/To Dates Unknown to Ongoin | | s, allergies, pregnancy with last m Type of History / Notes Relevant Med Hi | | Description | nyeloid leuk | ·emia | (Chr | oni | ∽ m\ | velo | nid le | uka | ≏m | ia) | | | | |
| Officiowit to Offigure | 19 | Noivain insu | Story . | Omomo | nyolola loc. | .011110 | (0 | 0 | U, | y 0. | JIG I | ,una | Σ 11. | ia, | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | FACTUR | FR INF | ORMATI | ΟN | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | 26. REM | | <u> </u> | | | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4048 | UNITED STATE | S | | | | | | | | | | | | | | | | |
| | 24b, MFR CO | ONTROL NO. | | 25b. NAN | ME AND ADDRE | SS OF F | REPOR | RTER | ! | | | | | | | | | |
| | 2021152 | | | NAME | AND ADDR | ESS \ | ΛΙΤΗ | IHE | LD. | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | | | NAME | AND ADDR | ESS \ | ΛΙΤΗ | IHE | LD. | | | | | | | | | |
| 25-OCT-2023 | M HEALTH PROFE | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 | | | | | | | | | | | | | | | | | | |

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 and second regimen since 08Dec2020 (ongoing) at 300 mg daily; spiramycine (SPIRAMYCINE), (Batch/Lot number: unknown); metronidazole (METRONIDAZOLE), (Batch/Lot number: unknown). The patient's relevant medical history included: "Chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported.

The following information was reported: GINGIVITIS (non-serious) with onset 2020, outcome "recovered" (08Dec2020). The event was rated grade 1. The action taken for bosutinib was dosage not changed. The action taken for spiramycine and metronidazole was dosage permanently withdrawn.

The investigator considered that the event was unrelated to bosutinib and related to concomitant drugs spiramycin and metronidazole.

Follow-up (24Jul2023): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047 received from the CRO. Updated information included: Bosulif details.

Follow-up (28Jul2023): This is a follow-up report from a Non-Interventional Study source for Protocol B1871047 received from the CRO. Updated information included: Bosulif details (new dosage regimens).

Follow-up (27Sep2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

Updated information: Bosutinib was taken at 200 mg daily from 25Sep2018 to 07Dec2020 then at 300 mg daily from 08Dec2020 and ongoing. Medical history included ongoing chronic myeloid leukemia. In response to the gingivitis, spiramycin and metronidazole were discontinued.

Follow-up (25Oct2023): This is a non-interventional study follow-up report received from clinical team. Updated information included: action taken updated to dose not changed.

Case Comment: In concurrence with the reporting investigator, the Company deems the reported gingivitis unrelated to bosutinib administration. The follow-up information received does not alter the previous company clinical evaluation.

| 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 | 08-DEC-2020 / |
| Regimen #2 | | | Ongoing; |
| | | | Unknown |
| | | | |
| #3) METRONIDAZOLE (METRONIDAZOLE) | UNK; Unknown | Unknown | Unknown; |
| ; Regimen #1 | | | Unknown |

| | | | | | | | | | | | | CIC |)MC | S F | OF | ₹M |
|---|---------------------------------------|---|--------------------------|---|---------------------|----------|-------------|---------------|--------------|----------|--------------|---------------------------------|-------------|-------|------|------------|
| | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | _ |
| | | | | | | | П | $\overline{}$ | П | Т | Τ | | Τ | | | |
| | | | | | | | 14 | | | | | | L | | | |
| | | I. REA | CTION II | NFOR | MATION | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 2a. AGE 55 Years F | 3. SEX emale | 3a. WEIGHT 85.00 kg | 4-6 R | Mont JAN | h | Year 2020 | 8-12 | API | ECK ALL PROPRIA VERSE R | ATE TO | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERS Increased hypoxia Urinary infection [U | RED TERM] (Related sympther [Hypoxia] | otoms if any separated by comma | as) | | | | | | | 7 7 |] INV PRO | OLVED O OLONGE SPITALIS | OR D INF | | NT | |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUATIO DF USE | ON OF EFF | TICACY | AND SAFET | ΓΥ OF | BOS | ULIF | | | OR DIS | OLVED F SIGNIFIC SABILITY | CANT OR | | NT | |
| This is a report from a Non-Intervention | | | 1871047 | ' (Study alia | s BOS | SEVAI | L). Th | nis is | _ | INC | :APACITY | ſ | | | | |
| | | | | (Conti | nued on Addit | tional I | nforma | ation P | Page) | LL | J THE | REATENI | NG | | | |
| 44 0U0DE0========= | | II. SUSPEC | T DRUG | (S) IN | FORMATI | ION | | | | I aa - | up == | A O.T. C | | | | |
| 14. SUSPECT DRUG(S) (ii #1) Bosutinib (BOS | - | | | | nued on Addit | _ | nforma | ation P | Page) | · / | | ACTION AFTER S | STOPE | PING | | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | |) Unkno | OF ADMINISTRA WN | ATION | | | | | YE | s 🔲 N | ○ [| NA NA | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | |
| 18. THERAPY DATES(from #1) 12-APR-2017 / | • | | | 19. THERAPY DURATION #1) 1 year 3 months 14 days | | | | | | | | | | NA 🔁 | | |
| | | III. CONCOMIT | | | AND HIS | STOF | RY | | | <u> </u> | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | ed to treat react | ion) | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| OR OTHER RELEVANTURE | 0T0DV (| 71.1 | 4 6 1 1 | | | | | | | | | | | | | _ |
| 23. OTHER RELEVANT HI From/To Dates Unknown Unknown to Ongoi | | allergies, pregnancy with last mo Type of History / Notes Past Drug Event Relevant Med His | De | escription | nyeloid leuk | emia | (Chro | nic m | ıyeloi | d leu | ıkaer | mia) | | | | |
| | | | | | | | | (Con | tinue | d on A | ∆dditi | onal Inf | form | ation | . Pa | na) |
| | | 1) / 846811.15 | ACTURE | יאים. | -ODMAT! | | | ,5511 | | 9117 | Jacob | J IIII | | | u | <i>,-/</i> |
| 24a. NAME AND ADDRES | S OF MANUFACTURER | ACTURE | 26. REM | ORMATION ARKS | UN | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | |
| | 24b. MFR CC 2021152 | | | | ME AND ADDRES | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES 10-OCT-2023 | 24d. REPORT STUDY HEALTH PROFES | LITERATURE | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 55-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB), first regimen from 12Apr2017 to 25Jul2018 at 300 mg daily and second regimen since 26Jul2018 (ongoing) at 400 mg daily. The patient's relevant medical history included: "chronic myeloid leukemia" (ongoing); "arterial hypertension" (ongoing). The patient's concomitant medications were not reported. Past drug history included: Dasatinib, reaction(s): "Pulmonary hypertension".

The following information was reported: HYPOXIA (non-serious) with onset Jan2020, outcome "unknown", described as "Increased hypoxia"; URINARY TRACT INFECTION (non-serious), outcome "unknown", described as "Urinary infection". Therapeutic measures were taken as a result of urinary tract infection.

The clinical course was reported as follows: The subject was hospitalized from 13Jan2020 to 14Jan2020 for a reassessment of a pulmonary arterial hypertension reported when taking dasatinib therefore before the study. This hospitalization should not be declared because there was no worsening of this pathology but increased hypoxia was noted during this hospitalization and should be controlled. The Urinary infection was treated with cefixime from Nov2020 to Nov2020. The subject did not have aggravation of her pulmonary state. She was very regularly medically followed in pneumology service unit and the short hospitalization in Jan2020 was scheduled to reassess her disease. No aggravation was noticed. The subject was seen on 24Aug2020 without any concern and no modification of the medical cares. The action taken with bosutinib in response to the events, clinical outcome and causality assessment was not provided. The investigator had not confirmed these events with the subject. As of 10Oct2023, it was reported the event urinary infection was non-serious and rated grade 1, outcome unknown, unrelated to bosutinib, action taken was not applicable. Onset date was deleted. The event Increased hypoxia was non-serious and rated grade 1, outcome unknown, unrelated to bosutinib, action taken was not applicable.

The reporter considered "increased hypoxia" and "urinary infection" not related to bosutinib.

Follow-up (09Apr2021): New information received from contactable physician includes: event details.

Follow-up (11Mar2023): This is a non-interventional study follow-up report received from the investigational site via CRO. Updated information included: patient data (age, gender, height, weight), reaction data (verbatim for event "urinary tract infection" updated to "Urinary infection").

Follow-up (10Oct2023): new information received from CRO is as follows: Medical history (chronic myeloid leukemia, arterial hypertension); for BOSULIF: dosage regimen added, Action taken updated as Not applicable; For events urinary infection and Increased hypoxia: Onset date removed, Reporter causality added (unrelated).

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported events Increased hypoxia and Urinary tract infection. Medical history of pulmonary hypertension may provide an alternative cause for hypoxia.

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 | 400 mg, daily; Unknown | Unknown | 26-JUL-2018 / |
| Regimen #2 | | | Ongoing; Unknown |

| From/To Dates | Type of History / Notes | Description |
|--------------------|-------------------------|---|
| Unknown | Past Drug Event | DASATINIB (DASATINIB); Drug Reaction: Pulmonary hypertension (Pulmonary hypertension) |
| Unknown to Ongoing | Relevant Med History | Arterial hypertension (Hypertension); |

| | | | | | | | | | | | | | | | CIC | OMS | F | OF | ιM |
|--|--|----------------------------|----------------|------------------------|---------------------|---|---|-------------------|-------------|------------|--------|------------------|-----------------------|-----|--------|------------------|-----|----|----|
| | | | | | | | | | | | | | | | | | | | |
| SUSPECT | T ADVERSE I | REACTION | REPO | RT | | | | | | | | | | | | | | | _ |
| | | | | | | | | | 1 | | Τ | П | | T | \top | П | П | П | |
| | | | | | | | | | 4 | | | | | | | | | | _ |
| | · COUNTRY | T . DATE OF | | | | MATION | _ | I DE | - 2710 | 2710 | | T _a , | . 0 | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF Day Month PRIVA | Year | 2a. AGE 23 Years | 3. SEX Female | 3a. WEIGHT 58.00 kg | Day | , [| Monti NO | | Year | | Al | PPR | | ATE TO REACTI | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) DIARRHEA [Diarrhoea] CYSTITIS [Cystitis] | | | | | | 1 | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | | | | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | (| – 0 | R SI | IGNIFIO BILITY | OR | 3TEN | ۱T | | | | | | | | |
| This is a non-interv B1871047. | This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol B1871047. | | | | | | | | | | PACITY | Y | | | | | | | |
| (Continued on Additional Information Pag | | | | | | | age | e) | ٦ | IFE HRE | ATENI | ING | | | _ | | | | |
| | | II. S | JSPEC | T DRU | G(S) IN | FORMA | TIOI | V | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (in #1) Bosulif (BOSUT | | tablet | | | ` | inued on Ad | | _ | forma | ition F | Page | | DID R ABAT DRUG | EAF | | STOPP | ING | | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | Т | 'ES | N | o 🛚 | NA | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) CHRONIC MYELOID LEUKEMIA (Chronic myeloid leukaemia) | | | | | 21. | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | |
| 18. THERAPY DATES(from/to) #1) 14-NOV-2018 / 20-NOV-2018 19. THERAPY DURATION #1) 7 days | | | | | | YES NO NA | | | | | | | | | | | | | |
| | | III. CON | COMIT | TANT D | RUG(S |) AND H | ISTO | OR' | Y | | | | | | | | | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | /INISTRATION (exc | lude those use | ed to treat rea | action) | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIS From/To Dates MAY-2009 to Ongo 2009 to 2009 | | Type of Hist Relevan | | story | Description Chronic | myeloid leu legaly (Spl | | | | nic m | ıyel | oid le | eukae | emi | ia) | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | IV. I | MANUF. | ACTUF | | ORMAT | TION | <u> </u> | | | | | | | | | | | _ |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | rd East I UNITED STATE: | S | | | 26. REM | MARKS | | | | | | | | | | | | | |
| | 24b. MFR CC 2021153 | | | | | ME AND ADDR | | | | | | | | | | | | | _ |
| 24c. DATE RECEIVED BY MANUFACTURER 15-SEP-2023 | 24d. REPOR STUDY HEALTH PROFES | | TERATURE | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE | DLLOWUP: | | 1 | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 23-year-old female subject started to receive bosutinib (BOSULIF) at 200 mg 1x/day from 14Nov2018 to 20Nov2018, at 300 mg 1x/day from 21Nov2018 to 27Nov2018, at 400 mg 1x/day from 28Nov2018 to 13Feb2019 and ongoing at 300 mg 1x/day from 14Feb2019 for chronic myeloid leukaemia. Relevant medical history included chronic myeloid leukaemia since May2009 and splenomegaly in 2009. Relevant concomitant medication, if any, was not provided. In Nov2018 the subject experienced diarrhea in the afternoon of taking bosutinib. In Feb2019 she experienced cystitis. Treated with Spasn from 13Feb2019 and with Tiorfan from 19Jan2021 she received antibiotic for repeat cystitis (Amoxicillin, Augmentin and Cefixime). It was reported that at the time of initial declaration with aggravation affecting quality of life. Due to diarrhea bosutinib dose was reduced while no action was taken in response to the event cystitis. The outcome of the event diarrhea was recovering while cystitis recovered on 03Jun2019.

The event diarrhea was rated with grade 2, reported as non serious, related to BOSULIF and unrelated to concomitant medication. The event cystitis was rated with grade 2, reported as non serious, unrelated to BOSULIF and unrelated to concomitant medication.

Follow-up (10May2022): This is a non-interventional study follow-up report received from a contactable reporter(s) (Physician) for protocol B1871047.

Updated information: event term "digestive disorders/diarrhea" was updated to "diarrhea".

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

Follow-up (15Sep2023): This is a non-interventional study follow-up report received from the investigational site via the CRO. Updated information includes: bosutinib daily dose, onset date and outcome of the event diarrhea.

Case Comment: Based on the information currently available, a possible contributory role of bosutinib to the reported event Diarrhoea cannot be completely excluded based on temporal association. There was not a reasonable possibility that the event Cystitis was related to bosutinib, but most likely represents patient intercurrent medical condition.

| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
|--|---|---------------------------|--|
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, 1x/day; Unknown | CHRONIC MYELOID | 21-NOV-2018 / |
| Regimen #2 | | LEUKEMIA (Chronic myeloid | 27-NOV-2018; |
| | | leukaemia) | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg, 1x/day; Unknown | CHRONIC MYELOID | 28-NOV-2018 / |
| Regimen #3 | | LEUKEMIA (Chronic myeloid | 13-FEB-2019; |
| | | leukaemia) | 2 months 17 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, 1x/day; Unknown | CHRONIC MYELOID | 14-FEB-2019 / |
| Regimen #4 | | LEUKEMIA (Chronic myeloid | Ongoing; |
| | | leukaemia) | Unknown |

| | | | | | | | | | | | | CIO | OMS | S F | OF | łМ |
|---|--------------------------------------|---|--------------------|-------------------------|------------------------------|------------|--------------|-----------|---|------------|--------------|-----------------------------|--------------|------------|----|----|
| | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | _ |
| | | | | | | | | | | Τ | T | | | | | _ |
| | | | | | | | | | Ш | | <u> </u> | | Ш | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | CTION IN | | IATION Ba. WEIGHT | 4-6 RF | ACTIO | N ONSE | FT . | 8-12 | CH | ECK ALL | | | | _ |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 25 Years F | | _ | Day | Month DEC | 1 | Year 019 | 1 | API | PROPRIA VERSE F | ATE TO | | | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR HAIR LOSS TEND FLU SYNDROME | ED TERM] (Related symplem [Alopecia] | tests/lab data) otoms if any separated by comma | as) | | | | | | | 7 |] INV PRO | OLVED OLONGE | OR ED INP | | NT | |
| 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 | | | | | | s is | | OR DIS | OLVED I SIGNIFI ABILITY APACIT | CANT OR | STEN | ΝΤ | | | | |
| a non-interventional clinical study case reporting non-serious events only. (Continued on Additional Information Page | | | | | | | ana) | _ | | E | INC | | | | | |
| (Continued on Additional Information Page) ☐ THREATENING II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (ir #1) Bosulif (BOSUT | - | | JI DROG | (<u>3) IIVI</u> | ORWATI | <u>JIN</u> | | | | · / | | ACTION AFTER S | STOPF | PING | | _ |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/day | | | | ROUTE(S) O) Unknow | F ADMINISTRAT N | TON | | | | | YE | s 🔲 N | o E | NA | | |
| 17. INDICATION(S) FOR U #1) Unknown | SE | | | | | | | | | F | REAPP | ACTION EAR AFT RODUCT | | | | |
| 18. THERAPY DATES(from #1) 14-NOV-2018 / | • | | | THERAPY DI) Unknow | | | | | | | YE | s 🔲 N | o E | N A | | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | TOR | Υ | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | sed to treat react | tion) | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 22 OTHER RELEVANT HI | STODY (a.g. diagnostics | allergies, pregnancy with last me | anth of pariod a | to \ | | | | | | | | | | | | |
| From/To Dates MAY-2009 to Ongo 2009 to 2009 | | Type of History / Notes Relevant Med His Relevant Med His | story C | escription Chronic m | yeloid leuke galy (Splend | | | nic m | yeloi | d leu | ıkaer | mia) | | | | |
| | | IV. MANUF | ACTURE | ER INFO | ORMATIC | N N | | | | | | | | | | _ |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | rd East 1 UNITED STATES | 7 | 2 | 26. REMA | | | | | | | | | | | | |
| | 24b. MFR CC 2021153 | | | | E AND ADDRESS | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 10-MAY-2022 | 24d. REPOR STUDY HEALTH | LITERATURE | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | | 1 | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 25-years-old female subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from 14Nov2018 and ongoing at 300 mg, 1x/day for an unspecified indication. Medical history included chronic myeloid leukaemia from May2009 and ongoing, splenomegaly in 2009. The patient's concomitant medications were not reported. The subject experienced hair loss tendency on Dec2019 with outcome of recovered on 30Sep2020, flu syndrome on 17Mar2020 with outcome of recovered. The event tendency hair loss was rated grade 1 and not serious. The event flu syndrome was rated grade 1 and not serious. The event flu syndrome was described as hyperthermia + asthenia + anosmia + agueusia evokative of a COVID infection. Serology test COVID was negative on 30Sep2020. The action taken in response to the events for bosutinib was dose not changed.

The investigator assessed the event hair loss tendency as unrelated to bosutinib and the event flu syndrome as unrelated to study drug bosutinib.

Follow-up (10May2022): This is a follow-up to a non-interventional study for protocol B1871047.

Updated information: onset date of the event hair loss tendency was corrected to Dec2019, causality assessment for the event hair loss tendency was corrected to unrelated to bosutinib, event "flu syndrome (suspicion COVID)" was corrected to "flu syndrome".

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

Case Comment: In concurrence with the investigator, the Company considers the reported events hair loss tendency and the event flu syndrome (suspicion COVID) as unrelated to the suspect drug bosutinib.

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|--------------------------------------|----------|-------------------|
| 1 | 30-SEP-2020 | SARS-CoV-2 antibody test Negative | negative | |

| | | | | | | | | | | | | | | CI | OM | IS I | FOI | RM |
|--|---|---|-------------------|-------------|--------------------------|---|-----------|---|--------|-----------------------------|----|---|--------|-------------------------|---------|------|-----|----|
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| SUSPEC | T ADVERSE | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | Т | T | 1 | | Τ | П | | Т | \top | Τ | Т | 1 | Τ |
| | | | | | | | | 4 | | | | Ш | \Box | | \perp | | | |
| | | | | | MATION | _ | 4 | | | | Ι. | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 62 Years | 3. SEX Male | 3a. WEIGHT Unk | Day 20 | | Month JAN | | Yea 202 | r | | APP | CK ALI ROPRI ÆRSE | ATE T | | ٧ | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) COPD DECOMPENSATION [Chronic obstructive pulmonary disease] Painful tendons [Tendon pain] Painful tendons cramps [Muscle spasms] rhinopharyngitis [Nasopharyngitis] | | | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | | | | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | - 1 | DISA | SIGNIF ABILITY APACIT | OR | Γ | | | | | | |
| This is a non-interventional study report (Post Authorization Safety (Continued on Additional Information Page) | | | | | | | | | | | | | | | | | | |
| • | | II. SUSPEC | T DRUC | G(S) IN | IFORMA | TIOI | V | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU #2) Atorvastatin Ca | TINIB) Film-coated | tablet ATIN CALCIUM) Unknov | wn | (Cont | inued on Ad | ditiona | al Inf | orma | tion I | Pag | | | ATE A | ACTION AFTER | | PINC | 3 | |
| 15. DAILY DOSE(S) #1) 400 mg, 1x/day #2) 80 mg, daily 16. ROUTE(S) OF ADMINISTRATION #1) Unknown #2) Oral | | | | | | YES NO NA | | | | | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown #2) DYSLIPIDEMIA (Dyslipidaemia) | | | | | 21 | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | |
| 18. THERAPY DATES(from/to) #1) 03-APR-2019 / 30-MAY-2019 #2) 2019 / Unknown #2) Unknown | | | | | | | YES NO NA | | | | | | | | | | | |
| | | III. CONCOMIT | TANT DE | RUG(S |) AND H | ISTO | OR' | Y | | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADI | MINISTRATION (exclude those us | sed to treat read | ction) | · | _ | _ | _ | _ | _ | _ | _ | _ | _ | _ | _ | _ | _ |
| | | | | 7 | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 22 OTHER RELEVANT H | ISTORY (a.g. diagnostics | alleraios eragnancy with last mu | anth of period | oto \ | | | | | | | | | | | | | | |
| From/To Dates Unknown to Ongo | 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown to Ongoing Relevant Med History Relevant Med History CML (Chronic myeloid leukaemia) COPD (Chronic obstructive pulmonary disease) | | | | | | | | | | | | | | | | | |
| | | 17 / 840 811 15 | | INI | | ri O N I | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | S OF MANUFACTURER | IV. MANUF | -ACTUR | 26. REI | | ION | | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATE | S | | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2021161 | ONTROL NO. | | | ME AND ADDR E AND ADD | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 27-OCT-2023 | 24d. REPOR STUDY HEALTH PROFE | LITERATURE | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | RT TYPE | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

A 62-year-old male patient started to receive bosutinib (BOSULIF) via an unspecified route of administration from 03Apr2019 to 30May2019 at 400 mg, once daily (1x/day), via an unspecified route of administration from an unspecified date and ongoing at 300 mg, once daily (1x/day) for an unspecified indication, atorvastatin calcium oral from 2019 to an unspecified date at 80 mg daily, via an unspecified route of administration from 09Feb2021 to an unspecified date at 40 mg, daily for dyslipidaemia. Medical history included ongoing chronic myeloid leukaemia (CML), ongoing chronic obstructive pulmonary disease (COPD), ongoing dyslipidaemia, ongoing arteriopathy. The patient's concomitant medications were not reported.

The patient experienced COPD decompensation on 24Jan2020, which rated grade 3, patient was hospitalized from 27Jan2020 to 30Jan2020 for COPD decompensation. On 20Jan2020, patient had rhinopharyngitis, non-serious grade 2. Consultation with the attending physician on 23Jan2020 with prescription of prednisone and amoxicillin/ clavulanate potassium (AUGMENTIN). Normal biological tests. On 25Jan2020, disappearance of nasopharyngeal symptoms but appearance of inspiratory breathlessness different from COPD. Patient must sleep sitting because feeling of suffocation when lying down. He was limited in his daily activities. In addition, there was a wet cough, no fever. Emergency visit on 27Jan2020 for acute dyspnea on COPD (neurologic examination: mild trembling of the left hand at the bar. no sign of focus, no meningeal sign, no sensory-motor deficit). Conclusion: decompensation of COPD, following a rhinopharyngitis, no pulmonary infectious focus. The patent also experienced painful tendons cramps on unknown date in 2020, non-serious, rated grade 1. Cramps with tendinous pain were possibly related to statins with reduced dose of atorvastatin (80 to 40mg / day) on 09Feb2021. The action taken in response to the events for bosutinib was dose not changed. Drug atorvastatin calcium was dose reduced due to painful tendons cramps. The outcome of event COPD decompensation was recovered on 30Jan2020, of event painful tendons cramps was recovered on 10Aug2021, of event rhinopharyngitis was resolved on 25Jan2020.

The investigator considered that the events COPD decompensation and rhinopharyngitis were unrelated to bosutinib or to any concomitant drug and that Painful tendons cramps was unrelated to bosutinib and related to concomitant drug atorvastatin.

Follow-up (10May2022): This is a follow-up report to notify that the cases AER 2021161629 and AER 2021192869 are duplicates. All subsequent follow-up information will be reported under manufacturer report number AER 2021161629. The new information reported from a contactable reporter(s) (Physician) includes: events details (COPD decompensation was rated grade 3 and occurred on 24Jan2020. The events painful tendons cramps was split for Cramps and Painful tendons and resolved on 10Aug2021, New event rhinopharyngitis).

Follow-up (27Oct2023): This follow-up report is being submitted to amend previously transmitted information: onset date of event COPD decompensation updated.

Case Comment: The Company concurs with the investigator that there is no sufficient evidence to conclude a causal role of study drug bosutinib to reported "decompensation of COPD", "rhinopharyngitis", and "painful tendons cramps". "Decompensation of COPD" and "rhinopharyngitis" are also considered unrelated to atorvastatin calcium, and are more likely associated with subject's ongoing medical conditions (including ongoing medical history of COPD). Based on available information and known safety profile of atorvastatin calcium, the reasonable possibility of an association between atorvastatin calcium and "painful tendons cramps" cannot be ruled out.

| ab [| Data |
|------|------|
| | ab [|

| # Date | Test / Assessment / Notes | Results | Normal High / Low |
|---------------|--|---|-------------------|
| 1 | Body temperature | no fever | |
| 2 23-JAN-2020 | Laboratory test | normal | |
| 3 27-JAN-2020 | Neurological examination no sign of focus, no meningeal sign, no sensory-me | mild trembling of the left hand at the bar otor deficit | |

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

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 | | | Unknown |
| | | | |
| #2) Atorvastatin Calcium (ATORVASTATIN | 40 mg, daily; Unknown | DYSLIPIDEMIA | 09-FEB-2021 / |
| CALCIUM) Unknown; Regimen #2 | | (Dyslipidaemia) | Unknown; |
| | | | Linknown |

| 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 I. PATENT INITIALS (first, last) PRIVACY FRANCE Day PRIVACY PRIVACY PRIVACY PRIVACY PRIVACY PRESCRIBE REACTION(S) (including relevant tests/lab data) PRIVACY PRIVA | | | | | | |
|--|--|--|--|--|--|--|
| I. REACTION INFORMATION 1. PATIENT INITIALS (first, last) FRANCE Day Month PREVACY FRANCE Day Month PREVACY FRANCE Day Month PREVACY FRANCE Day Month PREVACY France Month PREVACY France Month PREVACY France Month PREVACY France Month Prevent Verbatim (PREFERRED TEMM) (Related symptoms if any separated by commas) Slow increase of atheromatous lesions of lower limbs [Arteriosclerosis] Slow increase of atheromatous lesions of lower limbs [Condition aggravated] Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol (Continued on Additional Information Page) 11. 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 17. INDICATION(S) FOR USE | | | | | | |
| 1. PATIENT INITIALS (flist, list) FRANCE PRIVACY FRANCE TO Male RANCE TO Male RANCE PROPRIATE TO ADVERSE REACTION RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PROLOGICAL PRIVACY RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION PRIVACY PEAR MALE RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVERSE REACTION ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVENUE PROPRIATE TO ADVENCE PROPRIA | | | | | | |
| 1. PATIENT INITIALS (flist, list) FRANCE PRIVACY FRANCE TO Male RANCE TO Male RANCE PROPRIATE TO ADVERSE REACTION RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PROLOGICAL PRIVACY RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION PRIVACY PEAR MALE RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVERSE REACTION ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVENUE PROPRIATE TO ADVENCE PROPRIA | | | | | | |
| 1. PATIENT INITIALS (flist, list) FRANCE PRIVACY FRANCE TO Male RANCE TO Male RANCE PROPRIATE TO ADVERSE REACTION RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PRIVACY Pear Male RANCE PRIVACY RANCE PROLOGICAL PRIVACY RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION PRIVACY PEAR MALE RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVERSE REACTION ADVERSE REACTION RANCE PROLOGICAL PROPRIATE TO ADVERSE REACTION ADVENUE PROPRIATE TO ADVENCE PROPRIA | | | | | | |
| PRIVACY FRANCE Day Month Year The privacy Th | | | | | | |
| PRIVACY Years Male & Route State | | | | | | |
| Slow increase of atheromatous lesions of lower limbs [Arteriosclerosis] Slow increase of atheromatous lesions of lower limbs [Condition aggravated] Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol (Continued on Additional Information Page) 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 17. INDICATION(S) FOR USE 18. ROUTE(S) OF ADMINISTRATION #1) Unknown 19. DAILY DOSE(S) #1) INFORMATION 20. DID REACTION ABATE AFTER STOPPING DRUG? 19. PES NO NA 21. DID REACTION | | | | | | |
| Slow increase of atheromatous lesions of lower limbs [Condition aggravated] 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 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 17. INDICATION(S) FOR USE 21. DID REACTION ABATE AFTER STOPPING DRUG? 21. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | |
| UNDER REAL-LIFE CONDITIONS OF USE This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol (Continued on Additional Information Page) 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 17. INDICATION(S) FOR USE INVOLVED PERSISTENT OR SIGNIFICANT DRISON INCAPACITY INVOLVED PERSISTENT OR SIGNIFICANT DRISON INCAPACITY | | | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) received from a contactable Continued on Additional Information Page | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION 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 17. INDICATION(S) FOR USE 21. DID REACTION 22. DID REACTION ABATE AFTER STOPPING DRUG? 18. ROUTE(S) OF ADMINISTRATION #1) Unknown 17. INDICATION(S) FOR USE | | | | | | |
| (Continued on Additional Information Page) 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 21. DID REACTION | | | | | | |
| 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 21. DID REACTION | | | | | | |
| 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 20. DID REACTION ABATE AFTER STOPPING DRUG? 16. ROUTE(S) OF ADMINISTRATION #1) Unknown 21. DID REACTION | | | | | | |
| #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 21. DID REACTION | | | | | | |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/day 16. ROUTE(S) OF ADMINISTRATION #1) Unknown 17. INDICATION(S) FOR USE 21. DID REACTION | | | | | | |
| #1) 300 mg, 1x/day #1) Unknown | | | | | | |
| | | | | | | |
| #4.) Lipknown | | | | | | |
| #1) Unknown | | | | | | |
| 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 Description | | | | | | |
| 2013 to Ongoing Relevant Med History Cardiomyopathy (Cardiomyopathy) 2000 to Ongoing Relevant Med History Diabetes (Diabetes mellitus) | | | | | | |
| 2000 to Origothig Relevant instory Diabetes (Diabetes infellitus) | | | | | | |
| | | | | | | |
| | | | | | | |
| IV. MANUFACTURER INFORMATION 24a. NAME AND ADDRESS OF MANUFACTURER 26. REMARKS | | | | | | |
| Pfizer Inc Stella Pietrafesa | | | | | | |
| 66 Hudson Boulevard East New York, NY 10001 UNITED STATES | | | | | | |
| Phone: 212 733 4045 | | | | | | |
| 24b, MFR CONTROL NO. 25b. NAME AND ADDRESS OF REPORTER | | | | | | |
| 2021166309 NAME AND ADDRESS WITHHELD. | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 24d. REPORT SOURCE STUDY LITERATURE | | | | | | |
| 12-JUN-2022 HEALTH OTHER: | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 NINITIAL FOLLOWUP: | | | | | | |

Mfr. Control Number: 2021166309

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued B1871047.

A 71-year-old male patient received bosutinib (BOSULIF), first regimen from 31May2016 to 12Jun2019 at 300 mg 1x/day and second regimen since 13Jun2019 at 200 mg 1x/day. The patient's relevant medical history included: "Cardiopathy", start date: 2013 (ongoing); "Diabetes", start date: 2000 (ongoing); "Pancreas cancer", start date: 04Aug2015 (ongoing); "Hypertension arterial", start date: 1986 (ongoing); "asthma" (ongoing). The patient's concomitant medications were not reported.

The following information was reported: ARTERIOSCLEROSIS (non-serious), CONDITION AGGRAVATED (non-serious) all with onset 29Mar2018, outcome "not recovered" and all described as "Slow increase of atheromatous lesions of lower limbs". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage reduced. The reporter considered "slow increase of atheromatous lesions of lower limbs" related to bosutinib.

Additional information: The event was grade 2. This was also observed on ultrasound doppler in the beginning of Jun2019. As atheromatous lesions were present before the patient was enrolled to the study there was little probability that this increase was due to bosutinib. However this led to decrease of dose to 200 mg a day from 13Jun2019. At day of consultation on 12Jun2019 subject was also dyspneic with decrease of walking perimeter. Comment per reporter: The subject experienced dyspnea of effort on 23Apr2018, probably linked to her heart failure and therefore not be considered an adverse event. In the medical file, it is noted "the subject describes chronic dyspnea for minor efforts". The subject also has active asthma and the physician notes that the dyspnea may be of multifactorial origin. Heart failure and asthma are well declared in the history, which is why dyspnea was not considered as an adverse event. The investigator confirmed that the dyspnea was a symptom of subject's cardiac pathology and it not to be reported as additional SAE. According to the investigator event was related to study drug.

Follow-up (16Nov2021): new information received from the investigator via the CRO included updated onset date, grading and causality of the event.

Follow-up (10May2022): This is a follow-up Non-Interventional Study report (Post Authorization Safety Study) for protocol B1871047 from a contactable physician.

Updated information: the investigator confirmed that the dyspnea was a symptom of subject's cardiac pathology and it not to be reported as additional SAE and Medical history (asthma) added.

Amendment: This follow-up report is being submitted to amend previously reported information: last follow-up received date was corrected (updated to 10May2022) in the narrative; updated patient's age.

Case Comment: The Company, according to medical history suggesting that atheromatous lesions is a pre-existing medical condition deems there is not a reasonable possibility that the reported slow increase of atheromatous lesions of lower limbs is related to the study drug, bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

| # Date Test / Assessi | ment / Notes | Results | Normal High / Low |
|--|---|--|--|
| 1 JUN-2019 Ultrasound | d Doppler | slow increase of atheromatous lesions of lower lim | |
| 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 | 13-JUN-2019 / Unknown; Unknown |

| 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 | Hypertension arterial (Hypertension); |
| Unknown to Ongoing | Relevant Med History | Asthma (Asthma); |

| | | | | | | | | | | | | | CIC | OMS | FC | ЭR | M |
|---|--|--|-----------|---------------|----------------|----------|-------|---------|-------------------|-------------|---|------------|-------------------------|--------|---------|---------|---|
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| SUSPECT | Γ ADVERSE ! | REACTION REP | ORT | | | | | | | | | | | | | | _ |
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| | | | | | | | 4 | | | | \bot | \perp | | Ш | \perp | \perp | _ |
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| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | | . 53 | | 3a. WEIGHT Unk | 4-6 R | Mon | th | Year | | AF | PPR | K ALL OPRIA RSE R | TE TO | NC | | |
| Event Verbatim [PREFERRI | ED TERM] (Related sym | t tests/lab data) ptoms if any separated by com | mas) | | | | | | | 3 | | | NT DIE | | | | |
| | | | ION OF EF | FICACY | AND SAFE | TY OF | BOS | SULIF | | | Н | IOSP | PITALIS | D INPA | | | |
| reporter(s) (Physici | DER REAL-LIFE CONDITIONS OF USE s is a non-interventional study report (Post Authorization Safety Study) received from contactable orter(s) (Physician and Other HCP) for protocol B1871047. This is a Non-Interventional Study report with its analysis and other HCP) for protocol B1871047. This is a Non-Interventional Study report with its analysis and its analysis analysis and its analysis analysis analysis analysis and its analysis analysis analysis and its analysis an | | | | | | | [| — OI DI | OR SIGNAB | IVED P IGNIFIC BILITY (PACITY | OR | IENI | I | | | |
| | | | | (Conti | nued on Addi | tional I | nform | ation F | Page | <u>,) [</u> | 그 | IFE HRE | ATENII | NG | _ | | |
| | | II. SUSPE | CT DRU | G(S) IN | FORMAT | ION | | | | | | | | | | | _ |
| | - | tablet | | _ | | | | · | | 20. | DID RI ABATI DRUG | EAF | | STOPPI | ٧G | | |
| 15. DAILY DOSE(S) #1) UNK | | | | | | ATION | | | | | ПΥ | /ES | □ NO | · 🛛 | NA | | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | | | | | | | | | 21. | | PPEA | TION AR AFT DUCTI | | _ | _ | _ |
| 18. THERAPY DATES(from. #1) Unknown | /to) | | | | | _ | _ | _ | - | | ШΥ | ES | □ NO | · 🛛 | NA | | |
| | | III. CONCOM | IITANT D | RUG(S) | AND HIS | STOF | RY | | | | | | | | | | _ |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | | | $\overline{}$ | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | _ |
| From/To Dates | TORY. (e.g. diagnostics | Type of History / Notes | s | Description | | | | | | | | | | | | | |
| OTIKTIOWIT | | Neiovain woo i | Пэтогу | None () | | | | | | | | | | | | | |
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| | | IV. MANU | JFACTUR | ER INF | ORMATI | ON | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar | rd East I UNITED STATE | | | 26. REM | ARKS | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | | | | | | | | | | | | | | _ |
| | Continued FRANCE Day Mouth Vear 53 Female Unk Day Morth Vear V | | | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | I. REACTION INFORMATION PRIVACY FRANCE Day Mark of Birth To COUNTRY PRIVACY FRANCE To Day Mark of Birth To Day Mark of Birth To Day Mark PRIVACY FRANCE To Day Mark MAY *** *** *** *** *** *** *** | | | | | | | TELD. | | | | | | | | | |
| 30-MAY-2023 | | | | _ | | | | | | | | | | | | | |
| 27-FEB-2024 | I. REACTION INFORMATION I. REACTION INFO | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 53-year-old subject started to receive bosutinib (BOSULIF), via an unspecified route of administration from an unspecified date to an unspecified date at an unspecified dose for an unspecified indication. Medical history was none. The patient's concomitant medications were not reported. The subject experienced dental abscess in May2020. The event was reported as non-serious and rated grade 1. Corrective treatment included azithromycin. The action taken in response to the event for bosutinib was not applicable. The outcome of event was resolved in 02Jun2020.

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

Follow-up (07Apr2021):New information reported from the site includes: event downgraded to non-serious, rated grade 1 and action taken with bosutinib updated from "Unknown" to "Dose not changed".

Follow-up (30May2023) This is a non-interventional study follow up report received from the investigational site via CRO. Updated information includes: action taken (updated to not applicable) and event details (onset date and stop date updated).

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

Case Comment: Based on the information currently available, pending more details regarding the clinical course of the reported dental abscess, at this moment, in concurrence with the reporter, the Company deems the reported event an intercurrent disease, unrelated to the administration of bosutinib.

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|---|--|------------------------------|---------------------------------------|----------------------|---|----------------------|--------|--------|------------|------|------------|-----|-----------------|-------------|------------------------------|--------------|-------|-----|----|
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| SUSPECT | Γ ADVERSE F | REAC | TION REP | ORT | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 1 2 1 | I. RE | ACTION 2a. AGE | | MATION 3a. WEIGHT | 1-6 5 | REACT | TON C | ONSE | т. | 8-1 | 12 | CHE | CK ALL | | | | |
| PRIVACY | FRANCE | Day | Month Year | ar 46 | Female | 50.50 | Day | Мо | onth AR | Y | ear 020 | 1 | | APPI | ROPRIA ERSE F | ATE | | 1 | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERRI emotional eczema cough without fevel | ED TERM] (Related symp [Eczema] | t tests/lab o otoms if an | data) y separated by com | nmas) | | | | | | | | | | INVC PRO | ENT DI | OR ED IN | | ≣NT | |
| Case Description: 0 UNDER REAL-LIFE | | | | TION OF E | EFFICACY | AND SAFET | TY OI | F BO | SUL | LIF | | | ш | OR S | OLVED I SIGNIFI BILITY | CAN | SISTE | NT | |
| This is a non-interv reporter(s) (Physici | | | | | Study) red | ceived from c | ontac | ctable | е | | | | | LIFE | (PACIT | Y | | | |
| | (Continued on Additional Information Page) II. SUSPECT DRUG(S) INFORMATION | | | | | | | | |) | | THR | EATEN | ING | | | | | |
| LA QUEDECT DRUGGO (C) | II. SUSPECT DRUG(S) INFORMATION USPECT DRUG(S) (include generic name) 20. | | | | | | | | DID | DEA | OTION | | | | | | | | |
| #1) Bosulif (BOSUT | II. SUSPECT DRUG(S) INFORMATION SUSPECT DRUG(S) (include generic name)) Bosulif (BOSUTINIB) Film-coated tablet (Continued on Additional Information Page) | | | | | | | | | | ABA | | CTION FTER S | | PPINC |) | | | |
| 15. DAILY DOSE(S) #1) 400 mg, daily | | | 16. ROUTE(S #1) Unkno | OF ADMINISTRA DWN | ATION | | , | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR US #1) chronic myeloid | | | | 21 | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(from, #1) 24-FEB-2020 / 1 | • | | | | 19. THERAPY #1) 18 da | | | | | | | | | YES | Пи | 10 | ×Σ | A | |
| | | | CONCOM | | _ |) AND HIS | STO | RY | | | | | | | | | | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | MINISTRAT | TION (exclude those | e used to treat | reaction) | , | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIS From/To Dates Unknown | | Tyl R | pe of History / Note elevant Med I | s History | Description Depress | ion (Depress | , | | | | | | | | | | | | |
| Unknown to Ongoir | ng | R | elevant Med I | History | CML (CI | nronic myeloi | id leu | kaem | nia) | | | | | | | | | | |
| | | | IV/ M/\NII | IEACTU | DED IN | FORMATION | ON. | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | | IV. IVIAINO | JI AO I O | 26. REI | | OIN | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | UNITED STATES | 5 | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC 2021178 | | 0. | | | ME AND ADDRES | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR¹ | T SOURCE | LITERATUR | ·F | NAM | E AND ADDR | ESS \ | WITH | IHEL | D. | | | | | | | | | |
| 28-SEP-2023 | STUDY HEALTH | SSIONAL | OTHER: | ·- | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR¹ | Т ТҮРЕ | FOLLOWUP | : | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 46-year-old female patient received bosutinib (BOSULIF), first regimen from 24Feb2020 to 12Mar2020 at 400 mg daily, second regimen from 13Mar2020 to 18Mar2020 at 500 mg daily, third regimen from 19Mar2020 to Mar2020 at 400 mg daily and fourth regimen since Mar2020 (ongoing) at 500 mg daily for chronic myeloid leukaemia. Medical history included depression and ongoing chronic myeloid leukaemia (CML). The subject was aware that depression could interact with the pain felt. Concomitant medications were not reported. The subject experienced emotional eczema and cough without fever on Mar2020. Both events emotional eczema and cough without fever were reported as non-serious (grade 1). The subject also presented with trunk rash, diarrhea and cough without fever. The diarrhea was already declared and not resolved AE (AER 2019185788) and the skin rash corresponds to eczema. The subject performed a SARS-COV-2 PCR which was negative. The subject received anti-biotherapy with amoxicillin. The action taken in response to the events for bosutinib was dose not changed. The outcome of event emotional eczema was recovered on 01Dec2020, of event cough without fever was recovered in Mar2020. According to the investigator, the both events were unrelated to bosutinib and to concomitant drugs.

Follow-up (08Jun2021): New information received from the investigator via CRO included: The outcome of the event emotional eczema was resolved on 01Dec2020 (instead of "not resolved" as previously mentioned). No follow-up attempts are needed. No further information is expected.

Follow-up (12Jul2023): This is a follow-up to a non-interventional study for protocol B1871047 received from investigator site via the CRO. Updated information: No action was taken on bosutinib in response to event emotional eczema and cough without fever. No follow-up attempts are needed. No further information is expected.

Follow-up (28Jul2023): This is a follow-up report received from the CRO. Updated information included: Weight updated, Relevant medical history updated with CML.

Follow-up (28Sep2023): This is a follow-up to a non-interventional study received from the investigational site via the CRO. Updated information includes: additional dosage regimen (overall start date).

Case Comment: In concurrence of the reporting investigator, the Company deems the reported emotional eczema and cough are unlikely related to the suspect, bosutinib.

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

| # Date | Test / Assess | ment / Notes | Results | Normal High / Low |
|--|-----------------|---|-----------------------------|--|
| 1 | SARS-Co | V-2 test | Negative | |
| 14-19. SUSPECT DRUG(S) contin | | | | |
| 14. SUSPECT DRUG(S) (include generic nar | me) | 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; | 500 mg, daily; Unknown | chronic myeloid leukemia | 13-MAR-2020 / |
| Regimen #2 | | | (Chronic myeloid leukaemia) | 18-MAR-2020; |
| | | | | 6 days |
| | | | | |
| #1) Bosulif (BOSUTINIB) Film- | -coated tablet; | 400 mg, daily; Unknown | chronic myeloid leukemia | 19-MAR-2020 / |
| Regimen #3 | | | (Chronic myeloid leukaemia) | MAR-2020; |
| | | | | Unknown |
| #1) Bosulif (BOSUTINIB) Film- | -coated tablet; | 500 mg, daily; Unknown | chronic myeloid leukemia | MAR-2020 / Ongoing; |
| Regimen #4 | | • | (Chronic myeloid leukaemia) | Unknown |

| | | | | | | | | CIOMS FORM | | | | | |
|--|--|---|-----------------|---------------------------|-------------------|------------------|--|---|--|--|--|--|--|
| | | | | | | | | | | | | | |
| SUSPECT | ADVERSE RE | EACTION REPO | RT | | | | | | | | | | |
| 000. 20. | ADVENCE | .Aonon ne. o. | IX I | | | | - | | | | | | |
| | | | | | | | | | | | | | |
| | | | | INIEOR | MATION | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | | 4-6 REACTION ONS | SET 8-12 | | | | | | |
| (first, last) PRIVACY | FRANCE | PRIVACY Year | 47 Years | Female | 59.50 Da | | Year 2020 | APPROPRIATE TO ADVERSE REACTION | | | | | |
| 7 + 13 DESCRIBE REACTIO Event Verbatim [PREFERRE | N(S) (including relevant tes D TERM] (Related symptor | sts/lab data) ms if any separated by comma | s) | | | | 2 | PATIENT DIED | | | | | |
| ASTHENIA [Astheni Morose mood [Moro | • | | | | | | C | INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | |
| | | STUDY- EVALUATION | N OF EF | FICACY | AND SAFETY | OF BOSULIF | | I INVOLVED PERSISTENT | | | | | |
| UNDER REAL-LIFE | | | | | | | - | OR SIGNIFICANT DISABILITY OR | | | | | |
| | | rt (Post Authorization for protocol B187104 | | tudy) rec | eived from cor | ntactable | | INCAPACITY | | | | | |
| | | | | (Conti | nued on Addition | nal Information | Page) | LIFE THREATENING | | | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMATIO | N | | | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION SUSPECT DRUG(S) (include generic name)) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | 6. ROUTE(S) 11) Unkno | OF ADMINISTRATION | DN | | YES NO NA | | | | | |
| 17. INDICATION(S) FOR USI #1) Unknown | 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | | | |
| 18. THERAPY DATES(from/tr #1) MAR-2020 / Ong | • | | | 9. THERAPY 1) Unkno | | | [| YES NO NA | | | | | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND HIST | ORY | | | | | | | |
| 22. CONCOMITANT DRUG(S | 3) AND DATES OF ADMINI | ISTRATION (exclude those use | ed to treat rea | action) | | | | | | | | | |
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| | | | | | | | | | | | | | |
| | FORY. (e.g. diagnostics, all | ergies, pregnancy with last mor | | | | | | | | | | | |
| From/To Dates Unknown | | Type of History / Notes Relevant Med His | story | • | on (Depressio | , | | | | | | | |
| Unknown to Ongoin | g | Relevant Med His | itory | CML (Ch | ronic myeloid | leukaemia) | | | | | | | |
| | | | | | | | | | | | | | |
| | | | | | | | | | | | | | |
| | | IV. MANUF | - ACTUR | - RER INF | - FORMATIOI | N | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | | | 26. REM | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 | UNITED STATES | | | | | | | | | | | | |
| Phone: 212 733 4045 | | | | | | | | | | | | | |
| | 24b. MFR CONT | ROL NO. | | | ME AND ADDRESS | | | | | | | | |
| | 202118365 | .5 | | | AND ADDRES | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT S | OURCE LITERATURE | | NAME | AND ADDRES | SS WITHHELD | • | | | | | | |
| 28-SEP-2023 | HEALTH PROFESSION | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT T | YPE FOLLOWUP: | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 47-year-old female subject received bosutinib (BOSULIF), since Mar2020 (ongoing) at 500 mg daily. The subject's relevant medical history included: "Depression" (unspecified if ongoing); "CML" (ongoing). The subject's concomitant medications were not reported. The subject had been stopped from work for a week due to asthenia, with morose mood in Nov2020. The investigator clarified the known history of depression was not necessarily related to the event of morose mood (it can happen to have a morose mood without being in a depressive episode). The action taken in response to the events for bosutinib was dose not changed. The outcome of events asthenia and morose mood was resolved on 22Feb2021.

The events asthenia and morose mood were rated with grade 1, reported as non-serious, unrelated to bosutinib and unrelated to concomitant medication.

Follow-up (08Jun2021): New information received from the investigational site via the CRO included reaction date (the event morose mood updated).

Follow-up (20Dec2021): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information included: Event morose mood was updated with depression.

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

Follow-up (21Apr2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047.

Updated information includes: event depression changed to morose mood.

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

Follow-up (30May2023): new information received from the investigator via the CRO. Updated information included: Event Asthenia: stop date added (22Feb2021), outcome updated to recovered.

Follow-up (28July2023): new information received from the investigator via the CRO. Updated information included: Relevant medical history updated with CML

Follow-ups (28Sep2023): These are follow-ups of non-interventional study report (Post Authorization Safety Study) received from contactable reporters (Physician and Other HCP) for protocol B1871047; received via CRO/clinical team. Updated information included: Bosutinib dosing therapy dates (from Mar2020 ongoing).

Case Comment: The events asthenia and morose mood were reported as non-serious, unrelated to bosutinib (BOSULIF) and unrelated to concomitant medication. The follow-up information received does not alter the previous company clinical evaluation.

| | | | | | | | | | | | | CIC | DM | S F | OI | RМ |
|--|--|--|-------------------|------------|-----------------|---------|------------|--------|-------|--------|-----------------------------|--------------------|-----------|-------|----|----|
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| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | |
| | | | | | | | | 1 | П | Т | Т | | \top | Т | Ι | |
| | | I. REACTION INFORMATION a. COUNTRY D. Day Morth Vest 54 Male 91.00 Day Morth Your 2020 District Symptoms if any separated by commas) Medically Significant 1 h] SERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF ONDITIONS OF USE for instance of the separated by commas) Medically Significant 1 h] SERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF ONDITIONS OF USE for instance of the separated by commas) II. SUSPECT DRUG(S) INFORMATION III. SUSPECT DRUG(S) INFORMATION 13 Film-coated tablet (Continued on Additional Information Page) 14 ROUTE(S) OF ADMINISTRATION 19 PROPER OF ADMINISTRATION 19 PROPER OF ADMINISTRATION 10 DATES OF ADMINISTRATION (exclude those used to treat reaction) 19 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 19 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 10 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 10 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 10 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 11 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 12 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 13 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 14 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 15 PROPER OF ADMINISTRATION (exclude those used to treat reaction) 16 PROPER OF ADMINISTRATION (exclude those used to treat reaction) | | | | | | | | | | | | | | |
| | | I. REA | CTION II | NFORI | MATION | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | | ⊣ । | 3. SEX | | | | | | 8-12 | | ECK ALL PROPRIA | | о. | | |
| PRIVACY | FRANCE | | | Male | 31.00 | | | | | | AD۱ | /ERSE R | (EAC | TION | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERR | ION(S) (including relevant EED TERM] (Related symp | tests/lab data) btoms if any separated by comm | nas) | | | | | | | - | PAT | IENT DIE | ED | | | |
| | | nificant | | | | | | | | le | | OLVED O | | DATIE | NT | |
| | | | | | | | | | | | | SPITALIS | | | | |
| | | | ON OF EFFI | CACY A | ND SAFETY | OF E | BOSL | JLIF | | l ∟ |] INV | OLVED F | PERS | SISTE | NT | |
| UNDER REAL-LIF | E CONDITIONS (| OF USE | | 47 | | | • | | | | DIS | ABILITY | OR | • | | |
| This is a non-interv | ventional study rep | oort (Post Authorization | n Safety Stu | ıdy) for p | orotocol B187 | 71047 | 7 . | | | | | | | | | |
| | | | | (Contin | nued on Additio | onal In | forma | tion P | age) | [| LIFI THE | E REATENI | NG | | | |
| | PECT DRUG(S) (include generic name) | | | | | | | | | | | | | | | |
| | SPECT DRUG(S) (include generic name) Bosulif (BOSUTINIB) Film-coated tablet (Continued on Additional Information Page) LY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | ACTION AFTER S | | PING | | _ |
| #1) Bosuiii (BOSO1 | II. SUSPECT DRUG(S) INFORMATION SPECT DRUG(S) (include generic name) Bosulif (BOSUTINIB) Film-coated tablet (Continued on Additional Information Page) ILY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | [| RUG? | | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | ESCRIBLE EACTIONS) including the table that appropriate any specific plants (as a country in the | | | | | | |] [| YE | s 🔲 N | 0 [| N/ | A | | | |
| , , | I. REACTION INFORMATION IT ANTIALS IS COUNTRY FRANCE To y Morein FRANCE To Work (France FRANCE) To Work (France France F | | | | | | | | | | | _ | | | | |
| | R REAL-LIFE CONDITIONS OF USE s a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. (Continued on Additional Information Page) II. SUSPECT DRUG(S) INFORMATION PECT DRUG(S) (include generic name) Dosulif (BOSUTINIB) Film-coated tablet (Continued on Additional Information Page) Y DOSE(S) 16. ROUTE(S) OF ADMINISTRATION #1) Unknown CATION(S) FOR USE Bronic myeloid leukemia (Chronic myeloid leukaemia) RAPY DATES(from/to) P-DEC-2019 / 07-JAN-2020 III. CONCOMITANT DRUG(S) AND HISTORY COMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) | | | | | | | | F | REAPP | ACTION EAR AFT RODUCT | | | | | |
| 18. THERAPY DATES(from | EAT PRINCE 2. DATE OF BIRTH 2a. AGE 3. SEX 3. S | | | | | | | | | ١. | _ | _ | _ | _ | | |
| #1) 19-DEC-2019 / | 07-JAN-2020 | | #1 |) 20 day | S | | | | | [| YE | S N | 0 | X NA | A | |
| | | III CONCOMI | TANT DD | LIC(S) | VIID FIIG. | TOP | | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | | | | AND HIS | ION | . 1 | | | | | | | | | _ |
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| 23 OTHER RELEVANT HI | STORY (e.g. diagnostics | allergies pregnancy with last m | nonth of period e | tc) | | | | | | | | | | | | |
| From/To Dates Unknown | oronn (o.g. diagnosios, | Type of History / Notes | D | escription | nveloid leuke | mia (| Chror | nic m | veloi | id leu | ıkaer | nia) | | | | |
| Unknown | | | | | | | | | , | | | , | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF R REAL-LIFE CONDITIONS OF USE a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. (Continued on Additional Information Page) II. SUSPECT DRUG(S) INFORMATION ECT DRUG(S) (include generic name) Sulif (BOSUTINIB) Film-coated tablet (Continued on Additional Information Page) (II. ROUTE(S) OF ADMINISTRATION #1) Unknown ATION(S) FOR USE TODIC myeloid leukemia (Chronic myeloid leukaemia) APY DATES(from/to) -DEC-2019 / 07-JAN-2020 III. CONCOMITANT DRUG(S) AND HISTORY CONITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction) III. CONCOMITANT DRUG(S) AND HISTORY CONTANT HISTORY. (e.g., diagnostics, altergies, pregnancy with last month of period, etc.) Type off includy / Notes Relevant Med History Relevant Med History Relevant Med History IV. MANUFACTURER INFORMATION IV. MANUFACTURER INFORMATION 18. REMARKS 19. REMARKS 28b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS OF REPORTER NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD D | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS | S OF MANUFACTURER | | | | | | | | | | | | | | | |
| Stella Pietrafesa | rd Fast | | | | | | | | | | | | | | | |
| | 1 UNITED STATES | 3 | | | | | | | | | | | | | | |
| | I. REACTION INFORMATION INMINES II. COUNTRY PRIVACY P | | _ | _ | | | _ | | | | | | | | | |
| | The state of the s | | | | | | | | | | | | | | | |
| 240 DATE RECEIVED | | | | 4 | | •• | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | STUDY | | | | | | | | | | | | | | | |
| 13-DEC-2021 | | | | 1 | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 1_ | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 54-year-old male subject received bosutinib (BOSULIF) at 200 mg daily from 19Dec2019 to 07Jan2020, at 300 mg daily from 08Jan2020 to 18Feb2020, at 400 mg daily from 19Feb2020 to 31Mar2020 and at 500 mg daily from 01Apr2020 and ongoing for chronic myeloid leukaemia. Medical history included chronic myeloid leukemia, exertional tachycardia and post-traumatic left thoracic pain. Concomitant medications were not reported. The patient experienced chest pain on 13Oct2020. The event was assessed medically significant. An electrocardiogram on 14Oct2020 was normal. The patient recovered from the event on 15Oct2020. In Nov2020, the subject complained of pruriginous cutaneous lesions of variable localisation. The event was reported as polymorphic rash, with onset date of 20Nov2020. On 09Dec2020, a skin biopsy was performed and no specific lesions allowing specific diagnosis were found. Skin corticosteroids were prescribed but were slightly effective. The anti-histaminic drugs were ineffective. The patient had not recovered from this event. The events chest pain and polymorphic rash were assessed as non-serious and rated grade 2. The action taken in response to the events for bosutinib was dose not changed.

The investigator considered the event chest pain as neither related to the study drug bosutinib nor to a concomitant medication, and the event polymorphic rash as related to the study drug bosutinib and unrelated to any concomitant medication.

Reporter comment: in the report of 11Jan2021: the patient reports the apparition in Nov2020 of pruritic skin lesions of variable location. A biopsy was performed on 09Dec2020: no specific lesions to suggest a diagnostic. Dermocorticoids were prescribed with low efficacy, antihistamines were not effective. The biopsy did not allow a formal diagnosis. Passage to the emergency room on 14Oct2020 from 7:20 pm to 11:08 pm. Return to home.

Follow-up (13Dec2021): this is a follow-up non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: event chest pain was assessed as medically significant, bosutinib therapy dates and doses, medical history, reporter's comment. The case has been upgraded to serious.

Case Comment: The reported event chest pain is considered as unrelated to the study drug bosutinib. The patient had a medical history of post-traumatic left thoracic pain. The event polymorphic rash assessed as related to the study drug bosutinib, based on the reasonable temporal association and the known safety profile of bosutinib.

13. Lab Data

| # Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|---|---|--|
| 1 09-DEC-2020 | Biopsy skin | histological lesion not allowing formal diagnosis | 3 |
| 2 14-OCT-2020 | Electrocardiogram | normal | |
| 14-19. SUSPECT DRUG(S) contin | nued | | |
| 14. SUSPECT DRUG(S) (include generic na | 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 Regimen #2 | a-coated tablet; 300 mg, daily; Unkn | own chronic myeloid leukemia (Chronic myeloid leukaemia) | 08-JAN-2020 / 18-FEB-2020; 1 month 11 days |
| #1) Bosulif (BOSUTINIB) Film Regimen #3 | a-coated tablet; 400 mg, daily; Unkn | own chronic myeloid leukemia (Chronic myeloid leukaemia) | 19-FEB-2020 / 31-MAR-2020; 1 month 13 days |
| #1) Bosulif (BOSUTINIB) Film Regimen #4 | n-coated tablet; 500 mg, daily; Unkn | own chronic myeloid leukemia (Chronic myeloid leukaemia) | 01-APR-2020 / Ongoing; Unknown |

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|--------------------------|
| Unknown | Relevant Med History | Chest pain (Chest pain); |

| | | | | | | | | | | | | CIC | OMS | FO | RM |
|---|--|---|-------------|----------------------|------------------|---------|--------|-----------|--------------|---------|-----------------------------|---|---------------|------|----|
| | I. REACTION INFORMATION II. REACTION INFORMATION II. REACTION INFORMATION III. BUSINESS TARNOE III. SUSPECT DRUG(S) Secretary of the properties of the p | | | | | | | | | | | | | | |
| SUSPECT AD | VERSE REA | ACTION REPO | RT | | | | | | | | | | | | |
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| | | I REA | CTION | INFOR | ΜΔΤΙΟ |)NI | | 7 | | | | | | • | |
| | COUNTRY | | г т | | | | 4-6 RE | EACTION | ONSET | 8-12 | | CK ALL | | | |
| PRIVACY FRA | ANCE Da | | 24 Years | Female | | , | , | | Year 2019 | | | ROPRIA ERSE R | | N | |
| 7 + 13 DESCRIBE REACTION(S) (ir Event Verbatim [PREFERRED TER | ncluding relevant tests M] (Related symptoms | /lab data) if any separated by comma | s) | | | | | | | [| PATI | IENT DIE | :D | | |
| Fatigue [Fatigue] | | | | | | | | | | 1 |] INVO | OLVED C |)R D INPAT | IENT | |
| | | | N OF EF | FICACY | AND SA | AFETY | OF | BOSU | LIF | | HOS | SPITALIS | ATION | | |
| This is a report from a No | on-Interventiona | al Study source for I | Protocol E | 3187104 ⁻ | 7 (Study | alias | BOS | EVAL) | | | OR S | OLVED P SIGNIFIC ABILITY (APACITY | CANT OR | ENI | |
| | | | | (Conti | nued on <i>i</i> | Additio | nal In | nformatio | on Page) | , | LIFE | EATENII | NG | | |
| | | II. SUSPEC | T DRU | 3(S) IN | FORM | IATIC | DN | | | | | | | | |
| | SUSPECT DRUG(S) (include generic name)) Bosutinib (BOSUTINIB) Unknown DAILY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | | TOPPIN | G | |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/day | AILY DOSE(S) 300 mg, 1x/day 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | | | | S NO | > \ | NA | |
| 17. INDICATION(S) FOR USE #1) Unknown | 1) 300 mg, 1x/day #1) Unknown INDICATION(S) FOR USE 1) Unknown | | | | | | | | | | DID REA REAPPE REINTR | CTION EAR AFT ODUCTI | ER ON? | | |
| 18. THERAPY DATES(from/to) #1) 14-NOV-2018 / Ongoin | ng | | | | | | | | |] [| YES | S NO | > \ | NA | |
| | | III. CONCOMIT | ANT DI | RUG(S |) AND | HIST | ΓOR | Υ | | | | | | | |
| 22. CONCOMITANT DRUG(S) AND | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. (From/To Dates MAY-2009 to Ongoing | (e.g. diagnostics, allero | Type of History / Notes | | Description | myeloid | leuker | mia (| Chroni | c myelc | oid leu | ıkaem | nia) | | | |
| | | D / A / A A A H / I = | | | | A-TI-O | | | | | | | | | |
| | NUFACTURER | IV. MANUF | ACTUR | | | 4110 | IN | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNIT Phone: 212 733 4045 | | | | | | | | | | | | | | | |
| | 24b. MFR CONTRO | OL NO. | | 25b. NA | ME AND AD | DRESS | OF RE | PORTER | | | | | | | |
| | The state of the s | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | | | | 7 | | | | | | | | | | | |
| 10-MAY-2022 | HEALTH | NAL OTHER: | | | | | | | | | | | | | |
| 27-FEB-2024 | 25a. REPORT TYP | FOLLOWUP: | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 24-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB), since 14Nov2018 (ongoing) at 300 mg 1x/day. The patient's relevant medical history included: "Chronic myeloid leukemia", start date: May2009 (ongoing). The patient's concomitant medications were not reported.

The following information was reported: FATIGUE (non-serious) with onset 17Dec2019, outcome "recovered" (27May2020). The action taken for bosutinib was dosage not changed.

According to the reporter, the event was related to study drug bosutinib but not related to concomitant medication.

Follow-up (10May2022): This is a follow-up report to a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL).

Updated information: Patient's details provided (DOB, height, weight, gender), Medical history (chronic myeloid leukemia), Drug data (start date, dosage and frequency for bosutinib), Action taken (dose not changed) and Causality assessment.

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported event Fatigue.



| | | | | | | CIOMS FORM |
|---|--|---|--------------------------|-------------------------------------|-------------------|---|
| | | | | | | |
| SUSPECT | ADVERSE REACTI | ON REPORT | | | | |
| 000. 20. | ADVENUE HEALT. | OH ILL CIT | | 1 | | |
| | | | | | | |
| | | I. REACTIO | | PNANTIONI . | | |
| 1. PATIENT INITIALS | 1a. COUNTRY 2. DAT | TE OF BIRTH 2a. A | | | REACTION ONSET | 8-12 CHECK ALL |
| PRIVACY | | Month Year 32 Year | 2 ars Female | 68.00 Day 18 | Month Year 2020 | APPROPRIATE TO ADVERSE REACTION |
| | ON(S) (including relevant tests/lab data ED TERM] (Related symptoms if any se nital burning sensation] | i) eparated by commas) | | | | PATIENT DIED INVOLVED OR |
| | DBSERVATIONAL STUDY CONDITIONS OF USE | - EVALUATION OF | F EFFICAC | AND SAFETY C | F BOSULIF | PROLONGED INPATIENT HOSPITALISATION |
| | n a Non-Interventional Stud Il Study report with non-ser | | ocol B18710 | 47 (Study alias B0 | OSEVAL). This is | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | | (Con | tinued on Additiona | Information Page) | LIFE THREATENING |
| | | . SUSPECT DE | RUG(S) II | NFORMATION | l | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI | clude generic name) NIB) Film-coated tablet | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) UNK | | | 16. ROUTE(: #1) Unkr | S) OF ADMINISTRATION OWN | | YES NO NA |
| 17. INDICATION(S) FOR US #1) Unknown | E | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/t #1) Ongoing |) (a) | | 19. THERAP #1) Unkr | Y DURATION OWN | | YES NO NA |
| | III. Ç | CONCOMITANT | T DRUG(S | S) AND HISTO | PRY | |
| 22. CONCOMITANT DRUG(S | S) AND DATES OF ADMINISTRATION | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | TORY. (e.g. diagnostics, allergies, preg | | | | | |
| From/To Dates Unknown | | of History / Notes evant Med History | Description None () | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | IV. MANUFACT | TUR <u>ER IN</u> | FORMATION | | |
| 24a. NAME AND ADDRESS Pfizer Inc | | | | MARKS | | |
| Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | UNITED STATES | | | | | |
| | 24b, MFR CONTROL NO. | | 25b A | AND ADDRESS OF | PEROPIER | |
| | 245. MFR CONTROL NO. 2021192909 | | | AME AND ADDRESS OF E AND ADDRESS | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE | | | | | |
| 19-FEB-2021 | STUDY [HEALTH PROFESSIONAL [| OTHER: | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYPE | FOLLOWUP: | | | | |

7+13. DESCRIBE REACTION(S) continued

A 32-year-old female patient received bosutinib at an unknown dose and frequency for an unspecified indication from an unknown date.

Medical history was none.

Concomitant drugs were unspecified.

In consultation report of 23Nov2020: The subject was briefly hospitalized in emergency on 18Nov2020 for vulvar burning associated to macroscopic lesions. Sample did not reveled herpes, gonocoque or chlamydia infection. Symptoms well improved with Dermoval. Event was grade 2, non-serious.

Action taken with suspect drug was not reported.

The event was recovered on 23Nov2020.

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

Case Comment: Event Vulvar burning is most likely related to an intercurrent or underlying condition and unrelated to suspect drug BOSUTINIB.

| | | | | | | | | | | | | | CIO | MC | IS F | FOF | RM |
|--|-----------------------------|--|------------------|-------------|-------------------|--------------------|-----------|---|------------|---|---|--------------|----------------------------|----------|-------|-----|----|
| | | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE I | REACTION REPOR | RT | | | | | | | | | | | | | | |
| | | | | | | | П | | Τ | Τ | П | | Т | Τ | Τ | | |
| | | | | | | | И | | | | | | | <u>L</u> | | | |
| | | | | | MATION | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | Day Month Year PRIVACY | 75 Years | 3. SEX Male | | 4-6 R Day 07 | Mon DE | ith | Yea 202 | ar | -12 | APP | CK ALL ROPRIA ERSE F | ATE T | | I | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFER] Covid positive [SA | RED TERM] (Related sym | otoms if any separated by commas | 3) | | | | | | | | | INVO | ENT DI | OR | | | |
| Case Description: UNDER REAL-LIF | | L STUDY- EVALUATION OF USE | N OF EFF | ICACY | AND SAFETY | Y OF | BOS | ULIF | = | PROLONGED INPATIENT HOSPITALISATION | | | | | | | |
| | | port (Post Authorization P) for protocol B187104 | | udy) red | eived from co | ontac | table | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | | LIFE | EATEN | ING | | | |
| | | II. SUSPECT | Γ DRUG | S(S) IN | FORMATI | ON | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (#1) Bosulif (BOSU | | | | | | | |) | | 20 | AB. | REA ATE A | CTION AFTER S | STOP | PPING | 6 | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | ROUTE(S) | OF ADMINISTRATION | TION | | | | | | YES | s 🔲 N | 10 | X N | A | |
| 17. INDICATION(S) FOR I | USE | | | | | | | | | 21 | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | |
| 18. THERAPY DATES(froi #1) 19-AUG-2020 | • | | |) Unkno | DURATION WN | | | | | | | YES | 5 🔲 N | ю [| ×Μ | A | |
| | | III. CONCOMITA | ANT DR | RUG(S |) AND HIS | TOF | RY | | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those use | ed to treat reac | etion) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT H From/To Dates Unknown to Ongo | | allergies, pregnancy with last mon Type of History / Notes Relevant Med Hist | D | escription | myeloid leuke | amia | (Chre | nic r | mve | loid I | باداما | aan | nia) | | | | |
| Chikhowh to Ongo | ang . | Tolovalit Wed Files | iory c | 211101110 | myclold leak | Jiiia | (01110 | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | , c | ioia i | Cuit | acii | iiu) | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | IV. MANUFA | ACTURI | ER INI | FORMATIO | NC | | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | ard East 01 UNITED STATE | S | | 26. REM | MARKS | | | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NA | ME AND ADDRES | S OF R | EPOR | ΓER | | | | | | | | | |
| | 2021196 | 327 | | | AND ADDRE | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPOR | T SOURCE | | NAME | E AND ADDRE | SS V | VITH | HELD |). | | | | | | | | |
| 25-AUG-2023 | HEALTH PROFES | SSIONAL OTHER: | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE FOLLOWUP: | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male subject was recruited in the above-mentioned study and received bosutinib (BOSULIF), since 19Aug2020 (ongoing) at 300 mg daily. The patient's relevant medical history included: "chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported. On 07Dec2020, the patient had COVID-19 test positive rated grade 2. The event was assessed as non-serious. No action was taken with bosutinib in response to the event. The patient had recovered from the event in Dec2020.

The investigator considered the event not related to bosutinib.

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

Follow-up(21Jul2023): 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, start date and dosage for suspect drug bosutinib.

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

Amendment: This follow-up report is being submitted to amend previously reported information: update of the event "covid positive" to "COVID-19 test positive".

Case Comment: In concurrence with the investigator, the reported COVID positive is assessed as unrelated to the study drug, bosutinib. The patient's immunocompromised state and the global pandemic provide an alternative explanation for the event. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

| | ; | # | Date | Test / Assessment / Notes | | 4 | Results | Normal High / Low |
|---|---|---|-------------|-----------------------------|---|---|----------|-------------------|
| _ | | 1 | 07-DEC-2020 | SARS-CoV-2 test Positive | 4 | | Positive | |

| | | | | | | | CIOMS FORM | | | | | |
|---|------------------------------|--|-------------------------|-------------------------|--------------------------|---------------------------------------|---|--|--|--|--|--|
| | | | | | | | | | | | | |
| SUSPEC | T ADVERSE F | REACTION REPO | | | | | | | | | | |
| | | | - | | | | | | | | | |
| | | | | | | | | | | | | |
| | | I. REA | CTION | INFOR | MATION | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 3a. WEIGHT 4-6 RE. 97.00 | ACTION ONSET Month Year | 8-12 CHECK ALL APPROPRIATE TO | | | | | |
| PRIVACY | FRAINGL | PRIVACY | Years | Male | | AUG 2020 | ADVERSE REACTION | | | | | |
| | | tests/lab data) toms if any separated by comma | is) | | | | PATIENT DIED | | | | | |
| Diarrhea [Diarrhoea | - | | | | | | INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | |
| Case Description: (UNDER REAL-LIF | | L STUDY - EVALUATIC DF USE | ON OF EF | FICACY | AND SAFETY OF | BOSULIF | | | | | | |
| This is a non-interv reporter(s) (Physici | ctable | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | | | | |
| | | | 4 | (200) | A Life and Line | · · · · · · · · · · · · · · · · · · · | LIFE | | | | | |
| | | | | | inued on Additional In | ormation Page) | ☐ THREATENING | | | | | |
| 14. SUSPECT DRUG(S) (in | oclude generic name) | II. SUSPEC | T DRU | G(S) IN | FORMATION | | 20. DID REACTION | | | | | |
| #1) Bosulif (BOSUT | , | tablet | | (Cont | inued on Additional In | icomotion Page) | ABATE AFTER STOPPING DRUG? | | | | | |
| 15. DAILY DOSE(S) | | | | 6. ROUTE(S) | OF ADMINISTRATION | ofmation Fage, | | | | | | |
| #1) 200 mg, daily | | | # | 1) Unkno | own | | YES NO NA | | | | | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | |
| 18. THERAPY DATES(from #1) 27-FEB-2020 / 1 | • | | 9. THERAPY 1) 5 mon | DURATION ths 23 days | | YES NO NA | | | | | | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HISTOR | Y | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those use | | | <i>,</i> - | - | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| From/To Dates | | allergies, pregnancy with last mo Type of History / Notes | | Description | | | | | | | | |
| Unknown to Ongoin | ng | Relevant Med His | story | Chronic | myeloid leukemia (0 | Chronic myeloi | d leukaemia) | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | S OF MANUFACTURER | IV. IVIAINOI | AUTUI | 26. REM | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | 1 UNITED STATES | 3 | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. N/ | ME AND ADDRESS OF RE | PORTER | | | | | | |
| | 2021196 | | | | E AND ADDRESS W | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE LITERATURE | | ┦ | | | | | | | | |
| 21-JUL-2023 | HEALTH PROFES | ш | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), first regimen from 27Feb2020 to 18Aug2020 at 200 mg daily and second regimen since 19Aug2020 (ongoing) at 300 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: DIARRHOEA (non-serious) with onset Aug2020, outcome "recovered" (03Jun2021), described as "Diarrhea". The action taken for bosutinib was dosage not changed.

Clinical course: In the report of 14Dec2020, some diarrhea during treatment with Bosulif 300 mg.

The reporter considered "diarrhea" related to bosutinib.

Follow-up (04Jun2021): New information received from study site includes: Subject's date of birth updated (age remains unchanged), diarrhea resolved on 03Jun2021.

Follow-up (20Apr2022): 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 details.

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

Follow-up (21Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

Updated information included: medical history, suspect drug data (dosage regimens), clinical course.

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

Case Comment: Assuming the plausible temporal association and considering the known safety profile of bosutinib, the Company cannot completely exclude the possible causality between the reported diarrhea and the administration of the suspect. The follow up information does not alter the previous company clinical evaluation.

| 14. SUSPECT DRUG(S) (include generic name) | 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 | 19-AUG-2020 / | |
| Regimen #2 | | | Ongoing; | |
| | | 7 | Unknown | |

| CIOMS FORM | | | | | | | | | | | | | | | | | | |
|---|---|------------------------------------|------------------|------------|---------------|--------|--------|------|---|---|---|-------------|---|--|--|--|--|--|
| SUSPECT | | | | | | | | | | | | | | | | | | |
| | | | | | | | П | | | | П | | | | | | | |
| I. REACTION INFORMATION | | | | | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | | 3. SEX | 3a. WEIGHT | 4-6 RF | ACTION | ONSE | г 8- | -12 (| CHECK | ALL | | | | | | |
| (first, last) PRIVACY | emale | ar 19 | APPROPRIATE TO | | | | | | | | | | | | | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) CATARACT [Cataract] INVOLVED OR PROLONGED INPATIENT | | | | | | | | | | | NIT | | | | | | | |
| | 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. | | | | | | | | | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | LIFE THREATENING | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI | - | tablet | | | | | | | 20 | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | | | YES [| NO | ⊠ N⁄ | λ | | | | | |
| 17. INDICATION(S) FOR USE #1) Chronic myeloid leukemia (Chronic myeloid leukaemia) | | | | | | | | 21 | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | |
| 18. THERAPY DATES(from/t #1) 04-SEP-2018 / C | | THERAPY) Unkno | | YES NO NA | | | | | | | | | | | | | | |
| | | III. CONCOMIT | ANT DR | UG(S | AND HIS | STOR | Υ | | | | | | | | | | | |
| 22. CONCOMITANT DRUG(S | S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat reac | tion) | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| From/To Dates | | allergies, pregnancy with last mor | D | escription | | : . / | Ob see | | الد:حام | | | | | | | | | |
| 04-JAN-2011 to Ongoing Relevant Med History Chronic myeloid leukemia (Chronic myeloid leukaemia) | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 | 26. REM | ARKS | | | | | | | | | | | | | | | | |
| Phone: 212 733 4045 | | | | | | | | | | | | | | | | | | |
| | 24b, MFR CO 2021196 | | | | ME AND ADDRES | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE LITERATURE | | NAME | AND ADDR | ESS W | 'ITHHE | ELD. | | | | | | | | | | |
| 27-SEP-2023 | | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 SINITIAL FOLLOWUP: | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 70-year-old female subject started to receive bosutinib (BOSULIF) from 04Sep2018 and ongoing at 200mg daily, for chronic myeloid leukemia. Medical history included chronic myeloid leukemia since 04Jan2011 and ongoing. Concomitant medications, if any, were not reported. On an unknown date in 2019, the subject experienced cataract. The event was rated as grade 2, reported as non-serious. No action was taken in response to this event for bosutinib. On an unknown date in Mar2019, the subject recovered from the event.

The investigator assessed the event cataract as unrelated to bosutinib and unrelated to concomitant medications.

Follow-up (03Dec2021): This is a follow-up non-interventional study report for protocol B1871047. Updated information: medical history added (chronic myeloid leukemia since 04Jan2011 and ongoing).

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

Follow-up (27Sep2023): This is a follow-up non-interventional study report for protocol B1871047 received from the clinical team. Updated information: suspect product data (onset date added for bosutinib, ongoing ticked off for bosutinib and dose added).

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

Follow-up (27Sep2023): This is a follow-up non-interventional study report for protocol B1871047 received from the investigator. Updated information: Drug data (bosutinib frequency added).

Case Comment: In concurrence with the investigator, the reported cataract is assessed as unrelated to the study drug, bosutinib. It is most likely an intercurrent condition in this elderly subject.

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| SUSPECT | Γ ADVERSE I | REACTION RE | EPORT | | | | | | | | | | | | | | _ |
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| | | I. F | REACTION | N INFOR | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | | 3. SEX | | 4-6 RE | EACTIO | ON ONS | ET Year | 8-12 | | HECK PPRO | | TE TO | | | |
| PRIVACY | FRANCE | PRIVACY | Year 47 Years | Female | 59.50 c |)4 | JAI | | Year 202 | | ΑI | OVER | SE RI | EACTIO | NC | | |
| 7 + 13 DESCRIBE REACTION Event Verbatim [PREFERRE COVID infection [Co | ED TERM] (Related sym | t tests/lab data) ptoms if any separated by | commas) | | | _ | _ | | | ر ع آ | | ATIEN' | ED O |)R | | | |
| Case Description: C UNDER REAL-LIFE | | | ATION OF E | FFICACY | AND SAFETY | OF I | BOSI | ULIF | | | Н | OSPIT | ALIS | D INPATATION PERSIST | | | |
| This is a non-interver reporter(s) (Physicia | | | | Study) red | eived from co | ntact | able | | | | OI DI | R SIGI ISABIL ICAPA | NIFIC | CANT OR | LIN | | |
| | | | | (Cont | inued on Additio | onal Ir | nforma | ation P | Page | , [| ן וו | FE HREAT | TENII | NG | | | |
| | | | DECT DDI | | IFORMATIC | | | | 3- | <u>′1 </u> | | | | | | | _ |
| 14. SUSPECT DRUG(S) (inc | clude generic name) | 11. 5051 | PECIDA | JG(S) IIV | IFURIVIATIO | JN_ | | | | 20. | DID RE | | | TODDU | | | _ |
| #1) Bosulif (BOSUT | INIB) Film-coated | tablet | | | | | | , | | | DRUG | | EK o | TOPPI | NG | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | 16. ROUTE(S) #1) Unkno | OF ADMINISTRATI | ION | | | | | ☐ YI | ES [|] NC | · 🛛 | NA | - | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | | | | | 7 | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | _ |
| 18. THERAPY DATES(from/ #1) MAR-2020 / Ong | • | | | 19. THERAPY #1) Unkno | | | | | | | Y | ES [|] NC | · 🛛 | NA | | |
| | | III. CONCC | OMITANT | DRUG(S |) AND HIST | TOR | Υ | | | • | | | | | | | |
| 22. CONCOMITANT DRUG(| (S) AND DATES OF ADM | | | $\overline{}$ | | | | | | | | | | | | | _ |
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| 23. OTHER RELEVANT HIS From/To Dates | | Type of History / N | Notes | Description | | <u> </u> | | | _ | _ | _ | _ | _ | | _ | _ | _ |
| Unknown to Ongoir | ng | Relevant Me | d History | Chronic | myeloid leuke | mia (| Chro | nic m | iyel | oid le | ukae | emia |) | | | | |
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| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | IV. IVI/ VI | NOIACIO | 26. REN | | /1 N | | | | | | | | | | | _ |
| Stella Pietrafesa 66 Hudson Boulevan New York, NY 10001 Phone: 212 733 404 | UNITED STATE | S | | | | | | | | | | | | | | | |
| | 24b. MFR CO | NATROL NO | | 25h NA | ME AND ADDRESS | OF DE | -DODT | | | | | | | | | | _ |
| | 2021216 | | | | E AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | T SOURCE | TURE | NAME | AND ADDRES | SS W | /ITHH | IELD. | | | | | | | | | |
| 28-SEP-2023 | HEALTH PROFES | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE | WUP: | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 47-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since Mar2020 (ongoing) at 500 mg daily. The patient's relevant medical history included: "Chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported.

On 04Jan2021, the patient experienced COVID infection, which was considered non-serious, grade 2. No action was taken in response to the event for bosutinib. The outcome of the event was recovered on 12Feb2021.

The investigator considered the event unrelated to the study drug or to concomitant medications.

Follow-up (20Dec2021): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047 (Study alias BOSEVAL). Updated information: event verbatim term updated to COVID infection, onset date updated to 04Jan2021.

Follow-up (28Jul2023): This is a non-interventional study follow up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: patient weight and medical history.

Follow-up (28Sep2023): This is a non-interventional follow-up study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information includes: start date and daily dose of BOSULIF and removal of laboratory test: SARS-CoV-2 test.

Case Comment: The reported event of COVID infection is assessed as unrelated to the study drug bosutinib (BOSULIF) or to concomitant medications. The event is possibly favored by the immunosuppressive state associated with the underlying malignancy.

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

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| 1. PATIENT INITIALS | 1a, COUNTRY | I. REAC | CTION 2a. AGE | INFORI | MATION 3a. WEIGHT | 465 | REACTIO | N ONSI | | 8-12 |) (L | IECK AL | | | | |
| PRIVACY | FRANCE | Day Month Year PRIVACY | 66 | Female | Unk | Day 22 | Monti | n , | Year 019 | 1 | AP | PROPRI | IATE | | ٧ | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER asthenia grade 1 anxiety grade 1 [/ | [Asthenia] | t tests/lab data) otoms if any separated by comma | s) | | | | | | | 7 | | TIENT D VOLVED OLONG OSPITALI | OR ED IN | | ENT | |
| | : OBSERVATIONA FE CONDITIONS (| L STUDY - EVALUATIO OF USE | ON OF EF | FICACY | AND SAFE | ETY OF | BOS | ULIF | | - | → OF | VOLVED R SIGNIF SABILITY | ICAN | SISTI T | ENT | |
| | | oort (Post Authorization P) for protocol B187104 | | study) rec | eived from | contac | ctable | | | | | CAPACIT | | | | |
| | | | | (Conti | nued on Add | litional | Informa | tion P | age) | |] LIF | REATEN | IING | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMAT | ΓΙΟΝ | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) JTINIB) Film-coated | tablet | | | | | | | | | | ACTION AFTER ? | | PPING | 3 | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | 6. ROUTE(S) 1) Unkno | OF ADMINISTR WN | RATION | | | | | YE | s 🔲 1 | NO | ⊠ ⊦ | IA | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | | REAP | ACTION PEAR AF RODUC | TER | ? | | |
| 18. THERAPY DATES(fro #1) 23-JUL-2019 | • | | | 9. THERAPY 1) Unkno | | | | | | | YE | es 🔲 r | NO | ⊠⊦ | IA | |
| | | III. CONCOMIT | ANT D | RUG(S) | AND HI | STO | RY | | | | | | | | | |
| #1) PANTOPRAZ #2) BISOPROLO #3) EXFORGE (, #4) LEVOTHYRO #5) MEDIATENS | ZOLE (PANTOPRA DL (BISOPROLOL) AMLODIPINE BES OX (LEVOTHYRO) | ILATE, VALSARTAN) (INE SODIUM) ; 2010 DROCHLORIDE] (URAI | / Ongoin ; Ongoin / Ongoin | ng g ng | | | | (Cont | tinuec | d on | Addit | ional Ir | nform | natio | on Pa | age) |
| 23. OTHER RELEVANT I From/To Dates Unknown Unknown | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mor Type of History / Notes Relevant Med His Relevant Med His | story | Description Arterial h | ypertension blesterolem | | | | rolae | emia | n) | | | | | |
| | | IV. MANUF | ACTUR | RER INF | ORMAT | ION | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | 01 UNITED STATES | 5 | | 26. REM | ARKS | | | | | | | | | | | |
| | 24b. MFR CC 2021235 | | | NAME | ME AND ADDRE | RESS \ | WITHH | ELD. | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 22-JUN-2023 | ER 24d. REPOR STUDY HEALTH PROFES | LITERATURE | | NAME | AND ADDF | RESS \ | WITHH | ELD. | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 66-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since 23Jul2019 (ongoing) at 200 mg daily. The patient's relevant medical history included: "Arterial hypertension" (unspecified if ongoing); "Hypercholesterolemia" (unspecified if ongoing); "Hypothyroidism" (unspecified if ongoing); "Fibromyalgia" (unspecified if ongoing). Concomitant medication(s) included: PANTOPRAZOLE oral taken for pain prophylaxis, start date: 08Feb2019 (ongoing); BISOPROLOL oral taken for hypertension (ongoing); EXFORGE oral taken for hypertension (ongoing); LEVOTHYROX oral taken for hypothyroidism, start date: 2010 (ongoing); MEDIATENSYL [URAPIDIL HYDROCHLORIDE]; PRAVASTATIN; VITAMIN B12 [CYANOCOBALAMIN].

The following information was reported: ANXIETY (non-serious) with onset 22Aug2019, outcome "recovered" (Aug2019), described as "anxiety grade 1"; ASTHENIA (non-serious) with onset 16Dec2019, outcome "recovered" (13Dec2021), described as "asthenia grade 1". The action taken for bosutinib was dosage not changed.

The reporter considered "asthenia grade 1" and "anxiety grade 1" not related to bosutinib.

Follow-up (06Dec2022): New information received from investigational site via CRO.

Updated information included: reporter's details, Other Relevant History, Primary Regimen for suspect drug captured (start date, dose, unit, frequency), concomitant medications coded, outcome and stop date for event, causality for asthenia provided.

Follow-up (22Jun2023): New information received from the clinical team.

Updated information: concomitant drug data (updated dose, route, and indication for amlodipine besilate, levothyroxine sodium, and bisoprolol; updated dose, start date, and indication for pantoprazole), company causality confirmed as related for event asthenia.

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

Case Comment: The Company cannot completely exclude the possible causality between the reported asthenia and the administration of bosutinib, based on the reasonable temporal association and the known safety profile of the suspect. Conversely, the reported anxiety is unrelated to bosutinib.

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

#5) MEDIATENSYL [URAPIDIL HYDROCHLORIDE] (URAPIDIL HYDROCHLORIDE) ; Unknown

#7) VITAMIN B12 [CYANOCOBALAMIN] (CYANOCOBALAMIN) ; Unknown

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|----------------------------------|
| Unknown | Relevant Med History | Hypothyroidism (Hypothyroidism); |
| Unknown | Relevant Med History | Fibromyalgia (Fibromyalgia); |

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| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | |
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| | | | | | | | 14 | | | | | | | | | |
| | | I. REA | CTION | INFOR | MATION | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE 66 | 3. SEX | 3a. WEIGHT Unk | 4-6 R Day | EACTIO Month | | T ′ear | 8-12 | API | ECK ALL PROPRIA VERSE F | ATE TO | ON | | |
| PRIVACY | _ | PRIVACY | Years | Female | 0 | 4 | _ | 20 | 019 | | AD | VERSE | KEACTI | OIN | | |
| HEMORRHOIDS | TION(S) (including relevant RED TERM) (Related symp grade 2 [Haemorrh grade 1 [Pelvic disa | • | s) | | | | | | | 7 |] INV PR | OLVED OLONGE | OR ED INPA | | ΙΤ | |
| | : OBSERVATIONA FE CONDITIONS (| L STUDY- EVALUATION OF USE | N OF EF | FICACY A | AND SAFET | Y OF | BOSL | JLIF | | | OR | OLVED I SIGNIFI | CANT | TEN | Т | |
| | | oort (Post Authorization P) for protocol B187104 | | Study) rec | eived from c | contac | table | | | | INC | CAPACIT | | | | |
| | | | | (Conti | nued on Addit | tional I | nforma | tion Pa | age) | |] LIF | E REATEN | ING | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMATI | ION | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) JTINIB) Film-coated | tablet | | | | | | | | Α | | ACTION AFTER S | | NG | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | 6. ROUTE(S) #1) Unkno | OF ADMINISTRA WN | ATION | | | | | YE | s 🔲 N | • X | NA | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | R | REAPP | ACTION EAR AFT RODUCT | | | | |
| 18. THERAPY DATES(fro #1) 23-JUL-2019 | • | | | 9. THERAPY #1) Unkno | | | | | | [| YE | s 🔲 N | • × | NA | | |
| | | III. CONCOMIT | ANT D | RUG(S) | AND HIS | STOF | RΥ | | | | | | | | | |
| | JG(S) AND DATES OF ADM | MINISTRATION (exclude those use ZOLE) ; Ongoing | ed to treat re | eaction) | | | | | | | | | | | | |
| #2) BISOPROLO | L (BISOPROLOL) | | · Ongoin | a | | | | | | | | | | | | |
| #4) LEVOTHYRO | OX (LEVOTHYRO) | (INE SODIUM) ; 2010 DROCHLORIDE] (URA | / Ongoir | ng | | | | | | | | | | | | |
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| From/To Dates | | allergies, pregnancy with last mo Type of History / Notes | · | Description | , mortonoion | /I bana | , rtono | ion) | | | | | | | | |
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| | | IV. MANUF | ACTUF | RER INF | ORMATION | ON | | | | | | | | | | |
| 24a. NAME AND ADDRE Pfizer Inc | SS OF MANUFACTURER | | | 26. REM | ARKS | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulev New York, NY 100 Phone: 212 733 40 | 01 UNITED STATES | 5 | | | | | | | | | | | | | | |
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| | 24b. MFR CC 2021253 | | | | ME AND ADDRES AND ADDRI | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPORT | T SOURCE | | NAME | AND ADDRI | ESS V | /ITHH | ELD. | | | | | | | | |
| 06-DEC-2022 | ₩ HEALTH PROFES | Ш | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 66-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since 23Jul2019 (ongoing) at 200 mg daily. Ongoing medical histories included arterial hypertension, hypothyroidism, hypercholesterolemia, and fibromyalgia. Concomitant medications included pantoprazole taken for an unspecified indication from an unspecified start date and ongoing; bisoprolol taken for an unspecified indication from an unspecified start date and ongoing; amlodipine besilate, valsartan (EXFORGE) taken for an unspecified indication from an unspecified start date and ongoing; levothyroxine sodium (LEVOTHYROX) taken for an unspecified indication from 2010 and ongoing; urapidil hydrochloride (MEDIATENSYL) taken for an unspecified indication, start and stop date were not reported; pravastatin taken for an unspecified indication, start and stop date were not reported; and cyanocobalamin (VIT B12) taken for an unspecified indication, start and stop date were not reported. The subject experienced hemorrhoids grade 2 (non-serious) on 2019 with outcome of recovered in 2019 and, pelvic heaviness grade 1 (non-serious) on 2019 with outcome of recovered in 2019. The action taken in response to the events for bosutinib was dose not changed.

The investigator assessed the events hemorrhoids and pelvic heaviness as unrelated to the study drug or concomitant medications.

Follow-up (06Dec2022): This is a non-interventional study follow-up report received from the investigational site via CRO for protocol B1871047.

Updated information: bosutinib therapy details (start date, dose description).

Case Comment: In concurrence with the reporting investigator, the reported events hemorrhoids and pelvic heaviness are considered intercurrent disease, unrelated to the administration of bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

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

#5) MEDIATENSYL [URAPIDIL HYDROCHLORIDE] (URAPIDIL HYDROCHLORIDE); Unknown

#7) VIT B12 (CYANOCOBALAMIN) ; Unknown

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|--------------------|-------------------------|---|
| Unknown to Ongoing | Relevant Med History | Hypercholesterolemia (Hypercholesterolaemia); |
| Unknown to Ongoing | Relevant Med History | Fibromyalgia (Fibromyalgia); |

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| PRIVACY | FRANCE | Day Month Year PRIVACY | 75 Years | Male | 97.00 | Day | Monti | 1 | Year | 1 | AF | PPROP DVERSI | RIAT | | N | |
| Water and sodiur | m retention [Fluid re | tention] | s) | | | | | | | 5 | J IN | ATIENT IVOLVE ROLON OSPITA | D OF GED | R INPAT | IENT | |
| | | | ON OF EF | FICACY | AND SAFET | Y OF | BOS | ULIF | | | OI | IVOLVE R SIGN ISABILI | IFIC/ | TNA | ENT | |
| | | | | tudy) rec | eived from co | ontac | table | | | | IN | ICAPAC | ITY | N. | | |
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| | IVACY FRANCE Day PMonth Year 75 Years Male 97.00 kg 11 MAR 2021 | | , | | | | | | | | | | | | | |
| | | tablet | | | | | | | | l . | | EACTIC E AFTE S? | | OPPIN | G | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | | | TION | | | | | ☐ Y | ES | NO | ⊠¹ | NΑ | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | 1 | REAP | EACTIC PEAR A TRODU | AFTE | | | |
| 18. THERAPY DATES(fr #1) 19-AUG-2020 | • | | | | | | | | | | ☐ Y | ES | NO | × | NA | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND HIS | TOF | RΥ | | | | | | | | | |
| 22. CONCOMITANT DRI | UG(S) AND DATES OF ADM | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | _ | | | |
| 23. OTHER RELEVANT From/To Dates Unknown to Ong | | allergies, pregnancy with last mo Type of History / Notes Relevant Med His | • | Description | myeloid leuke | amia I | Chro | nic m | مامر | id la | ukac | mia) | | | | |
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| | | IV. MANUF | ACTUR | ER IN | FORMATIO | NC | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | 01 UNITED STATES | 3 | | 26. REN | IARKS | | | | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURI 21-JUL-2023 | ER 24d. REPORT STUDY HEALTH PROFES | LITERATURE | | T. W. WILL | | -50 1 | | | | | | | | | | |
| DATE OF THIS REPORT | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), since 19Aug2020 at 300 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: FLUID RETENTION (non-serious), SODIUM RETENTION (non-serious) all with onset 11Mar2021, outcome "recovered" (Mar2021) and all described as "Water and sodium retention". Relevant laboratory tests and procedures are available in the appropriate section. The event water and sodium retention was considered not serious and rated grade 2. The subject fully recovered from water and sodium retention in Mar2021. The patient had bilateral voluminous oedema of lower limbs, tended, pitting, hepatojugular reflux. In response to water and sodium retention, bosutinib dose was reduced. The patient received furosemide (LASILIX) and had rapid cardiologic consultation for evaluation of left ventricular ejection fraction, repeat electrocardiogram. On 18Mar2021, cardiologist consultation was performed: water retention, iatrogenic / no cardiac cause was reported. The action taken for bosutinib was dosage reduced. Events did not recurred with drug reintroduction. Bosutinib reported as ongoing at the time of the report.

The investigator assessed the event as related to study drug bosutinib and unrelated to concomitant medication.

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

Follow-up (04Jun2021): New information received from investigator via CRO includes: subject's gender, lab data, outcome of the events and investigator comment.

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

Follow-up (20Apr2022): This is a report from a Non-Interventional Study from the investigator site via the CRO.

Updated information includes: action taken of bosutinib updated.

Follow-up (12Jul2023): This is a Non-Interventional Study follow up report from the investigator site via the CRO. Updated information: drug reintroduction details.

Follow-up(21Jul2023): 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, start date for suspect drug bosutinib.

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

Case Comment: Based on the available information, the company considers that a causal relationship between water and sodium retention and bosutinib cannot be excluded due to plausible temporal association and/or known drug safety profile. The follow-up information received does not alter the previous company clinical evaluation.

| 13 | I ah | Data |
|-----|------|------|
| 13. | Lab | Data |

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|---------------------------|--|-------------------|
| 1 | 18-MAR-2021 | Specialist consultation | water retention, iatrogenic / no cardiac cause | |

| | | | | | | | | | | | | CIO | DΝ | 1S F | OF | RM |
|---|--------------------------------------|------------------------------------|---------|----------------------|------------------------------|---------------|----------|---------------|------------|------------|---------------|-----------------------------------|-----------|----------------|----|----|
| | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPOR | RT | | | | | | | | | | | | | |
| | | | | | | Τ | | $\overline{}$ | П | Т | T | П | Т | Τ | | П |
| | | | | | | | 4 | | | | | | L | | | |
| | | I. REAC | CTION I | NFOR | MATION | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | _ | 4-6 RE | ACTIO | N ONS | ET Year | 8-12 | AF | HECK ALL PPROPRIA OVERSE F | ATE | | | |
| PRIVACY | _ | PRIVACY | Years | emale | kg | | MAI | ₹ 2 | 019 | 1 | AL | VERSER | (EAC | JIION | | |
| | | tests/lab data) | s) | | | | | | | [|] PA | TIENT DII | ED | | | |
| Cervical arthrosis | syndrome [Sleep a | | | | | | | | | Ţ | ⊸ PF | VOLVED (ROLONGE DSPITALIS | ED IN | | NT | |
| Headaches [Head Dry scalp [Dry sk | - | | | | | | | | | | | JOHNALIC | ,,,,,, | 014 | | |
| Scalp folliculitis [For Melanonychia of | Folliculitis] toes [Nail pigmenta | tion] | | | | | | | | [| OF DI | VOLVED F R SIGNIFI SABILITY | CAN OR | SISTE IT | NT | |
| | [Urinary tract infecti | | | | | 7 |) | | | | IN | CAPACIT | ľ | | | |
| | - | _ STUDY - EVALUATIO | NOE | (Canti | and an Addition | | . f = | D | \ | ۱, | 7 Lif | | | | | |
| Case Description | . OBSERVATIONAL | | | | nued on Additio | | norma | ition P | age) | L <u>-</u> | | IREATENI | NG | | | |
| 14. SUSPECT DRUG(S) | (include generic name) | II. SUSPEC | I DRUG | S(S) IN | FORMATIC | <u>N</u> | | | | | | ACTION | | | | |
| | JTINIB) Film-coated | tablet | | (Conti | nued on Additio | nal In | ıforma | ition P | age) | | ABATE DRUG | AFTER S | 3TOF | PPING | | |
| 15. DAILY DOSE(S) | | | | ROUTE(S) | OF ADMINISTRATI | $\overline{}$ | | | ugo, | 1 | П | ≣s ∏n | 10 | M _N | ٨ | |
| #1) 100 mg | | | #1 |) Unkno | wn | | | | | L | ш | -5 U'' | | ∠ | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | 4 | | | | | | 1 | REAPI | EACTION PEAR AFT RODUCT | | ? | | |
| 18. THERAPY DATES(fro #1) 12-NOV-2018 | • | | | THERAPY) 7 days | | | | | | | ☐ YE | ES □N | οΙ | X N | A | |
| | | III. CONCOMIT | ANT DE | NIG(S) | | TOR | · V | | | <u> </u> | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | IINISTRATION (exclude those use | | | ANDTHO | | . ! | | | | | | | | | |
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| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mor | | etc.) Description | | | | | | | | | | | | |
| Unknown | | type of motory victors | _ | occupaci. | | | | | | | | | | | | |
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| | | D/ MANUE | A OTUD | | ODMATIO | N.I. | | | | | | | _ | | | |
| | SS OF MANUFACTURER | IV. MANUFA | ACTUR | 26. REM | | IN | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | vord Foot | | | | | | | | | | | | | | | |
| | 01 UNITED STATES | 3 | | | | | | | | | | | | | | |
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| | 24b. MFR CO 2021319 | | | | ME AND ADDRESS AND ADDRES | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPORT | SOURCE | | NAME | AND ADDRES | SS W | 'ITHH | ELD. | | | | | | | | |
| 06-SEP-2023 | STUDY HEALTH PROFES | LITERATURE OTHER: | | | | | | | | | | | | | | |
| DATE OF THIS REPORT | | | | 1 | | | | | | | | | | | | |
| 27-FEB-2024 | ⊠ INITIAL | FOLLOWUP: | | | | | | | | | | | | | | |

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 63-year-old female patient received bosutinib (BOSULIF), first regimen from 12Nov2018 to 18Nov2018 at 100 mg, second regimen from 19Nov2018 to 25Nov2018 at 200 mg, third regimen from 26Nov2018 to 02Dec2018 at 300 mg and fourth regimen since 03Dec2018 (ongoing) at 400 mg. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: NAIL PIGMENTATION (non-serious) with onset Mar2019, outcome "recovering", described as "Melanonychia of toes"; SLEEP APNOEA SYNDROME (non-serious) with onset 21Jun2019, outcome "recovering", described as "mild sleep apnea syndrome"; DRY SKIN (non-serious) with onset Nov2019, outcome "recovered" (2020), described as "Dry scalp"; FOLLICULITIS (non-serious) with onset 26Dec2019, outcome "recovered" (2020), described as "Scalp folliculitis"; SPINAL OSTEOARTHRITIS (non-serious) with onset Apr2020, outcome "recovered" (2020), described as "Cervical arthrosis"; HEADACHE (non-serious) with onset Apr2020, outcome "recovered" (2020), described as "Headaches"; URINARY TRACT INFECTION (non-serious) with onset 26Oct2020, outcome "recovered" (17Nov2020), described as "Urinary infection"; SEBORRHOEIC KERATOSIS (non-serious) with onset 09Dec2021, outcome "recovering", described as "seborrheic keratosis". The action taken for bosutinib was dosage not changed.

The reporter considered "melanonychia of toes" related to bosutinib. The reporter considered "mild sleep apnea syndrome", "cervical arthrosis", "dry scalp", "scalp folliculitis", "urinary infection" and "seborrheic keratosis" not related to bosutinib. The reporter's assessment of the causal relationship of "headaches" 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.

Additional information: The event "Melanonychia of toes" and urinary infection were non-serious, grade 2, event mild sleep apnea syndrome was rated grade 1, cervical arthrosis was rated grade 2, dry scalp was rated grade 1, seborrheic keratosis rated grade 2, Scalp folliculitis was rated grade 1.

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

Follow-up (16Dec2021): This is a follow-up non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: Patient's gender, date of birth, height and weight added. Event verbatim term "Nail discoloration in the toes" was updated to "Melanonychia of toes", outcome updated to recovering, causality updated to related. New event added: urinary infection.

Follow-up (19Jan2022): This is a follow-up non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: patient's date of birth and age, new event "seborrheic keratosis" added, onset date of event mild sleep apnea syndrome and dry scalp, outcome of event mild sleep apnea syndrome updated from not recovered to recovering and of event Scalp folliculitis updated from not recovered to recovered, causality assessment for events mild sleep apnea syndrome, right scaputalgia, cervical arthrosis, dry scalp and scalp folliculitis.

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

Follow-up (06Sep2023): 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: therapy dates and regimens for bosutinib.

Follow-up (06Sep2023): 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 right scapulalgia was removed.

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

Case Comment: The events mild sleep apnea syndrome, cervical arthrosis, seborrheic keratosis, headaches, dry scalp, scalp folliculitis, and Melanonychia of toes (previously reported as nail discoloration)" more likely represent an intercurrent medical conditions, not related to the suspect product bosutinib. This case will be re-assessed should additional 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; | 200 mg; Unknown | Unknown | 19-NOV-2018 / |

| 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 | | | 25-NOV-2018; |
| | | | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg; Unknown | Unknown | 26-NOV-2018 / |
| Regimen #3 | | | 02-DEC-2018; |
| | | | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg; Unknown | Unknown | 03-DEC-2018 / |
| Regimen #4 | | | Ongoing; |
| | | | Unknown |

| | | | | | | | | | | | | | CIC | MS | FC | RN |
|--|---|---|--------------------|------------------------|----------------|---------|--------|-------|--------------------|-----------------|-------------------------|-------------|-------------------------------------|-----------------|------|----|
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | |
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| | | I DEA | CTION I | | MATION | | | | <u> </u> | | | <u> </u> | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. KEA 2. DATE OF BIRTH | CTION IN | 3. SEX | 3a. WEIGHT | 4-6 R | EACTIO | ON ON | SET | 8-1 | 2 CI | HECK | K ALL | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 75 Years | Male | 79.00 kg | Day | AP | | Year 202 | | | | OPRIA ⁻ RSE RI | TE TO EACTIO | N | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER cramps [Muscle s | | tests/lab data) toms if any separated by comm | as) | | | | | | | 1 | | | NT DIE | | | |
| | OBSERVATIONAL | L STUDY - EVALUATION | ON OF EFF | TICACY | AND SAFET | Y OF | BOS | SULIF | F | | ⊸ PI | ROLO | ONGE | INPAT | TENT | - |
| | | oort (Post Authorization P) for protocol B18710 | | ıdy) rece | eived from co | ontac | table | | | | — O | R SIC | VED P GNIFIC ILITY (ACITY | | ENT | |
| | | | | (Contir | nued on Additi | ional l | nform | ation | Page | _{e)} [| 그 片 | IFE HREA | ATENIN | IG | | |
| | | II. SUSPEC | T DRUG | (S) INI | FORMATI | ON | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (#1) Bosulif (BOSU | include generic name) TINIB) Film-coated | tablet | | (Contir | nued on Additi | ional l | nform | ation | Page | | DID RI ABATI DRUG | EAF | | TOPPIN | IG | |
| 15. DAILY DOSE(S) #1) 100 mg, daily | | | | ROUTE(S) () Unknow | OF ADMINISTRAT | TION | | | | | × | ÆS [| NC | | NA | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | 21. | | PEAF | TION R AFTE DUCTIO | | | |
| 18. THERAPY DATES(fro #1) 06-JUL-2019 / | | | | THERAPY (| | | | | | | ПΥ | ÆS [| NC | | NA | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | TOF | RY | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | sed to treat react | tion) | | | | | | | | | | | | |
| | | | , | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT H From/To Dates Unknown | IISTORY. (e.g. diagnostics, | allergies, pregnancy with last m Type of History / Notes | | tc.) escription | | | | | | | | | | | | |
| Officiowif | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTURE | ER INF | ORMATIC | ON. | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc | SS OF MANUFACTURER | | | 26. REM. | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | | ME AND ADDRES | | | | | | | | | | | |
| | 2021319 | 256 | | | AND ADDRE | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPORT | SOURCE LITERATURE | | NAME | AND ADDRE | :55 V | VIIHH | 1ELD |). | | | | | | | |
| 28-JUL-2023 | HEALTH PROFES | SSIONAL OTHER: | | _ | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), first regimen since 06Jul2019 at 100 mg daily, second regimen since 16Jul2019 at 200 mg daily, third regimen since 23Jul2019 at 300 mg daily, fourth regimen since 01Aug2019 at 400 mg daily, fifth regimen since 21Aug2019 at 300 mg daily, sixth regimen since 24Apr2020 at 200 mg daily and seventh regimen from 05Nov2020 to 20Oct2022 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: MUSCLE SPASMS (non-serious) with onset Apr2020, outcome "recovered" (Apr2020), described as "cramps". The action taken for bosutinib was dosage reduced.

The causality for event cramps was considered as related to bosutinib by the investigator Causality of hypertension was considered unrelated to bosutinib by the investigator.

Follow-up (02Jun2022): This is a follow-up for a non-Interventional Study source reporting the subject's age and gender, additional event of hypertension, causality assessment between events and study product, and information regarding event outcome.

Follow-up (17Jul2023): This is a follow-up for a non-Interventional Study source from the investigational site via the CRO. Updated information: event hypertension removed.

Follow-up (28Jul2023): This follow-up is received from the clinical team included query response regarding rational of deletion of event hypertension on 11May2021: no aggravated or unbalanced hypertension, confirmed by the investigator. Change of treatment for hypertension following a stock shortage of urapidil (MEDIATENSYL). Dosage regimen of bosutinib updated.

Case Comment: The Company cannot completely exclude the possible causality between the reported cramps and the administration of bosutinib, based on the reasonable temporal association and lacking alternative explanations. 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 | 200 mg, daily; Unknown | Unknown | 16-JUL-2019 / Unknown; Unknown |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3 | 300 mg, daily; Unknown | Unknown | 23-JUL-2019 / Unknown; Unknown |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #4 | 400 mg, daily; Unknown | Unknown | 01-AUG-2019 / Unknown; Unknown |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #5 | 300 mg, daily; Unknown | Unknown | 21-AUG-2019 / Unknown; Unknown |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #6 | 200 mg, daily; Unknown | Unknown | 24-APR-2020 / Unknown; Unknown |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #7 | 300 mg, daily; Unknown | Unknown | 05-NOV-2020 / 20-OCT-2022; 1 year 11 months 16 days |

| | | | | | CIOMS FORM | | | | |
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| SUSPECT | ADVERSE F | REACTION REPOR | RT. | | | | | | |
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| | | I. REAC | TION I | INFORMATION | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX 3a. WEIGHT 4-6 REACTION ONSET | 8-12 CHECK ALL APPROPRIATE TO | | | | |
| PRIVACY | FRANCE | PRIVACY Year | 51 Years | Female 98.00 Day Month FEB 2020 | ADVERSE REACTION | | | | |
| 7 + 13 DESCRIBE REACTIO Event Verbatim [PREFERRE COVID-19 infection | | tests/lab data) toms if any separated by commas | s) | | PATIENT DIED INVOLVED OR | | | | |
| Case Description: C UNDER REAL-LIFE | PROLONGED INPATIENT HOSPITALISATION INVOLVED PERSISTENT | | | | | | | | |
| This is a non-interve reporter(s) (Physicia | OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | |
| | | II. SUSPECT | T DRUG | G(S) INFORMATION | | | | | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI | - | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | |
| 15. DAILY DOSE(S) #1) UNK | | | | ROUTE(S) OF ADMINISTRATION 1) Unknown | YES NO NA | | | | |
| 17. INDICATION(S) FOR US #1) Unknown | SE . | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | |
| 18. THERAPY DATES(from/t #1) Ongoing | to) | | | . THERAPY DURATION 1) Unknown | YES NO NA | | | | |
| | | III. CONCOMITA | ANT DE | RUG(S) AND HISTORY | | | | | |
| 22. CONCOMITANT DRUG(S | S) AND DATES OF ADM | INISTRATION (exclude those use | d to treat rea | ction) | | | | | |
| | | | | | | | | | |
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| | | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown Relevant Med History none () REFER TO PREVIOUS AEs | | | | | | | | | |
| IV. MANUFACTURER INFORMATION | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | d East UNITED STATES | 7 | _ | 26. REMARKS | | | | | |
| | 24b. MFR COI | NTROL NO. | | 25b. NAME AND ADDRESS OF REPORTER | | | | | |
| | 20213192 | 277 | | NAME AND ADDRESS WITHHELD. | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE LITERATURE | | NAME AND ADDRESS WITHHELD. | | | | | |
| 07-SEP-2022 | HEALTH PROFES | SIONAL OTHER: | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 51-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), (ongoing). The patient had no relevant medical history. The patient's concomitant medications were not reported.

The following information was reported: COVID-19 (non-serious) with onset Feb2020, outcome "recovered" (Mar2020), described as "COVID-19 infection". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed.

The reporter considered "covid-19 infection" not related to bosutinib.

Additional information: No concomitant medication was reported. Event COVID-19 infection was rated grade 1 and considered not serious. The investigator assessed this event as unrelated to concomitant drug also.

Investigator's comment: patient was infected by COVID-19 in Feb-Mar2020 with a SARS-Cov-2 serology positive on 25Apr2020 and IgM on 18Jun2020. The patient had not yet did her IgG seroconversion. A PCR test was lately performed in May2020 which was negative.

Follow-up (05Apr2022): This is a follow-up to a non-interventional study for protocol B1871047. Updated information: patient's partial birthdate, gender, height and weight, medical history (no), reaction data (event term, onset date, causality assessment), investigator's comment.

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

Follow-up (07Sep2022): 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: stop date for Covid-19 (Mar2020).

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

Case Comment: There is not a reasonable possibility to consider the reported COVID-19 infection is related to the administration of the suspect, 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 | 18-JUN-2020 | SARS-CoV-2 antibody test Positive | positive | |
| 2 | 25-APR-2020 | SARS-CoV-2 test Positive | positive | |
| 3 | MAY-2020 | SARS-CoV-2 test | negative | |

| | | | | | | | | | | | | CIC | MS | FΟ | RM |
|---|------------------------------|---|------------------|--------------------|-------------------|----------|---------|----------|------------|------|--------------|---|-----------------|--------|----|
| 2000 | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE I | REACTION REPO | RT | | | | | | | | | | | | |
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| | | | | | | \dashv | 7 | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION II | NFOR 3. SEX | MATION 3a. WEIGHT | 4-6 RE | ACTION | ONSE | т Тя | 8-12 | CHE | CK ALL | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 75 | emale | — | Day | Month | Ye | ear 020 | 0 12 | APP | ROPRIA | TE TO EACTIO | N | |
| | | t tests/lab data) otoms if any separated by comma sive anxiety syndrome v | | grade 1 | [Mixed anxio | ety and | l depr | essiv | е | | INVO PROI | ENT DIE |)R D INPAT | IENT | |
| UNDER REAL-LIF | rentional study re | port (Post Authorization | Safety St | | | | | JLIF | | | OR S DISA | LVED P IGNIFIC BILITY (PACITY | OR | ENT | |
| reporter(s) (Physician and Other HCP) for protocol B1871047. (Continued on Additional Information Page | | | | | | | | | (ap. | | LIFE | EATENII | VIC. | | |
| | | " CHOREO | T DDI 10 | | | | IOI max | luii i u | (ge) | | Ima | ALEIM | NG | | |
| 14. SUSPECT DRUG(S) (| include generic name) | II. SUSPEC | TDRUG | i(S) IN | FORMATI | ON | | | 12 | | | CTION | | | |
| #1) Bosulif (BOSU | | tablet | | | | | | | | AB | | | TOPPIN | G | |
| 15. DAILY DOSE(S) #1) 300 mg/ 200 mg, alternately 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | | | | YES | NO | | NA | |
| 17. INDICATION(S) FOR USE #1) chronic myeloid leukemia (Chronic myeloid leukaemia) | | | | | | | | | | | APPE | CTION AR AFTI DDUCTI | | | |
| 18. THERAPY DATES(from #1) Unknown / 30- | · | | | THERAPY) Unkno | Duration wn | | | | | | YES | □ NO | ⊃ ⊠ ı | NA | |
| | | III. CONCOMIT | | | AND HIS | TOR | Y | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those use | ed to treat reac | tion) | | | | | | | | | | | |
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| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown Relevant Med History none () | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | ard East 01 UNITED STATE: | 7 | | 26. REM | | <u>-</u> | | | | | | | | | |
| | 24b. MFR CC | NTROL NO. | | 25b. NA | ME AND ADDRES | S OF RE | PORTER | R | | | | | | | |
| | 2021319 | 297 | | NAME | AND ADDRE | ESS W | ITHHE | LD. | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPOR | T SOURCE | | NAME | AND ADDRE | ESS W | ITHHE | LD. | | | | | | | |
| 30-NOV-2023 | HEALTH PROFES | SSIONAL OTHER: | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old female patient received bosutinib (BOSULIF), till 30Jun2022 at alternate day (300 mg/ 200 mg, alternately) for chronic myeloid leukaemia. The patient had no relevant medical history. The patient's concomitant medications were not reported. The following information was reported: MIXED ANXIETY AND DEPRESSIVE DISORDER (non-serious) with onset 2020, outcome "not recovered", described as "anxio depressive syndrome/ Depressive anxiety syndrome was rated grade 1". The action taken for bosutinib was dosage not changed.

Additional information: There was no mention of progression of the neoplasm.

The reporter considered "anxio depressive syndrome/ depressive anxiety syndrome was rated grade 1" not related to bosutinib.

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

Follow-up (07Sep2023): This is a follow up report combining information from duplicate reports 2021319297 and PV202200059001. The current and all subsequent follow up information will be reported under manufacturer report number 2021319297. The new information reported from a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047 from case PV202200059001 included: new reporter, patient data, suspect product data, Action taken, relationship and clinical information.

Follow-up (24Oct2023): 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: there was no mention of progression of the neoplasm.

Follow-up (14Nov2023): This is a follow-up report from the clinical team Following reconciliation.

Updated information includes: event "lack of efficacy" was removed as no notion of neoplasm progression in the patient's record (site staff replied), event "Cutaneous xerosis" was removed as it was a symptom of scalp itching (refers to AER#2020493488).

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

Follow-up (30Nov2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: event seborrheic keratosis deleted.

Case Comment: Based on available information, the reported anxio depressive syndrome/ Depressive anxiety syndrome is considered unrelated to the study drug, bosutinib.

| | | | | | | | | | CIO | OMS | FORM |
|---|---|--|-------------------|----------------------|----------------|-----------------|-----------|-----|-----------------------------------|--------|------|
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| SUSPECT | Γ ADVERSE F | REACTION REPO | RT | | | | | | | | |
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| | | I. REA | CTION I | NFOR | MATION | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION ON | | | CHECK ALL | | |
| PRIVACY | FRANCE | PRIVACY Year | 63 Years | Male | 81.00 D kg | AUG Month | Year 2019 | | ADVERSE I | | N |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERRI ACHILLES TENDO | | tests/lab data) toms if any separated by comma ndon rupture] | as) | | | | | | PATIENT DI NVOLVED PROLONGE | OR | ENIT |
| Case Description: (UNDER REAL-LIFE | | _STUDY - EVALUATION F USE | ON OF EF | FICACY | AND SAFETY | OF BOSULI | IF | | HOSPITALI: | SATION | |
| This is a report fron | This is a report from a Non-Interventional Study source for Protocol B1871047 (Study alias BOSEVAL). OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATIC | N | | | | | |
| 14. SUSPECT DRUG(S) (in #1) Bosulif (BOSUT | , | tablet | | | | | | | REACTION TE AFTER : IG? | | 3 |
| 15. DAILY DOSE(S) #1) UNK | OF ADMINISTRATION | ON | | | YES N | 0 X N | IA | | | | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | |
| 18. THERAPY DATES(from #1) Ongoing | /to) | | | THERAPY) Unkno | DURATION WN | | | | YES N | o 🛛 N | IA |
| | | III. CONCOMIT | TANT DF | RUG(S |) AND HIST | ORY | | | | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | INISTRATION (exclude those us | sed to treat read | ction) | | | | | | | |
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| From/To Dates | STORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | |
| Unknown | | | | | | | | | | | |
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| IV. MANUFACTURER INFORMATION | | | | | | | | | | | |
| 24a. NAME AND ADDRESS | OF MANUFACTURER | IV. WANUF | ACTUR | 26. REN | | IN | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | UNITED STATES | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NA | ME AND ADDRESS | OF REPORTER | | | | | |
| | 2021325 | | | | AND ADDRES | | D. | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE | | | | | | | | | |
| 23-MAR-2021 | HEALTH PROFES | ш | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 63-years-old male patient received bosutinib (BOSULIF), via an unspecified route of administration from an unspecified date and ongoing, at unspecified dose and frequency for an unspecified indication. The patient's medical history and concomitant medications were not reported. The patient experienced achilles tendon rupture on Aug2019. The event rupture of Achille's heel was reported serious as hospitalization with grade 2. The action taken in response to the event for bosutinib was dose not changed. The outcome of event was recovered on 16Aug2019. According to the investigator, the event was unrelated to bosutinib or to concomitant drugs.

Case Comment: The reported event rupture of Achille's heel was reported serious as hospitalization and is unrelated to the study drug, bosutinib (BOSULIF). This case will be reassessed when further information is provided.

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| SUSPEC | T ADVERSE I | REACTION REPO | RT | | | | | | | | | | | | | | |
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| | | I. REA | CTION I | NFOR | MATION | | 9 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 R | EACTION | | SET Yea | 8- ⁻ | A | APPI | CK ALI | IATE | | | |
| PRIVACY | FRANCE | PRIVACY | 68 Years | Male | 103.00 kg | 13 | SE | | 201 | | A | ۹DV | 'ERSE | REA | CTIO | N | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER EXTRASYSTOLE | | nt tests/lab data) ptoms if any separated by comma | as) | | | 7 | | | | | | INVC | DLVED | OR | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | TION RSIST | | | | | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. A 68-year-old male patient received bosutinib (BOSULIF), via an unspecified route of administration from 14Dec2017 to ongoing at 500 mg | | | | | | | | | | | | | | | | | |
| | (Continued on Additional Information Page) | | | | | | | | NING | ; | | | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) TINIB) Film-coated | | | | | | | , | | 20 | . DID F ABAT DRU | TE A | CTION AFTER | STO |)PPIN | G | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/da | | | | | | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 14-DEC-2017 | | | | . THERAPY I) Unkno | DURATION DWN | | | | | | | YES | i 🔲 | NO | ×. | NA | |
| | | III. CONCOMIT | TANT DF | RUG(S | AND HIS | STOF | RY_ | | | | | _ | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | | | | | | | | | | | | | | | |
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| From/To Dates | HISTORY. (e.g. diagnostics | , allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | _ | | _ | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | | ACTOR | 26. REN | | OIN | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATE | S | | | | | | | | | | | | | | | |
| | 24h MER CO | ONTROL NO | | 25h NA | AAT AND ADDRE | 20 OE B | -CDODI | | | | | | | _ | | | |
| | 24b. MFR CC 2021325 | | | | ME AND ADDRE | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | | | NAME | E AND ADDR | ESS V | VITHE | HELD. | | | | | | | | | |
| 16-MAY-2022 | STUDY HEALTH PROFE | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

daily for an unspecified indication. The patient's medical history and concomitant medications were not reported. The patient experienced extrasystole on 13Sep2019. The action taken in response to the event for bosutinib was dose not changed. The outcome of event was not recovered. The reporter considered event extrasystoles was non-serious, grade 1, unrelated to the study drug or concomitant medications.

Follow-up (28Feb2022): This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047. Updated information included: The event "extrasystoles" was considered as grade 1.

Follow-up (16May2022): new information received from the investigator via the CRO. Updated information included: suspect product data (dose, frequency, and dates) added

Case Comment: The company concurs with the investigator that the event Extrasystoles was unrelated to bosutinib. Of note, the action taken in response to the event for bosutinib was dose not changed. The follow-up information received does not alter the previous company clinical evaluation.

| | CIOMS FORM | | | | | | | | | | |
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| SUSPEC | T ADVERSE I | REACTION REPO | RT | | | | | | | | |
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| | | I. REA | CTION | INFOR | MATION | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION C | | | CHECK ALL | | |
| PRIVACY | FRANCE | Day PRIVACY Year | 67 Years | Male | 86.00 ^E | Day Month | Year 2019 | 1 | ADVERSE I | | N |
| Other Serious Crit Retinal haemorrha | eria: Medically Sig age [Retinal haem | | as) | | | | | 00 | PATIENT DI INVOLVED PROLONGI HOSPITALI | OR ED INPATII | ENT |
| 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 | | | | | | | | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) | | | | | | | | | | | |
| | | | | (Cont | inued on Addition | onal Information | n Page) | | THREATEN | ING | |
| | | II. SUSPEC | T DRUC | G(S) IN | IFORMATIO | ON | | | | | |
| 14. SUSPECT DRUG(S) (#1) Bosulif (BOSU | , | tablet | | | | | | ABA | REACTION ATE AFTER UG? | | 3 |
| 15. DAILY DOSE(S) #1) UNK | | | | | | | | | YES N | IO 🛛 N | IA |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | RE/ | REACTION APPEAR AF NTRODUCT | TER | |
| 18. THERAPY DATES(from #1) Ongoing | m/to) | | | . THERAPY | DURATION | | | | YES N | IO 🛛 N | IA |
| | | III. CONCOMIT | | |) AND HIS | TORY | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | ed to treat rea | ction) | | | | | | | |
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| From/To Dates | IISTORY. (e.g. diagnostics | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | |
| Unknown | | | | | | | | | | | |
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| | | | | | | | | | | | |
| IV. MANUFACTURER INFORMATION | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUF | ACTUR | 26. REI | | VIN . | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | |
| | 24b. MFR CC | NTROL NO. | | | ME AND ADDRESS | | | | | | |
| | 2021333 | 797 | | | E AND ADDRE | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPOR | SOURCE LITERATURE | | NAMI | E AND ADDRE | SS WITHHEL | - υ. | | | | |
| 14-NOV-2023 | HEALTH PROFES | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

for protocol B1871047.

A 67-year-old male patient received bosutinib (BOSULIF), (ongoing). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: RETINAL HAEMORRHAGE (medically significant) with onset 2019, outcome "recovered" (2020); IRON DEFICIENCY ANAEMIA (non-serious) with onset Oct2019, outcome "recovered" (04Dec2019), described as "IRON DEFICIENCY ANEMIA". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of retinal haemorrhage. The patient experienced retinal haemorrhage on an unspecified date in 2019, rated grade 2, serious (since it required surgery); and iron deficiency anemia in Oct2019, rated grade 3, non-serious. The reporter considered the events were unrelated to the study drug bosutinib. Comment: Hemorrhage operated (no trace of hospitalization).

The reporter considered "retinal haemorrhage" and "iron deficiency anemia" not related to bosutinib.

Follow-up (07Feb2022): This is a follow-up report from a non-interventional study report (Post Authorization Safety Study) for protocol B1871047

Updated information: outcome of both events was updated and stop date added.

Amendment: This follow-up report is being submitted to amend previous information: gender was updated to male.

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

Updated information includes: Seriousness of event retinal haemorrhage was confirmed as serious.

Case Comment: In agreement with the investigator, the reported retinal haemorrhage and iron deficiency anemia are most likely related to intercurrent or underlying conditions and unrelated to suspect drug bosutinib. The action taken of suspect drug was dose not changed and events were resolving.

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



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|--|--|--|-------------|-------------------------|--------------|-------|-------|------|-----------|------------|---------------|----------------------|-----------------------------|------------|-------------|-------|------|
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| SUSPEC | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | |
| | | | | | | | T | | | | T | | | | \top | Τ | Π |
| | | L RFA(| CTION | INIFOR | MATION | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | | _ | TION | _ | - | 8-12 | | ECK AL PROPR | | | | |
| PRIVACY | FRANCE | PRIVACY Year | 58 Years | Male | 70.00 kg | 06 | | AN | | ear)21 | | | VERSE | | | N | |
| Left renal colic [R | | t tests/lab data) otoms if any separated by commassis [Lithiasis] | s) | | | | | | | | | IN\ PR | TIENT D OLVED OLONG SPITAL | OR ED I | INPAT | ENT | |
| | : OBSERVATIONAI IFE CONDITIONS (| L STUDY - EVALUATIO OF USE | N OF EF | FICACY | AND SAFE | ETY C |)F B(| OSUI | LIF | | |] IN\ OR | OLVED | PEFICAL | RSIST NT | ENT | |
| 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) | | | | | | | | | | | | | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | |
| | 4. SUSPECT DRUG(S) (include generic name) 11) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | A | | ACTION AFTER ? | |)PPIN | G | | |
| 15. DAILY DOSE(S) | | | | | | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) chronic myeloid leukemia (Chronic myeloid leukaemia) | | | | | | | | | | | F | REAPF | ACTION PEAR AF RODUC | TER | | | |
| 18. THERAPY DATES(fro #1) 22-JAN-2019 | • | | |). THERAPY 1) Unkno | | | | | | | ا | YE | s 🔲 | NO | × I | √A | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND HI | STC | RY | | | | | | | | _ | _ | _ |
| #1) METFORMIN #2) VICTOZA (LI #3) TAHOR (ATC #4) APROVEL (II #5) PANTOPRAZ | N (METFORMIN) ; IRAGLUTIDE) ; 12 DRVASTATIN CALC RBESARTAN) ; 12 ZOLE (PANTOPRA | 2-APR-2018 / Ongoing |) / Ongoin | g | | | | (0 | Conti | nued | l on <i>i</i> | Addit | ional Ir | nfor | rmatic | on Pa | age) |
| From/To Dates Unknown to Ongo | 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown to Ongoing Relevant Med History currently treated Unknown to Ongoing Relevant Med History currently treated Relevant Med History currently treated Relevant Med History currently treated | | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION | | | | | | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | 01 UNITED STATES | 3 | | 26. REM | MARKS | | | | | | | | | | | | |
| | 24b. MFR CO 2021386 | | | | ME AND ADDRE | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 20-JUL-2023 DATE OF THIS REPORT | ₩ HEALTH PROFES | LITERATURE SSIONAL OTHER: | | | | | | | | | | | | | | | |
| 27-FEB-2024 | | | | | | | | | | | | | | | | | |

X INITIAL

7+13. DESCRIBE REACTION(S) continued

A 58-year-old male patient received bosutinib (BOSULIF), since 22Jan2019 (ongoing) at 400 mg daily for chronic myeloid leukaemia. The patient's relevant medical history included: "Diabetes" (ongoing), notes: currently treated; "Hypercholesterolemia" (ongoing), notes: currently treated; "Psoriasis" (ongoing), notes: currently treated; "Neo bladder" (ongoing); "Hypertension arterial" (unspecified if ongoing), notes: currently treated; "Nausea" (ongoing); "Diarrhea" (ongoing), notes: currently treated; "Kidney stones" (ongoing); "Appetite decreased" (unspecified if ongoing). Concomitant medication(s) included: METFORMIN taken for diabetes mellitus (ongoing); VICTOZA taken for diabetes mellitus, start date: 12Apr2018 (ongoing); TAHOR (ongoing); APROVEL taken for hypertension, start date: 12Apr2018 (ongoing); PANTOPRAZOLE taken for gastrooesophageal reflux prophylaxis, start date: 21Jan2019 (ongoing); AUGMENTINE [AMOXICILLIN;CLAVULANIC ACID] taken for pneumonia, start date: Feb2019, stop date: 14Feb2019; ROCEPHINE taken for pyrexia, nephritis, start date: Feb2019, stop date: 03Mar2019; ONDANSETRON taken for prophylaxis of nausea and vomiting, start date: 21Feb2019, stop date: 22Feb2019; PARACETAMOL taken for nephritis, start date: 20Feb2019, stop date: 22Feb2019; CERAT DE GALIEN taken for psoriasis (ongoing).

The following information was reported: RENAL COLIC (hospitalization) with onset 06Jan2021, outcome "recovered" (04Feb2021), described as "Left renal colic"; LITHIASIS (non-serious) with onset 04Feb2021, outcome "recovering", described as "Left intermittent asymptomatic lithiasis". The patient was hospitalized for renal colic (start date: 04Feb2021, discharge date: 15Mar2021, hospitalization duration: 39 day(s)). The patient underwent the following laboratory tests and procedures: examination: (Jan2021) discovery of left intermittent lithiasis; Ureteroscopy: (2021) unknown results. The action taken for bosutinib was dosage not changed..

The reporter considered "left renal colic" and "left intermittent asymptomatic lithiasis" not related to bosutinib.

Additional information: Left renal colic and left intermittent asymptomatic lithiasis were grade 2. The patient was hospitalized from 12Jan2021 to 13Jan2021 for examination and discovery of left intermittent lithiasis and was hospitalized from 04Feb2021 to 15Mar2021 for ureteroscopy.

Follow-up (25Jan2022 and 28Jan2022): This is a follow-up report for a Pfizer sponsored interventional study B1871047. Updated information includes reaction data (onset date of "left renal colic" updated from "08Jan2021" to "06Jan2021", verbatim of "intermittent asymptomatic lithiasis" updated to "right intermittent asymptomatic lithiasis" and outcome updated from "not resolved" to "recovered on 15Mar2021"), medical history and concomitant drugs (previously not reported), seriousness criteria (updated to serious due to hospitalization for event "left renal colic"), and lab data.

Follow-up (22Mar2022). This follow-up is received from the study coordinator. Updated information: verbatim of the event 'right intermittent asymptomatic lithiasis' was updated to 'left intermittent asymptomatic lithiasis'

Follow-up(23Feb2023): New information received from investigational site via CRO included: outcome for 'left intermittent asymptomatic lithiasis' updated to recovering (stop date deleted)

Follow-up (20Jul2023): This is a non-interventional study report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047.

Updated information included: updated start date of Bosulif (from 04Mar2020 to 22Jan2019).

Case Comment: Both reported left renal colic and intermittent asymptomatic lithiasis are deemed intercurrent diseases, unrelated to bosutinib. The follow up information received does not alter the previous company clinical evaluation.

13. Lab Data

| | # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|--|---|----------|---------------------------|--|-------------------|
| | 1 | JAN-2021 | Investigation | discovery of left intermittent lithiasis | |
| | 2 | 2021 | Ureteroscopy | unknown results | |

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

#7) AUGMENTINE [AMOXICILLIN:CLAVULANIC ACID] (AMOXICILLIN, CLAVULANIC ACID) ; FEB-2019 / 14-FEB-2019

#8) ROCEPHINE (CEFTRIAXONE SODIUM); FEB-2019 / 03-MAR-2019

#9) ONDANSETRON (ONDANSETRON) ; 21-FEB-2019 / 22-FEB-2019

#10) PARACETAMOL (PARACETAMOL) ; 20-FEB-2019 / 22-FEB-2019

27-Feb-2024 14:27

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

#11) ACUPAN (NEFOPAM HYDROCHLORIDE) ; 21-FEB-2019 / 22-FEB-2019

#12) CERAT DE GALIEN (BEESWAX WHITE, PRUNUS DULCIS OIL) ; Ongoing

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|--------------------|--|--|
| Unknown to Ongoing | Relevant Med History currently treated | Psoriasis (Psoriasis); |
| Unknown to Ongoing | Relevant Med History | Bladder repair (Bladder repair); |
| Unknown | Relevant Med History currently treated | Hypertension arterial (Hypertension); |
| Unknown to Ongoing | Relevant Med History | Nausea (Nausea); |
| Unknown to Ongoing | Relevant Med History currently treated | Diarrhea (Diarrhoea); |
| Unknown to Ongoing | Relevant Med History | Kidney stones (Nephrolithiasis); |
| Unknown | Relevant Med History | Appetite decreased NOS (Decreased appetite); |

| | | | | | | | | CIOMS FOR |
|--|---|--|------------------|------------------------|----------------|-----------------|---------|---|
| | | | | | | | | |
| SUSPEC: | T ADVERSE F | REACTION REPO | RT | | | | | |
| 000.20 | TADVERGET | CEAGIION NEI O | | | | 1 1 | | |
| | | | | | | | | |
| | | I RFA | CTION | INFOR | MATION | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | | 4-6 REACTION | N ONSET | 8-12 CHECK ALL APPROPRIATE TO |
| PRIVACY | FRANCE | PRIVACY Year | 73 Years | Male | | ay Month JUL | | ADVEDSE DEACTION |
| | oral bridge occlusi | tests/lab data) stoms if any separated by comma on [Vascular graft occlu ncreased] | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| UNDER REAL-LIF This is a non-interv | E CONDITIONS (| port (Post Authorization | n Safety S | | | | JLIF | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| reporter(s) (Physician and Other HCP) for protocol B1871047. (Continued on Additional Information Page) | | | | | | | | |
| | | II. SUSPEC | T DRUC | 3(S) IN | FORMATIC |)N | | |
| 14. SUSPECT DRUG(S) (ir #1) Bosulif (BOSUT | - | | | , / | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | | | | | YES NO NA |
| 17. INDICATION(S) FOR U #1) Unknown | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(from #1) 07-JUL-2020 / 0 | • | | | . THERAPY 1) Unkno | DURATION WN | | | YES NO NA |
| | | III. CONCOMIT | TANT DI | RUG(S |) AND HIST | TORY | | • |
| 22. CONCOMITANT DRUG | S(S) AND DATES OF ADM | MINISTRATION (exclude those us | sed to treat rea | ction) | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.) From/To Dates Unknown | | | | | | | | |
| IV. MANUFACTURER INFORMATION | | | | | | | | |
| 24a. NAME AND ADDRESS | S OF MANUFACTURER | IV. WANUF | AUTUR | 26. REN | | I N | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATES | 3 | | | | | | |
| | 24b, MFR CC | | | | ME AND ADDRESS | | | |
| 24c. DATE RECEIVED | | | | NAME | AND ADDRES | SS WITHHI | ELD. | |
| 24c. DATE RECEIVED BY MANUFACTURER 23-MAY-2023 | STUDY HEALTH PROFES | LITERATURE | | NAME | AND ADDRES | SS WITHHI | ELD. | |
| DATE OF THIS REPORT 27-FEB-2024 | DATE OF THIS REPORT 25a. REPORT TYPE | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 73-year-old male patient received bosutinib (BOSULIF), since 07Jul2020 (ongoing) at 200 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: BLOOD URIC ACID INCREASED (non-serious) with onset 07Jul2020, outcome 'recovered' (21Sep2021), described as 'increased uric acid'; VASCULAR GRAFT OCCLUSION (hospitalization) with onset 06Apr2021, outcome 'not recovered', described as 'right popliteal femoral bridge occlusion'. The patient underwent the following laboratory tests and procedures: Echocardiogram: aggravation of the arteriopathy of the lower limbs, notes: Accentuation of walking disorder, echo-doppler showing an aggravation of the arteriopathy of the lower limbs with stage ii arteriopathy for a walking distance LT 100 m, the right femoro-popliteal bypass is unfortunately occluded. Scheduled surgical appointment. Limited internal carotid stenosis. The action taken for bosutinib was dosage not changed.

The reporter considered 'right popliteal femoral bridge occlusion' and 'increased uric acid' not related to bosutinib or to any concomitant drug.

Additional information: The event Vascular graft occlusion was rated grade 3. Event reported as serious.. The started date of bosutinib also reported on 08Jul2020.

Follow-up (01Mar2023): This is a follow-up report from a Non-Interventional Study source for Protocol ID: B1871047. Updated information includes: Bosulif start date updated from 04Apr2018 to 07Jul2020.

Follow-up (06Mar2023): This is a follow up non-interventional study report received from investigational site via CRO. Updated information included: new event 'increased uric acid' added, onset date of lower limb arteriopathy, outcome of event lower limb arteriopathy updated from not recovered to unknown, causality for event lower limb arteriopathy updated as related to bosutinib (previously unrelated), lab data.

Follow-up (23Mar2023): new information received from investigational site. Updated information: outcome of Arteriopathy updated.

Follow-up (24Mar2023): This is a follow up non-interventional study report received from investigational site. Updated information included: Event description changed from 'lower limb arteriopathy' to 'right popliteal femoral bypass occlusion', additional reporter added.

Follow-up (23May2023): This is a follow up non-interventional study report received from investigational site via CRO. Updated information included: for the event Vascular graft occlusion seriousness criteria of hospitalization added, causality updated from related to unrelated.

Case Comment: Based on the available information, the Company considers the reported events 'right popliteal femoral bypass occlusion', increased uric acid, are unrelated to suspect drug bosutinib and more likely due to underlying or inter-current medical condition.

| 13 | I ah | Data |
|----|------|------|

| IJ. Lab | Data | | | | | | | | | | | |
|---------|---|------|--|--------------------------------|------------------------|--|--|--|--|--|--|--|
| | # | Date | Test / Assessment / Notes | Results | Normal High / Low | | | | | | | |
| | 1 | | Echocardiogram | aggravation of the | · | | | | | | | |
| | | | | arteriopathy of the lower | | | | | | | | |
| | | | | limbs | | | | | | | | |
| | | | Accentuation of walking disorder, echo-doppler showing an aggravation of the | | | | | | | | | |
| | | | arteriopathy of the lower limbs with st | age ii arteriopathy for a walk | king distance < 100 m, | | | | | | | |
| | the right femoro-popliteal bypass is unfortunately occluded. Scheduled surgical | | | | | | | | | | | |
| | | | appointment. Limited internal carotid stenosis. | | | | | | | | | |

| | | | | | | | | | | | | CI | OM | S F | FOI | RM | | | | |
|---|--|--|---------------------------|--------------------------|---------------------------------------|-----------|--------------|---------|----------------------|--|-----------------------------|----------------------|-----------------|------|----------|----|--|--|--|--|
| | | | | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | Τ | | Τ | Γ | Π | | | | | |
| | | | | ::::: | · · · · · · · | | | Ш | | | | Ш | | L | <u> </u> | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION 2a. AGE | 3. SEX | MATION 3a. WEIGHT | 4-6 R | EACTION | N ONSE | т | 8-12 | СН | IECK ALL | | | | | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 56 Years | Male | 73.00 kg | Day 08 | Month APR | Y | /ear 021 | U | API | PROPRI VERSE I | ATE TO | | 1 | | | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER pleural effusion [F | | t tests/lab data) ptoms if any separated by comma | ıs) | | | | | | | _ | | TIENT DI | | | | | | | | |
| | : OBSERVATIONA FE CONDITIONS (| L STUDY- EVALUATION | N OF EF | FICACY | AND SAFET | ΓY OF | BOSU | LIF | | | → PRI HO | OLONGI OSPITALI | ED INF SATIO | N | | | | | | |
| This is a report fro | om a Non-Intervent | B1871047 | 7, Study alia | as BOS | SEVAL | | | | OR DIS | VOLVED R SIGNIFI SABILITY CAPACIT | ICANT / OR | ISTE | :NT | | | | | | | |
| | | | | (Conti | nued on Addi | itional l | nforma | tion Pa | aue) | ge) LIFE THREATENING | | | | | | | | | | |
| | | II. SUSPEC | T DRU | | | | | | ا ' ^{- و ه} | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) JTINIB) Film-coated | | | | nued on Addi | | nforma | tion Pa | age) | P | | ACTION AFTER ? | | PING | . | | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/da | ау | | 6. ROUTE(S) 41) Unkno | OF ADMINISTRA WN | | YES NO NA | | | | | | | | | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | F | REAPP | ACTION PEAR AF RODUCT | TER | | | | | | | | |
| 18. THERAPY DATES(fro #1) 14-MAY-2018 | · | | | 9. THERAPY t1) 1 mon | | | | _ | | [| ☐ YE | s 🔲 N | 10 [2 | ZN | Α | | | | | |
| | | III. CONCOMIT | Γ <u>ANT</u> D | RUG(S | AND HIS | STOF | RY_ | | | | | | | | | | | | | |
| | JG(S) AND DATES OF ADM | MINISTRATION (exclude those use L); Ongoing | ed to treat rea | action) | | | | | | | | | | | | | | | | |
| #2) TAHOR (ATO | DRVASTATIN CALC | , | ing | | | | | | | | | | | | | | | | | |
| #4) LEVOTHYR | OX (LEVOTHYRO) | KINE SODIUM) ; Ongo TE (TESTOSTERONE | oing | OATE) Ir | ijection ; Or | ngoing | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT I | HISTORY. (e.g. diagnostics, | , allergies, pregnancy with last mo | onth of period | , etc.) Description | | | | | | | | | | | | | | | | |
| Unknown to Ongo Unknown to Ongo | | Relevant Med His Relevant Med His | , | Panhypo | pituitarism (olesterolemi | | | | rolae | mia) |) | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTUF | | | ON | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRE Pfizer Inc Stella Pietrafesa | SS OF MANUFACTURER | | | 26. REM | ARKS | | | | | | | | | | | | | | | |
| 66 Hudson Boulev | 01 UNITED STATES | S | | | | | | | | | | | | | | | | | | |
| | Lavis MED CO | | | OSS NA | · · · · · · · · · · · · · · · · · · · | -22 OF B | | | | | | | | | | | | | | |
| | 24b. MFR CC 2021490 | | | | ME AND ADDRE | | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | ER 24d. REPORT | T SOURCE LITERATURE | | | | | | | | | | | | | | | | | | |
| 30-APR-2021 DATE OF THIS REPORT | HEALTH PROFES | | | 4 | | | | | | | | | | | | | | | | |
| 27-FEB-2024 | 25a. REPOR | FOLLOWUP: | | | | | | | | | | | | | | | | | | |

13. Lab Data

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

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

A 56-years-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 14May2018 to 13Jun2018, at 200 mg, once daily, via an unspecified route of administration from 14Jun2018 to 20Apr2021 at 300 mg, once daily for an unspecified indication. Medical history included ongoing panhypopituitarism and ongoing hypercholesterolemia. Concomitant medications included allopurinol taken for panhypopituitarism from an unspecified start date and ongoing; atorvastatin calcium (TAHOR) taken for hypercholesterolemia from an unspecified start date and ongoing; hydrocortisone taken for panhypopituitarism from an unspecified start date and ongoing; levothyroxine sodium (LEVOTHYROX) taken for panhypopituitarism from an unspecified start date and ongoing; testosterone heptanoate taken for an unspecified indication from an unspecified start date and ongoing. The subject experienced pleural effusion on 08Apr2021. Event pleural effusion was reported as non serious, grade 1. Before a gradual dyspnoea appearance in 15 days, chest x-ray requested by the doctor. Chest x-ray of 08Apr2021: bilateral pleural outflow but predominant on the right. Set up treatment with furosemide 40 mg/day from 08Apr2021 to 15Apr2021. Chest x-ray check on 19Apr2021: left basal pleural effusion disappearance and very clear regression right pleural effusion (filling of the bottom of costo-diaphragmatic bag g). Hematology consultation on 20Apr2021: discreet decrease in vesicular murmure right base, decision to stop of treatment with bosulif because criteria for test stopping and recurrent pleural effusion, no therapeutic relay. In response to the event BOSULIF was withdrawn. The outcome of the event was recovering.

The investigator considered that the event was related to Bosulif and unrelated to concomitant medications.

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.

| is. Lab Data | | | | | | | | | | | | |
|----------------|-----------------------------|---|---|--|--|--|--|--|--|--|--|--|
| # | Date | Test / Assessment / Notes | Results | Normal High / Low | | | | | | | | |
| 1 | 08-APR-2021 | Chest X-ray | bilateral pleural outflow | | | | | | | | | |
| | | | but predominant on the r | | | | | | | | | |
| | | bilateral pleural outflow but predom | inant on the right | | | | | | | | | |
| | 10.100.001 | OL 1V | | | | | | | | | | |
| 2 | 19-APR-2021 | Chest X-ray | left basal pleural effusion disappearance and ver | | | | | | | | | |
| | | left basal pleural effusion disappea | • • | , | | | | | | | | |
| | | (filling of the bottom of costo-diaphi | | ocioni ngin pioarai on acion | | | | | | | | |
| | | (g or allo bottom or obotto anap | agaus sag g/. | | | | | | | | | |
| 14-19. SUSPE | ECT DRUG(S) continue | ed | | | | | | | | | | |
| 14. SUSPECT DR | UG(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-co | pated tablet; 300 mg, 1x/day; Unknown | Unknown | 14-JUN-2018 / | | | | | | | | |
| Regimen #2 | | | | 20-APR-2021; | | | | | | | | |
| | | | | 2 years 10 months 7 | | | | | | | | |
| | | | | days | | | | | | | | |

| | | | | | | | | | | | | CIO | DM | S F | OI | RM | | | |
|--|--|---|--------------------|---------------------------|----------------|-----------|--------------|--------|-------------|---|---|---|------------|----------|----------|----|--|--|--|
| | | | | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE I | REACTION REPO | ORT | | | | | | | | | | | | | | | | |
| | | | | | | | 1 | | Т | Τ | Τ | | Τ | | | | | | |
| | | I DEA | ACTION II | | MATIONI | | | | | | | | | <u> </u> | <u> </u> | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | | | 3a. WEIGHT | 4-6 RE | ACTIO | N ONSE | ΞT | 8-12 | | ECK ALL | | | | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 77 Years | emale | | Day 02 | Month FEE | | rear 021 | | | PROPRIA VERSE F | | | | | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER | TION(S) (including relevan RED TERM] (Related sym | t tests/lab data) ptoms if any separated by comm | nas) | | | | | 7 | | _ |] PAI | TIENT DI | ED | | | | | | |
| Knee pain [Arthra Sleep apnea [Slee | lgia] ep apnoea syndror | me] | | INVOLVED OR PROLONGED INP | | | | | | | | | | | NT | | | | |
| | | L STUDY - EVALUATI | ON OF EFF | FICACY A | ND SAFET | Y OF | BOSI | JLIF | | | | 7 | | | | | | | |
| | FE CONDITIONS (| | 47 | | | | | | [| OR DIS | OLVED I SIGNIFI SABILITY CAPACIT | CANT OR | SISTE F | NT | | | | | |
| | This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | | | | APACII | Y | | | | | | |
| | (Continued on Additional Information Page) | | | | | | | | | | | E REATEN | ING | | | | | | |
| | | II. SUSPEC | CT DRUG | (S) INF | ORMATIC | ON | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (#1) Bosulif (BOSU | (include generic name) | tablet | | | | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | |
| 15. DAILY DOSE(S) | | | 16 | ROUTE(S) C | OF ADMINISTRAT | ION | <u> </u> | | _ | | | | | | | | | | |
| #1) 200 mg, 1x/da | у | | |) Unknow | | YES NO NA | | | | | | | | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(fro | | | | 19. THERAPY DURATION | | | | | | | | 1 | | | | | | | |
| #1) 23-OCT-2020 | / Ongoing | | #1 | #1) Unknown | | | | | | | | | 0 | XI N/ | Α | | | | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | TOR | Y | | | | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those u | used to treat reac | tion) | | | | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT H | HSTORY, (e.g. diagnostics | , allergies, pregnancy with last m | nonth of period, e | tc.) | | | | | | | | | | | | _ | | | |
| From/To Dates Unknown | (13.13.11 | Type of History / Notes Relevant Med H | D | escription lone () | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | 177 84481111 | | | | N.I. | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUI | FACTURE | 26. REMA | | JIN | | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva | ard East | | | | | | | | | | | | | | | | | | |
| New York, NY 1000 Phone: 212 733 40 | 01 UNITED STATE 145 | S | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | 25b. NAM | E AND ADDRESS | S OF RE | PORTE | :R | | | | | _ | | | | | | |
| | 2021523 | | | | AND ADDRE | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPOR | T SOURCE LITERATURE | | NAME | AND ADDRE | SS W | ITHHI | ELD. | | | | | | | | | | | |
| 24-JAN-2023 | HEALTH PROFES | | | | | | | | | | | | | | | | | | |
| 27-FEB-2024 | 25a. REPOR | T TYPE FOLLOWUP: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 77-year-old female subject received bosutinib (BOSULIF), since 23Oct2020 (ongoing) at 200 mg 1x/day. Subject did not have any medical history. The patient's concomitant medications were not reported. The patient experienced sleep apnea grade 1 on 02Feb2021. On 02Feb2022, Total left knee prosthesis on 02Nov2021 was reported, rated as grade 3 and which required hospitalization. On 03Feb2022, event "Total left knee prosthesis" was updated to "Knee pain" with onset date in 2021. The action taken in response to the event for bosutinib was dose not changed. The outcome of the event sleep apnea grade was not resolved. Knee pain resolved on 15Dec2021.

The investigator considered there was not a reasonable possibility that the events "sleep apnea" and "knee pain" were related to bosutinib.

Follow-up (02Feb2022 and 03Feb2022): This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. Updated information: Action taken updated to "Dose not changed". New event "Knee pain" added. Case upgraded to serious in this follow-up.

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

Follow-up (24Jan2023): 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: start date and dosage for study drug bosutinib.

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

Case Comment: In concurrence with the reporting investigator, the Company deems the reported events knee pain and sleep apnea grade 1 unrelated to the suspect, bosutinib, administration.

| | | | | | | | | | | | | | CIO | ON | /IS | FO | RM | | | |
|---|---------------------------------|---|------------------------|---|------------------------------------|--------|--------------|---------------|------|---|-----|---|-----------------------------|-------------|------|-----|----|--|--|--|
| | | | | | | | | | | | | | | | | | | | | |
| SUSPECT | ADVERSE F | REACTION REPO | RT | | | | | | | | | | | _ | | | | | | |
| | | | | | | Π | | $\overline{}$ | Π | П | | | Т | Τ | T | T | | | | |
| | | | | | | | 4 | | | | | | | \perp | | | | | | |
| | | I. REA | CTION I | NFOR | MATION | | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 2a. AGE 67 Years | 3. SEX Male | 63.00 Da | | Monti MAI | n T | Year | APPROPRIATE TO | | | | | | | | | | |
| 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 Myalgia [Myalgia] | | | | | | | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | | | OR S | OLVED SIGNIFI ABILITY | ICAN 'OR | ١T | ENT | | | | |
| This is a report from a Non-Interventional Study source for Protocol B1871047. | | | | | | | | | | | | | APACIT | Y | | | | | | |
| | | | | (Cont | inued on Additio | nal Ir | forma | tion F | age | e) | | LIFE | EATEN | ING | | | | | | |
| | | II. SUSPEC | CT DRUG | S(S) IN | FORMATIC | N | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (inclui #1) Bosulif (BOSUTIN | | tablet | | (Cont | inued on Additio | nal Ir | nforma | ition P | age | | AB. | REA ATE A UG? | AFTER : | STO | PPIN | 3 | | | | |
| 15. DAILY DOSE(S) #1) 100 to 500 mg, 1x, | ′day | | | . ROUTE(S) OF ADMINISTRATION I) Unknown | | | | | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | |
| 18. THERAPY DATES(from/to) #1) 08-AUG-2019 / 19 | -AUG-2020 | | | 9. THERAPY DURATION \$\pmu_1\) 1 year 12 days \textsquare \textsq | | | | | | | | ⊠⊦ | IA | | | | | | | |
| | | III. CONCOMI | | |) AND HIST | OR | Υ | | | | | | | | | | | | | |
| #1) CORTANCYL (P | | IINISTRATION (exclude those us ; Ongoing | sed to treat read | ction) | | | | | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | | | | | |
| • | | | | | | | | | | | | | | | | | | | | |
| OS OTHER RELEVANT HOTO | DV (E E | | | | | | | | | | | | | | | | | | | |
| From/To Dates Unknown 21-JUL-2017 to Unkn | | allergies, pregnancy with last m Type of History / Notes Relevant Med Hi Relevant Med Hi | story F | Description Pseudop | oolyarthritis (Po myelogenous I | | | | | | | d lei | ukaer | nia) |) | | | | | |
| | | IV MANUE | FACTUR | FR INI | ORMATIO | N | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard I New York, NY 10001 Phone: 212 733 4045 | East | | 7101011 | 26. REM | | | | | | | | | | | | | | | | |
| | 24b. MFR CC 2021527 | | | NAME | ME AND ADDRESS E AND ADDRES | SS W | /ITHH | ELD. | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 22-APR-2022 | 24d. REPORT STUDY HEALTH PROFES | LITERATURE | | NAME | E AND ADDRES | SS W | /ITHH | ELD. | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | TTYPE FOLLOWUP: | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 67-year-old male subject received bosutinib (BOSULIF), via an unspecified route of administration from 08Aug2019 to 19Aug2020, at 100 to 500 mg, once daily, via an unspecified route of administration from 20Aug2020 and ongoing, at 500 mg, once daily for an unspecified indication. Medical history included pseudopolyarthritis, chronic myelogenous leukemia from 21Jul2017. Concomitant medication included prednisone (CORTANCYL) taken for pseudopolyarthritis from an unspecified start date and ongoing. The subject experienced myalgia on 06Mar2021 06:30. On 06Mar2021, 06:30 AM, the subject had left leg intense pain with functional impotence. He was taken to the emergencies by her wife, he arrived at 10:45 AM and he left at 04:15 PM. The subject underwent lab tests and procedures which included arterio-venous doppler on 06Mar2021 which was normal and no venous thrombosis was reported. Therapeutic measures were taken as a result of myalgia which included: oxycodone hydrochloride (OXYNORMORO), 5 mg oral, once per day and paracetamol (manufacturer unknown), 1 g, once per day. The subject returned home with a final diagnosis of myalgia which was rated grade 3. Treatment when the subject was discharged, was diazepam (VALIUM), 2 mg if pain. The subject had recovered from the event on 07May2021. The action taken in response to the event for bosutinib was dose not changed.

The event myalgia was confirmed as medically significant as the subject went to the emergency. According to the investigator, the event was unrelated to study drug bosutinib and to concomitant drug.

Follow-up (15Dec2021): New information received from a contactable investigator from the Non-Interventional Study source for Protocol B1871047.

Updated information: Event myalgia was updated from nonserious to serious (medically significant).

Follow-up (22Apr2022): This is a non-interventional study follow-up report received from the investigational site for protocol B1871047. Updated information confirmation of seriousness.

Case Comment: In concurrence with the investigator, the reported myalgia is unrelated to the study drug, bosutinib. It is mostly likely an intercurrent condition. Of note, the event occurred more than 18 months after start of treatment and resolved without any modification in the administration of bosutinib.

13. Lab Data

| # | # | Date | Test / Assessr | ment / Notes | | Results | Normal High / Low |
|-------------|--------|------------------------------|----------------|---|-----|------------------------------|--|
| | 1 | 06-MAR-2021 | Ultrasound | Doppler | | Normal, No venous thrombosis | |
| 14-19. SUS | SPE | CT DRUG(S) continue | d | • | | | |
| 14. SUSPECT | T DR | UG(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) Bosu | ılif (| BOSUTINIB) Film-co | ated tablet; | 500 mg, 1x/day; Unkno | own | Unknown | 20-AUG-2020 / |
| Regimen | #2 | | | | | | Ongoing; |
| | | | | | | | Unknown |

| | | | | | | | | | | | | CI | ON | IS F | OF | RM | |
|--|---|--|---|---|--|---------------|--------|---------|--------------|--------------|-----------|-------------------------------|------------|-------|----|----|--|
| | | | | | | | | | | | | | | | | | |
| SUSPEC | CT ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | | |
| | | | | | | Т | П | T | T | П | Τ | П | Τ | Τ | | | |
| | | | | | | | 4 | | | | | | \perp | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | ACTION II | NFOR 3. SEX | MATION 3a. WEIGHT | 1-6 P | EACTIO | NI ONS | SET. | 8-1: | 2 CL | HECK ALI | | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 78 | Male | 83.00 kg | Day 03 | Month | h | Year 2020 | 1 | AF | PROPRI | ATE | | | | |
| Other Serious Cri Prostatic adenoca | arcinoma, hormone | S [Second primary malignancy] S [Prostate cancer metastatic] PATIENT DIED INVOLVED OR PROLONGED INPATIEN HOSPITALISATION | | | | | | | | | | :NT NT | | | | | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | | OF DI: | SIGNIF SABILITY CAPACIT | ICAN OR | | | | |
| | | (Conti | nued on Addit | tional I | nforma | ation I | Page |) [| | E IREATEN | IING | | | | | | |
| | | II. SUSPE | CT DRUG | (S) IN | FORMATI | ION | | | | | | | | | | | |
| | (include generic name) ITINIB) Film-coated | tablet | | • | nued on Addit | $\overline{}$ | nforma | ation I | Page | | | EACTION E AFTER ? | | PPING | i | | |
| 15. DAILY DOSE(S) #1) 100 mg, 1x/da | у | | 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | YES NO NA | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 01-APR-2019 | • | | | 19. THERAPY DURATION #1) 14 days ☐ YES ☐ NO ☑ NA | | | | | | | | | A | | | | |
| | | III. CONCOM | ITANT DR | UG(S |) AND HIS | STOF | RY | | | | | | | | | | |
| 22. CONCOMITANT DRU | IG(S) AND DATES OF ADM | MINISTRATION (exclude those | used to treat reac | ion) | | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT F From/To Dates Unknown to Ongo 17-JUL-2020 to 1 | ping | allergies, pregnancy with last r Type of History / Notes Relevant Med H Relevant Med H suspicion of car | listory P | escription rostate rinary r | adenoma (F etention (Uri tent catheter | nary r | etenti | | na) | | | | | | | | |
| | | IV. MANU | FACTURE | | | ON | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva | 1 UNITED STATES | | 26. REM | IARKS | | | | | | | | | | | | | |
| | 24b. MFR CC 2021664 | | | | ME AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 29-JUN-2023 | 24d. REPOR STUDY HEALTH PROFES | LITERATURE | Ē | NAME AND ADDRESS WITHHELD. | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

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

A 78-year-old male subject received bosutinib (BOSULIF), from 01Apr2019 to 14Apr2019, at 100 mg, once daily; from 15Apr2019 to 02Jul2019, at 200 mg, once daily; from 03Jul2019 to 07Mar2021, at 300 mg, once daily; and from 08Mar2021 and ongoing at 200 mg, once daily, all via an unspecified route of administration for an unspecified indication. Medical history included ongoing benign hypertrophy of prostate and acute urinary retention from 17Jul2020 to 11Aug2020 with a suspicion of cancer and required persistent catheterization. The subject's concomitant medications were not reported. The subject experienced prostatic adenocarcinoma, hormone sensible, with bone metastases on 03Sep2020. The subject experienced Micturition burning on 03Jul2020. The subject underwent lab tests and procedures which included prostate biopsy on 03Sep2020 which showed prostatic adenocarcinoma hormone sensible, with bone metastases from the beginning; bone scintigraphy on 19Nov2020 which showed condensation and intense hyperfixation of the upper part of the right iliac wing, of the right iliac wing opposite the sacroiliac and of the right crowned aileron in favor of secondary locations; Eastern Cooperative Oncology Group performance status: 0 on an unknown date; histology on 03Sep2020 which showed prostatic adenocarcinoma GLEASON 7 (4 + 3) (90% grade 4) ISUP 3 on 20% of the shavings; Pelvic magnetic resonance imaging on 18Aug2020 which showed PIRADS 5 lesion on the right, 23mm long axis, in contact with the urethra with capsular bulging without sign crossing. Some external iliac nodes without pathological lymphadenopathy; Prostatic specific antigen (PSA) on 25Jul2020: 5.7 ng/ml and 3.16 ng/ml on 10Nov2020, weight: 81 kg on an unknown date on examination. The action taken in response to the event for bosutinib was dose not changed. Therapeutic measures were taken as a result of prostatic adenocarcinoma, hormone sensible, with bone metastases. The outcome of the events Prostatic adenocarcinoma, hormone sensible, with bone metastases was not recovered. The outcome of Micturition burning was resolved on Jul2020.

The investigator considered the event Prostatic adenocarcinoma, hormone sensible, with bone metastases as non-serious (grade 3) and there was not a reasonable possibility that the event was related to the study medication bosutinib or to concomitant treatments. The investigator considered the event Micturition burning as non-serious (grade 1) and there was not a reasonable possibility that the event was related to the study medication bosutinib or to concomitant treatments.

Follow-up (14Dec2021 and 15Dec2021): This is a Non-Interventional Study follow-up report from the clinical team. Updated information: new event (Micturition burning).

Follow-up (29Jun2023): This is a Non-Interventional Study follow-up report from investigational site via CRO. Updated information includes: Medical history acute urinary retention start date updated to 17Jul2020.

Case Comment: In concurrence with the investigator, the reported "prostatic adenocarcinoma, hormone sensible, with bone metastases", as a second primary malignancy, is deemed unrelated to the study drug, bosutinib. Micturition burning considered symptom of Prostate cancer metastatic, unrelated to bosutinib, as well.

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|---|---|--------------------|
| 1 | 03-SEP-2020 | Biopsy | prostatic adenocarcinoma | |
| | | prostatic adenocarcinoma hormone se beginning. | ensible, with bone metastas | es from the |
| 2 | 19-NOV-2020 | Bone scan | condensation and intense hyperfixation | |
| | | condensation and intense hyperfixation right iliac wing opposite the sacroiliac secondary locations | on of the upper part of the rig | , 0, |
| 3 | | Eastern Cooperative Oncology Group performance status | 0 | |
| 4 | 03-SEP-2020 | Histology | prostatic adenocarcinoma GLEASON 7 (4 + 3) | |
| | | prostatic adenocarcinoma GLEASON shavings | | JP 3 on 20% of the |
| 5 | 18-AUG-2020 | Magnetic resonance imaging pelvic | PIRADS 5 lesion on the right, 23mm long axis | |

| 13. Lab Data # | a Date | Test / Assess | ment / Notes | Results | Normal High / Low |
|---------------------------|--------------------------------|---------------|---|---------------------------|--|
| | | | lesion on the right, 23mm thout sign crossing. Some nopathy | • | • |
| 6 | 25-JUL-2020 | Prostatic s | specific antigen | 5.7 ng/ml | |
| 7 | 10-NOV-2020 | Prostatic s | specific antigen | 3.16 ng/ml | |
| 8 | | Weight | | 81 kg | |
| 14-19. SUSF | PECT DRUG(S) continue | d | | | |
| 14. SUSPECT E | 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) Bosulit Regimen # | f (BOSUTINIB) Film-cc 2 | pated tablet; | 200 mg, 1x/day; Unknown | Unknown | 15-APR-2019 / 02-JUL-2019; 2 months 18 days |
| #1) Bosulit Regimen # | f (BOSUTINIB) Film-cc 3 | pated tablet; | 300 mg, 1x/day; Unknown | Unknown | 03-JUL-2019 / 07-MAR-2021; 1 year 8 months 5 days |
| #1) Bosulii Regimen # | f (BOSUTINIB) Film-cc 4 | pated tablet; | 200 mg, 1x/day; Unknown | Unknown | 08-MAR-2021 / Ongoing; Unknown |

| | | | | | | | | | | | | | CIO | MS | 3 F | OF | ₹M |
|--|--|---|-----------------|---|-----------------------|--------|-------|-------|-------------|---------------|-------------|--------------------------|-------------|----|-----|----|----|
| | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | |
| | | | | | | | | T | | Τ | | Τ | Τ | | | | - |
| | | | | | | Т, | И | | | | | <u> </u> | | Ш | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION | NFOR 3. SEX | MATION 3a. WEIGHT | 1-6 PE | ACTIO | N ONS | ET | 8-12 | 2 C | HEC | K ALL | | | | _ |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 47 | Female | | ay | Month | n | Year 020 | 1 | Α | PPR | OPRIAT | | | | |
| Vocal cords nodu | CTION(S) (including relevant RRED TERM] (Related symp Ile [Vocal cord thick ation [Ear discomfo | 0. | | | | | | | 2 |] N | NVOL ROL | NT DIE VED O ONGEE | OR D INP | | NT | | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | | GNIFIC | CANT | STE | NT | | | |
| | | oort (Post Authorization P) for protocol B187104 | | tudy) rec | eived from co | ntact | able | | | | IN | NCAF | PACITY | JK | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | | | | | | | |
| | | II. SUSPEC | T DRUC | G(S) IN | FORMATIC | ON | | | | | | | | | | | |
| | 4. SUSPECT DRUG(S) (include generic name) 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | . ROUTE(S) 1) Unkno | OF ADMINISTRATI WN | ON | | | | ☐YES ☐NO 【 NA | | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | |
| 18. THERAPY DATES(fr #1) MAR-2020 / C | • | | | 19. THERAPY DURATION #1) Unknown YES NO | | | | | | | | | NA | ı | | | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND HIST | ΓOR | Υ | | | • | | | | | | | |
| 22. CONCOMITANT DRI | UG(S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat rea | ction) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 22 OTHER RELEVANT | LIICTORY (a.g. diagnostics | allergies, pregnancy with last mor | nth of nariad | ata \ | | | | | | | | | | | | | 4 |
| From/To Dates Unknown to Ong | | Type of History / Notes Relevant Med His | | Description | nyeloid leuke | mia (| Chro | nic m | yelo | id le | ukae | emi | a) | | | | |
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| | | | | | | | | | | | | | | | | | |
| 24a NAME AND ADDRE | IV. MANUFACTURER INFORMATION 243. NAME AND ADDRESS OF MANUFACTURER 26. REMARKS | | | | | | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | vard East 01 UNITED STATES | S | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2021675 | | | | ME AND ADDRESS | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURI | 24d. REPORT | | | NAME | AND ADDRES | SS W | /ITHH | ELD. | | | | | | | | | |
| 28-SEP-2023 | Marian | SSIONAL LITERATURE | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | TE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 47-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since Mar2020 (ongoing) at 500 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: VOCAL CORD THICKENING (hospitalization) with onset Jun2020, outcome "recovered" (26Aug2021), described as "Vocal cords nodule"; EAR DISCOMFORT (non-serious) with onset Feb2021, outcome "recovered" (18Oct2021), described as "blocked ear sensation". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of vocal cord thickening.

Additional information: The dysphonia was rated grade 2 and blocked ear sensation was rated grade 1.

The site stated: in the report of 07Jun2021 dysphonia was noted (polyps of the vocal cords with a surgery to be planned), and sensation of blocked ears. In the report of 22Feb2021, dysphonia was noted since 7-8 months (ENT assessment was reassuring). Patient had surgery of vocal cords nodule on 26Aug2021.

The reporter considered "vocal cords nodule" and "blocked ear sensation" not related to bosutinib.

Follow-up (25Oct2021 and 07Jan2022): This is a follow-up for a report from a Non-Interventional Study source for Protocol B1871047.

Information updated: onset date, outcome and stop date of dysphonia; treatment for dysphonia.

Follow-up (30May2023): This is a follow-up for a report from a Non-Interventional Study received from investigational site via CRO. Updated information: event onset date and stop date updated.

Follow-up (28Jul2023): This is a follow-up report from the investigator via CRO. Updated information included: medical history (chronic myeloid leukemia).

Follow-up (28Sep2023): new information received from Clinical team.

Updated information included: Query response (confirmed: it was reported dysphonia is a symptom of the vocal cords nodule. Vocal cords nodule has been recorded as the main event. As a surgery occurred on 26Aug2021 to remove the nodule, the AE has been turned into a Serious Adverse Event with Hospitalization as the seriousness criteria.

Follow-up (28Sep2023): This is a follow-up report from the investigator via CRO. Updated information included: bosutinib details.

Case Comment: The reported events, Vocal cord thickening and blocked ear sensation are deemed intercurrent diseases, unrelated to the study drug, bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

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|--|--|----------------------------|--|----------------------------|-----------------------------------|--|-----------------|---------|---------|-----------|-----------|----------------|-----------------|---------------|---------------------------|-----------|---------|-----------------|---------|----|---|
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| SUSPECT | ADVERSE | REAC ⁻ | TION REF | POR | Т | | | | | | | | | | | | | | | | |
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| | | | | | | | | | \perp | 4 | | | | L | | \perp | <u></u> | Ш | \perp | | |
| | | | | | | INFOR | | | 4 | 7 | | | - 1. | | 211 | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | Day | Month Yea | ear | ^{2a. AGE} 61 Years | 3. SEX Male | 3a. WEIG Unk | 0 | 4-6 RI | Mon MA | ith | Ye 20 | ar | 8-12 | API | | PRIA | TE TO EACTIO | NC | | |
| 7 + 13 DESCRIBE REACTIO Event Verbatim [PREFERRE Other Serious Criter pericardial effusion | :D TERM] (Related sym ria: Medically Sig | nptoms if any gnificant | y separated by cor | mmas) | | | | | | | | | | | INV PR | VOLV | | | | ΙΤ | |
| Case Description: C UNDER REAL-LIFE | | FFICACY | AND SA | AFETY | Y OF | BOS | SULI | F | | | OR DIS | R SIG SABII | NIFIC LITY (| OR | TEN | т | | | | | |
| This is a report from | This is a report from a Non-Interventional Study source for protocol B187104 | | | | | | | | | | L. | | | _ | | | ACITY | | | | |
| | | | | | | (Cont | inued on | Additio | onal Ir | nform | ation | Pag | ge) | $\overline{}$ | THI | E IREA | TENI | NG | | | _ |
| | | | II. SUSPE | <u>ECT</u> | DRU | G(S) IN | FORM | 1ATIC | ON | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) UNK | | | | | | 6. ROUTE(S) #1) Unkno | | ISTRATI | ION | | | | | |]YE | ≣s [| NC | · 🛛 | NA | | |
| 17. INDICATION(S) FOR US #1) Unknown | E | | | | | | | | 7 | | | | | R | ID RE. REAPP REINTF | PEAR | R AFTI | | | | |
| 18. THERAPY DATES(from/t #1) Unknown | .o) | | | | | 19. THERAPY DURATION #1) Unknown YES NO NA | | | | | | | | | NA | | | | | | |
| | | III. | CONCON | MITA | NT D | RUG(S |) AND | HIS | TOR | RY | | | • | | | | | | | | |
| 22. CONCOMITANT DRUG(S | | MINISTRATI | ION (exclude thos | | | | , | | | | | | | | | | | | | | |
| , , <u> </u> | , | ر <u>ن</u> | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIS' From/To Dates 01-JUN-2000 to One 01-JAN-2005 to One | going | Typ | oregnancy with las be of History / Note elevant Med elevant Med | _{tes} l Histoi | ory | d, etc.) Description Renal fa Hepatitis | | | |) | | | | | | | | | | | |
| | | | IV. MANI | I IFA | CTUF | RFR INI | =ORM | ΔΤΙΩ | N | | | | | | | | | | | | _ |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | d East UNITED STATE | 7 | 14 | <u>0,,,,</u> | <u>0, c.</u> | 26. REM | | ,,,, | | | | | | | | | | | | | |
| | 24b. MFR CC | |). | | | | ME AND AL | | | | |). | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | RT SOURCE | LITERATUR | IRE | | - | | | | | | | | | | | | | | | |
| 05-NOV-2021 DATE OF THIS REPORT | HEALTH PROFE | | OTHER: | | | _ | | | | | | | | | | | | | | | |
| 27-FEB-2024 | INITIAL ≥ | | FOLLOWUR | JP: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 61-year-old male subject started to receive bosutinib (BOSULIF, tablet) on an unspecified date, dose, frequency and route of administration for an unspecified indication. Relevant medical history included ongoing mild renal failure since 01Jun2000 and ongoing old hepatitis B since 01Jan2005. Concomitant medications included ongoing entecavir for hepatitis B. On 06May2021, the subject experienced pericardial effusion. The event was rated grade 2 and assessed as medically significant. Ultrasound on 06May2021 found pericardial effusion. Outcome of the event was recovered on an unspecified date in May2021. No action was taken for bosutinib in response to the event.

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

Follow-up (25Oct2021): New information reported includes an update about relevant medical history and causality assessment for concomitant medication.

Follow-up (05Nov2021): New information received from the investigational site via CRO includes: Event onset date was updated to 06May2021 (previously 14Jun2021), outcome was updated to recovered (previously recovering).

Case Comment: Based on the known drug safety profile, a contributory role of bosutinib to the reported pericardial effusion cannot be excluded. The follow up information received does not alter the previous company clinical evaluation.

| 13. Lab | Data | | | | |
|---------|------|-------------|---------------------------|----------------------|-------------------|
| | # | Date | Test / Assessment / Notes | Results | Normal High / Low |
| | 1 | 06-MAY-2021 | Ultrasound scan | pericardial effusion | |

| | | | | | | | | | | | | CIO | MC | 3 F | OF | M | | |
|--|---|--|---------------------|--|----------------------------|---------------|--------------|---------|-----------------|-------|--------------|------------------------------|--------------|------|----|--------|--|--|
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| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | T | | | _ | | |
| | | | OTIONII | L | 4471011 | | | Ш | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | ACTION IN | | ATTON 3a. WEIGHT | 4-6 RE | ACTION | N ONSE | т | 8-12 | CHE | ECK ALL | | | | \neg | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 59 Years | | | Day | Month DEC | Y | ^{(ear} | | APF | PROPRI VERSE I | | | | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERI abdominal pain [A Diarrhea [Diarrhoe | RED TERM] (Related symp bdominal pain] | tests/lab data) otoms if any separated by comm | nas) | | | | | | | U U |] INV PRO | OLVED OLONGE SPITALI | OR ED INP | | NT | | | |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUATI OF USE | ON OF EFF | FICACY A | ND SAFET | Y OF | BOSI | JLIF | | ⊏ | OR DIS | OLVED SIGNIFI SABILITY | CANT | STE | NT | | | |
| | | oort (Post Authorization P) for protocol B18710 | | udy) rece | ived from co | ontact | able | | | | | APACIT | Y | | | | | |
| | | | | (Contin | ued on Addition | onal In | format | tion Pa | age) | | THE | E REATEN | NG | | | | | |
| | | II. SUSPEC | CT DRUG | (S) INF | ORMATIC | NC | | | | ı | | | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | - | tablet | | • | ued on Additio | $\overline{}$ | format | tion Pa | age) | Α | | ACTION AFTER | | PING | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day | У | | | 6. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(from #1) 25-SEP-2018 / | • | | | 19. THERAPY DURATION #1) 2 years 2 months 13 days | | | | | | | | | NA | ı | | | | |
| | | III. CONCOMI | | | AND HIS | TOR | Υ | | | | | | | | | _ | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those u | ised to treat react | tion) | | | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT H | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last m | nonth of period, e | etc.) | | | | | | | | | | | | 4 | | |
| From/To Dates Unknown to Ongo | ing | Type of History / Notes Relevant Med Hi | | escription Chronic m | yeloid leuke | mia (| Chron | nic my | yeloid | d leu | ıkaer | mia) | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUI | FACTURE | ER INFO | | N | | | | | | | | | | \neg | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | ard East 11 UNITED STATES | 3 | | 20. 112.111 | | | | | | | | | | | | | | |
| | 24b. MFR CC 2021769 | | | | E AND ADDRESS AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTUREI | 24d. REPOR | r source | | NAME | AND ADDRE | SS W | ITHHE | ELD. | | | | | | | | | | |
| 05-OCT-2023 | STUDY HEALTH PROFES | LITERATURE SSIONAL OTHER: | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 59-year-old female patient received bosutinib (BOSULIF), first regimen from 25Sep2018 to 07Dec2020 at 200 mg 1x/day and second regimen since 08Dec2020 at 300 mg 1x/day. The patient's relevant medical history included: "chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported.

The following information was reported: DIARRHOEA (non-serious) with onset Dec2020, outcome "recovered" (12Oct2021), described as "Diarrhea"; ABDOMINAL PAIN (non-serious) with onset Dec2020, outcome "recovered" (12Oct2021). The action taken for bosutinib was dosage reduced.

The reporter considered "abdominal pain" and "diarrhea" related to bosutinib.

Additional information: The events diarrhea and abdominal pain were reported as non-serious with grade 2. As of 03Dec2021, medical report included failure of increase of bosutinib 300 mg with diarrhea, abdominal pain and soft abdomen from 12Oct2021. In response to the event, bosulif was reduced to 200 mg daily on 31Mar2021.

According to the investigator, both events were related to study drug bosutinib and unrelated to concomitant drugs.

Follow-up (03Dec2021): New information received from the investigator via the CRO included reaction data (outcome of events diarrhea and abdominal pain updated to recovered on 12Oct2021) and additional information.

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

Follow-up (12Jul2023): New information received from the investigator via the CRO included: new reporter (slide #2), Dechallenge and Rechallenge Results for suspect drug.

Follow-up (24Jul2023): This is a follow up non-interventional study report received from the CRO. Updated information included: last name of second reporter.

Follow-up (28Jul2023): This is a follow up non-interventional study report received from the CRO. Updated information included: None was removed from patient's medical history.

Follow-up (27Sep2023): This is a non-interventional study follow-up for protocol B9991045 received from the investigator site via the CRO. Updated information: medical history (ongoing chronic myeloid leukemia) and dosage regimen of bosutinib.

Follow-up (05Oct2023): 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: clinical course details.

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

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 diarrhea and abdominal pain and the administration of the suspect.

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 ta | ablet; | 300 mg, 1x/day; Unknown | Unknown | 08-DEC-2020 / |
| Regimen #2 | | | | Unknown; |
| | | | | Unknown |

| | | | | | | | | | | | | | CIC | ON | IS I | FOI | RM |
|---|---|--|------------------|---|--------------------|--------|-------------|-------|------|-------------|------------------------------|-------------|--------|-----|------|-----|----|
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| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | |
| | | | | | | Π | | | Τ | П | T | Т | Τ | Τ | Τ | | |
| | | | | | | Ь, | И | L | | | | | | L | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION I | NFOR 3. SEX | MATION 3a. WEIGHT | 4 C DE | EACTIO | NI ON | 057 | Tak | 10 / | OUE | CK ALL | | | | |
| PRIVACY | FRANCE | emale | 56.00 Da 2 | ay | Mont | th | Year 202 | | , | APPI | ROPRIA ERSE F | ATE | | | | | |
| | CTION(S) (including relevant RRED TERM] (Related symp dominal pain upper Diarrhoea] | | | | | | | 1 | | INVO PRO | ENT DII | OR ED IN | | ENT | | | |
| | : OBSERVATIONAL FE CONDITIONS (| CACY A | AND SAFETY | OF I | BOSI | JLIF | | 1 | ш, | OR S | OLVED F SIGNIFI BILITY | CAN | | NT | | | |
| | | oort (Post Authorization P) for protocol B187104 | | udy) rec | eived from cor | ntact | able | | | | | INCA | PACIT | | | | |
| | | | | (Conti | nued on Addition | nal In | form | ation | Page | ;) [| | LIFE | EATENI | ING | | | |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATIO | N | | | | | | | | | | | |
| #1) Bosulif (BOSU | II. SUSPECT DRUG(S) INFORMATION 4. SUSPECT DRUG(S) (include generic name) 4.) Bosulif (BOSUTINIB) Film-coated tablet 42) FLUVASTATINE [FLUVASTATIN] (FLUVASTATINE) (Continued on Additional Information Page) 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily #2) UNK | | | #1 | ROUTE(S)) Unkno !) Unkno | | ON | | | | | × | YES | □ N | 0 | ΠN | A | |
| #1) Unknown #2) Unknown | USE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 04-SEP-2018 #2) Ongoing | · | | #1 | 19. THERAPY DURATION #1) 1 year 5 months 1 day #2) Unknown | | | | | | | | | □N | A | | | |
| | | III. CONCOMIT | ANT DE | RUG(S | AND HIST | OR | Υ | | | | | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat read | ction) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT I From/To Dates Unknown | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last more Type of History / Notes Relevant Med His | | etc.) Description None () | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTUR | | | N_ | | | | | | | | _ | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | 01 UNITED STATES | 3 | | 26. REM | ARKS | | | | | | | | | | | | |
| | 24b. MFR CO | | | | ME AND ADDRESS | | | | | | | | | _ | | | |
| 04 84====== | 2021773 | | | | AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 27-JUL-2023 | Marion | LITERATURE | | | | , | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | ATE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 72-year-old female patient received bosutinib (BOSULIF), first regimen from 04Sep2018 to 04Feb2020 at 200 mg daily, second regimen from 05Feb2020 to 07Mar2021 at 300 mg daily and third regimen since 08Mar2021 (ongoing) at 400 mg daily; fluvastatine [fluvastatin] (FLUVASTATINE [FLUVASTATIN]), (ongoing) (Batch/Lot number: unknown). The patient had no relevant medical history. The patient's concomitant medications were not reported.

The following information was reported: DIARRHOEA (non-serious) with onset 21Jun2021, outcome "recovering", described as "Diarrhea 1x/day"; ABDOMINAL PAIN UPPER (non-serious) with onset 21Jun2021, outcome "recovered" (14Oct2021), described as "Epigastralgia". The action taken for bosutinib was dosage reduced; for fluvastatine [fluvastatin] was dosage not changed. Additional information: The patient experienced epigastralgia on 21Jun2021 which resolved on 14Oct2021, diarrhea 1x/day on 21Jun2021. The events epigastralgia rated with grade 2 and diarrhea rated with grade 1 were reported as non serious. Since the last consultation, liquid stools once a day. Epigastralgia just after the intake of drugs bosutinib and fluvastatin. The event diarrhea was resolved on 20Mar2023. No action was taken with fluvastatin in response to epigastralgia while bosutinib dose was reduced in response to epigastralgia. No action taken with bosuitnib in response to diarrhea. Event did not reappeared with reintroduction of medication. Bosutinib reported as ongoing at the time of the report.

According to the reporter, epigastralgia was related to study drug bosutinib and related to co-suspect medication fluvastatine while diarrhea was related to bosutinib but not related to fluvastatine.

Follow-up (19May2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information included: The patient had no medical history. Bosutinib was taken at 200 mg until 04Feb2020 then at 300 mg. Epigastralgia resolved on 14Oct2021. No action was taken with fluvastatin in response to epigastralgia while bosutinib dose was increased.

Follow-up (23May2023): This is a non-interventional study follow-up report received from CRO for protocol B1871047. Updated information included: updated outcome for diarrhea and recovery date, updated action taken with bosutinib.

Follow-up (12Jul2023): This is a non-interventional study follow up report from same contactable other HCP. Updated information: bosutinib reintroduction details.

Follow-up (27Jul2023): This is a non-interventional study follow-up report received from CRO for protocol B1871047. Updated information included: Investigator Initial Aware Date, suspect drug Bosulif details (ongoing selected), event Diarrhoea details (stop date, outcome).

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

Case Comment: Due to a reasonable drug-event temporal association and the known drug safety profile, the company deems there is a reasonable possibility that epigastralgia and diarrhea are related to the suspect drug bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION | |
|--|---|---------------------------|--|--|
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, daily; Unknown | Unknown | 05-FEB-2020 / | |
| Regimen #2 | | | 07-MAR-2021; | |
| | | | 1 year 1 month 3 days | |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg, daily; Unknown | Unknown | 08-MAR-2021 / | |
| Regimen #3 | | | Ongoing; | |
| | | | Unknown | |

| | | | | | | | | | | | | CIO | ON | /IS I | FO | RM | | |
|--|--|--|-----------------|--|----------------------------------|-----------|----------|-------|-------|------|-----------|----------------------------------|-----------------|-------|-----|----|--|--|
| | | | | | | | | | | | | | | | | | | |
| SUSPEC | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | Τ | | T | | Т | | П | Τ | Τ | T | Π | | |
| | | | | | | | 14 | | | | | | | | | | | |
| | | | CTION | INFOR | MATION | 4 | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 68.00 Da | ay | Mont | h | Year | 8-12 | AF | IECK ALL PROPRI OVERSE I | ATE | | ı | | | |
| PRIVACY | | PRIVACY | Years | Female | kg 03 | 3 | JUI | V 2 | 2021 | | AL | VERGE | \LA | 01101 | • | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER Unplanned pregn | | | | | 2 | J J IN | TIENT DI | OR | | | | | | | | | | |
| | : OBSERVATIONAL FE CONDITIONS (| _ STUDY- EVALUATION OF USE | N OF EFF | FICACY | AND SAFETY | OF I | BOSI | JLIF | | | НС | OLONGE OSPITALI: VOLVED | SATI | ION | | | | |
| This is a non-inte | , , | oort received from conta | actable re | eporter(s) | (Physician and | d Ot | ther F | HCP) | for | L | OF DI: | R SIGNIFI SABILITY CAPACIT | ICAN 'OR | ΝT | INI | | | |
| A 32-year-old female subject (pregnant) received bosutinib (BOSULIF) (Continued on Additional Information Page) | | | | | | | | | | | | | | | | | | |
| | | II. SUSPEC | T DRUC | G(S) IN | FORMATIO | N | | | | • | | | _ | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION S. SUSPECT DRUG(S) (include generic name) 1) Bosulif (BOSUTINIB) Film-coated tablet 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | (Continued on Additional Information Page) 5. DAILY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | | | | | | | |
| 17. INDICATION(S) FOR | USE | | | | | | | | | | | | 1. DID REACTION | | | | | |
| #1) chronic myelo | id leukaemia (Chroni | ic myeloid leukaemia) | | REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 19-NOV-2019 | · | | | 19. THERAPY DURATION #1) 1 month 7 days | | | | | | | | | ×Ω | Α | | | | |
| | | III. CONCOMIT | ANT DE | RUG(S |) AND HIST | OR | Υ | | | | | | | | | | | |
| | JG(S) AND DATES OF ADM E (DESOGESTRE | IINISTRATION (exclude those use L); Unknown | ed to treat rea | action) | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | |
| From/To Dates | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | Description | MD (| | | | | | | | | | | | | |
| 24-MAY-2021 Unknown to Ongo | | Relevant Med His | tory | Chronic i | .MP for pregna myeloid leuken | nia (| Chro | | • | | | , | | | | | | |
| 26-SEP-2017 to U | Jnknown | Relevant Med His | tory | Immune | thrombocytope | enia | (lmm | nune | thror | nboc | ytop | enia) | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | IV. MANUF. | ACTUR | ER INF | ORMATION | N | | | | | | | | | | | | |
| 24a. NAME AND ADDRE Pfizer Inc | SS OF MANUFACTURER | 10.100.01 | | 26. REM | | | | | | | | | _ | | | | | |
| Stella Pietrafesa | Stella Pietrafesa 66 Hudson Boulevard East | | | | | | | | | | | | | | | | | |
| New York, NY 1000 Phone: 212 733 40 | 01 UNITED STATES 045 | 3 | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | 24b, MFR CO 2021857 | | | | ME AND ADDRESS (E AND ADDRES | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPORT | SOURCE | | NAME | AND ADDRES | S W | /ITHH | IELD. | | | | | | | | | | |
| 10-FEB-2023 | | ш | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | ATE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

(Batch/Lot number was not reported), via an unspecified route of administration, from 19Nov2019 to 25Dec2019 at 200 mg daily, from 26Dec2019 to 30Dec2019 at 300 mg daily, from 31Dec2019 to 17Dec2020 at 200 mg daily, and from 18Dec2020 to 23Jun2021 at 300 mg daily (taken intermittently since May2021 - 12 tablets of 100 mg between 01Jun and 23Jun2021), for chronic myeloid leukaemia. Medical history included chronic myeloid leukaemia from an unknown date and ongoing, corticosensitive immunological thrombopenia from 26Sep2017 to an unknown date. The subject had had 2 pregnancies without complication, one abortion on 26Jul2017, one healthy child born on 13Sep2019, with vaginal delivery /Child APGAR 10. Concomitant medication(s) included desogestrel (OPTIMIZETTE) taken for contraception, start and stop date were not reported. The subject experienced unplanned pregnancy on 03Jun2021. The event unplanned pregnancy was rated grade 3. It was "accidental" pregnancy under optimizette, oral contraception. The estimation conception date was May2021 and date of last menstrual period was 24May2021. The patient is expected to deliver one baby on 28Feb2022. Pregnancy was declared following human chorionic gonadotropin (HCG) and ultrasound results. HCG was 2001.0 IU/L on 24Jun2021, commented as pregnancy 4 to 5 weeks. Ultrasound scan on 29Jun2021 revealed monoembryonic pregnancy, 5 weeks of amenorrhea. The subject did not smoke, drink alcohol, use illicit drugs during this pregnancy. The subject stopped bosutinib definitely when she made beta HCG on 24Jun2021. But bosutinib was taken intermittently since May2021 - 12 tablets of 100 mg between 01Jun and 23Jun2021. The subject was seen the hematologist on 01Jul2021, bosutinib was withdrawn on prescription. The action taken in response to the event for bosutinib was permanently withdrawn. The outcome of the unplanned pregnancy was resolved on 22Feb2022.

Reporter's comment: "delivery on 22Feb2022".

The investigator assessed the event as not related to bosutinib.

Follow-ups (29Oct2021): This is a non-interventional study report for protocol B1871047. Updated information includes: event onset date, and bosutinib stop information.

Follow-up (13Jul2022): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: the outcome of the event and reporter's comment.

Follow-up (10Feb2023): This is a non-interventional study follow up report for protocol B1871047. Updated information includes: update start date of bosutinib (19Nov2019) and event upplanned pregnancy (03Jun2021).

| 13 | I ah | Data |
|-----|------|------|
| 10. | Lav | Data |

| # | Date | Test / Assessment / Notes | | Results | Normal High / Low | |
|---|-------------|--------------------------------|-------|------------------|-------------------|---|
| 1 | 24-JUN-2021 | Human chorionic gonadotropin | | 2001.0 IU/I | | ٠ |
| | | Pregnancy 4 to 5 weeks | | | | |
| 2 | 29-JUN-2021 | Ultrasound scan | | Monoembryonic | | |
| | | Gestational age 5 weeks of ame | norrh | pregnancy nea | | |

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 | chronic myeloid leukaemia | 26-DEC-2019 / |
| Regimen #2 | | (Chronic myeloid leukaemia) | 30-DEC-2019; |
| | | | 5 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 200 mg, daily; Unknown | chronic myeloid leukaemia | 31-DEC-2019 / |
| Regimen #3 | | (Chronic myeloid leukaemia) | 17-DEC-2020; |
| | | | 11 months 17 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, daily (taken | chronic myeloid leukaemia | 18-DEC-2020 / |
| Regimen #4 | intermittently since | (Chronic myeloid leukaemia) | 23-JUN-2021; |
| | May2021 - 12 tablets of | | 6 months 6 days |

14-19. SUSPECT DRUG(S) continued

15. DAILY DOSE(S);
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

100 mg between 01Jun and 23Jun2021); Unknown

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|---|
| - Unknown | Relevant Med History | Pregnancy (Pregnancy); |
| | • | 1 healthy child born on 13Sep2019, with vaginal delivery /Child |
| | APGAR 10 | |

| | | | | | | | CIOMS FORM |
|--|--|---|-------------|-------------|-------------------|----------------------|---|
| | | | | | | | |
| SUSPECT | ADVERSE F | REACTION REPO | RT | | | | |
| | | | | | | | |
| | | | | | | | |
| | | | 1 1 | | | | T |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 33 Years | 3. SEX Male | 115.00 Day | / Month Year | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
| | | tests/lab data) ttoms if any separated by comma | as) | | | | PATIENT DIED INVOLVED OR |
| | | | ON OF EF | FICACY | AND SAFETY | OF BOSULIF | HOSPITALISATION |
| | | | ı Safety S | tudy) red | ceived from a co | ntactable | OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | | | (Cont | inued on Addition | al Information Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRU | G(S) IN | IFORMATIO | N | |
| | - | tablet | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/day | | | | | | N | YES NO NA |
| 17. INDICATION(S) FOR US #1) Unknown | SE . | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/t #1) Ongoing | | | | | | | YES NO NA |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HIST | ORY | |
| 22. CONCOMITANT DRUG(S | APPROPRIATE Day Name Year Say Name Year Name Name Name Year Name Nam | | | | | | |
| | | | | | | | |
| | | | | | | | |
| -2 OTHER RELEVANT HIS | TODY (= di-gnostice | | " -f-priod | | | | |
| From/To Dates | | Type of History / Notes | | Description | myeloid leukem | ia (Chronic myelo | id leukaemia) |
| | | | | | | | |
| | | IV. MANUF | ACTUR | ER IN | FORMATION | I | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard | d East UNITED STATES | 3 | | 26. REI | MARKS | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NA | AME AND ADDRESS C | F REPORTER | |
| | 2022000 | 12620 | | NAMI | E AND ADDRES | S WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURER | | | | | | | |
| 27-OCT-2023 | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 1 | <u></u> | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 33-year-old male patient received bosutinib (BOSULIF), (ongoing) at 500 mg 1x/day. The patient's relevant medical history included: "Chronic myeloid leukemia", start date: 12Oct2018 (ongoing). The patient's concomitant medications were not reported. The following information was reported: VERTIGO (non-serious) with onset 01Apr2021, outcome "recovered" (08Apr2021), described as "Benign vertigo". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of vertigo.

The reporter considered "benign vertigo" not related to bosutinib.

Additional information: The event benign dizziness was reported as non-serious with grade 2. Benign paroxystic dizziness a few days, recovered with an unspecified drug and swing test (rehabilitation of the internal ear).

Follow-up (27Oct2023): This follow-up report is being submitted to amend previously transmitted information following reconciliation between safety and clinical databases: Event term coding was updated: Benign vertigo (previously coded as Benign dizziness).

Case Comment: Based on the information provided, upon FU, the event vertigo is assessed as unrelated to bosutinib. No action was taken for bosutinib for the event.

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| SUSPEC | T ADVERSE | REACTION RE | PORT | | | | | | | | | | | | | | _ | |
| | | | | | | | П | | Γ | П | \top | Т | \top | П | | П | | |
| | | | | | | | 4 | | | | | \perp | | Ш | | Ш | | |
| | · SOUNTRY | | REACTION | ı | | 100 | TOTIC | 0210 | | Las | - 0 | | | | _ | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month PRIVACY | 2a. AGE Year 73 Years | 3. SEX Male | 3a. WEIGHT 96.00 kg | Day | Mont DE | | Year 201 | | APPROPRIATE TO | | | | | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF anemia [Anaemia] STOMACH ACHE | RED TERM] (Related sym | nptoms if any separated by o | commas) | | | | | | | l I | | NVO | | | | NT | | |
| UNDER REAL-LIF | E CONDITIONS | | | | | | | | | (| – 0 | OR SI | SIGNIFI BILITY | OR | 13T2 | NT | | |
| This is a non-interreporter(s) (Physic | | port (Post Authoriz 31871047. | ation Safety S | Study) red | ceived from a | conta | actabl | e | | | | | PACIT | Y | | | | |
| | | | | (Cont | inued on Addit | ional li | nforma | ation P | Page | e) L | 그 ii | IFE THRE | EATEN | ING | _ | | _ | |
| C | | II. SUSF | PECT DRU | G(S) IN | IFORMATI | ON | | | | 1,,, | -: | 316 | =:211 | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU ⁻ #2) INEXIUM [ESC | TINIB) Film-coated | | | | <u> </u> | | | , | | 20. | DID R ABAT DRUG | TE AF | | STOPP | ING | | | |
| 15. DAILY DOSE(S) #1) UNK #2) UNK | | | # | 1) Unkno | own | TION | | | | \perp | | | | ю [|]NA | ١. | | |
| 17. INDICATION(S) FOR U #1) Unknown #2) Unknown |) UNK | | | | | | | 21. | | PPE/ | CTION AR AFT DDUCT | TER | | | | | | |
| 18. THERAPY DATES(from #1) Unknown #2) Unknown | INDICATION(S) FOR USE 1) Unknown 2) Unknown I. THERAPY DATES(from/to) 1) Unknown 19. THERAPY DURATION #1) Unknown | | | | | | | | П | YES | Пν | ю 🔀 |] NA | 4 | | | | |
| | | III. CONCC | OMITANT D | RUG(S |) AND HIS | STOF | RY | | | • | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADI | MINISTRATION (exclude th | | _ |) | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT HI From/To Dates Unknown | ISTORY. (e.g. diagnostics | s, allergies, pregnancy with Type of History / N | | I, etc.) Description | | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | | |
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| | | | | | <u> </u> | | | | | | | | | | | | | |
| | | IV. MAN | NUFACTUR | RER IN | FORMATIC | NC | | | | | | | | | | | _ | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | ard East 1 UNITED STATE | | | 26. REN | MARKS | | | | | | | _ | | | _ | | _ | |
| | 24b. MFR Co | ONTROL NO. | | 25b. N/ | ME AND ADDRES | SS OF R | EPORT | ER | | | | | | | _ | | _ | |
| | 2022000 | | | | E AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | 24d. REPOR | | TURE | | | | | | | | | | | | | | | |
| 17-JAN-2022 | ₩ HEALTH PROFE | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | VUP: | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 73-year-old male patient received bosutinib (BOSULIF); esomeprazole magnesium (INEXIUM [ESOMEPRAZOLE MAGNESIUM]), (Batch/Lot number: unknown). The patient's relevant medical history and concomitant medications were not reported. The following information was reported: ABDOMINAL PAIN UPPER (non-serious) with onset Dec2019, outcome "recovered" (24Feb2020), described as "STOMACH ACHES"; ANAEMIA (non-serious) with onset 23Jan2020, outcome "recovering", described as "anemia". The action taken for bosutinib was dosage reduced; for esomeprazole magnesium was dosage not changed.

The reporter considered "anemia" and "stomach aches" related to bosutinib.

Additional information: The anemia resulted in headaches and fatigue. Anemia was rated grade 2. In response to anemia, bosutinib dose was reduced and no action taken for concomitnat drug INEXIUM. Anemia was related to bosutinib and to concomitant drug INEXIUM. Stomach aches as rated grade 2, related to bosutinib and unrelated to any concomitant drug. No action was taken for bosutinib in response to stomach aches.

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

Case Comment: A causal association between administration of bosutinib and the onset of "anemia" and "stomach aches" cannot be excluded, considering the temporal association and the known adverse event profile of the suspect product.

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| SUSPECTAD | VERSE REA | ACTION REPO | KI | | | | | | | | | | | | |
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| | | I. REA | CTION | INFOR | MATION | Ļ | | | , | | | | | | |
| (first, last) | ANCE Da | 2. DATE OF BIRTH y Month Year | 2a. AGE 74 | 3. SEX | 3a. WEIGHT 96.00 | 4- Day | 6 REACTION Month | | ┪ | CHECK APPRO | PRIATE | | | | |
| PRIVACY FR. | ANCE | PRIVACY | Years | Male | 96.00 kg | 28 | | | | ADVER | SE REA | CTION | | | |
| 7 + 13 DESCRIBE REACTION(S) (i Event Verbatim [PREFERRED TER | including relevant tests | /lab data) | as) | | | | | | | PATIEN [*] | T DIED | | | | |
| tremor of extremities [Tre | | any obparation by dominion | 20) | | | | | | 15 | INVOLV | ED OR | | | | |
| Case Description: OBSE | RVATIONAL ST | TUDY - EVALUATIO | ON OF E | FICACY | AND SAF | ETY (| OF BOSI | JLIF | | PROLO HOSPIT | NGED I ALISAT | NPATIE ION | NT | | |
| UNDER REAL-LIFE COI | | | | | | | | | _ | INIVOLV | בם מבי | CICTE | NIT | | |
| This is a non-intervention | nal study report | received from a co | ntactable | reporter | s) (Physici | ian) fo | or protoc | ol | ╽╙ | INVOLV OR SIG DISABIL | NIFICA LITY OF | NΤ | INT | | |
| B1871047. | | | | 47 | | | | | | INCAPA | CITY | | | | |
| A 74-year-old male patie | nt received bos | utinib (BOSULIF). | | | | | 7 | | | | | | | | |
| · | | , | | (Cont | nued on Ad | dition | al Informat | ion Page) | | LIFE THREAT | TENING | | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMA | TIOI | N | | | | | | | | |
| 14. SUSPECT DRUG(S) (include ge | | | | ` ' | | | | | | REACTI | | PPING | i | | |
| #1) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | JG? | LICOIC | 7 7 1140 | | | |
| 15. DAILY DOSE(S) | | | | | OF ADMINIST | RATION | 1 | | 1 , | F | ٦ | | | | |
| #1) | | | # | t1) Unkno | own | | | | ╽╙ | YES | NO | M N | 4 | | |
| 17. INDICATION(S) FOR USE | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER | | | | | |
| #1) Unknown | | | | | | | | | REINTRODUCTION? | | | | | | |
| 18. THERAPY DATES(from/to) | | | | 9. THERAPY 1) Unkno | | | | | TYES TNO NA | | | | | | |
| #1) Unknown | | | " | ri) Ulikili | OWII | | | | THES LING MINA | | | | | | |
| | | III. CONCOMIT | TANT D | DLIC(S |) VND 🗖 | IST | 1 DV | | | | | | | | |
| 22. CONCOMITANT DRUG(S) AND | | | | |) AND H | 1310 | ו אכ | | | | | | | | |
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| | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. From/To Dates | (e.g. diagnostics, allerg | gies, pregnancy with last mo | onth of period | , etc.) Description | | | | | | | | | | | |
| Unknown | | Type of filology / Holes | | Description | | | | | | | | | | | |
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| | | IV. MANUF | ACTUE | RER INI | -ORMAT | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF MA | NUFACTURER | IV. IVIAINOI | , (0101 | 26. RE | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa | | 7 | | | | | | | | | | | | | |
| 66 Hudson Boulevard Eas New York, NY 10001 UNI | | | | | | | | | | | | | | | |
| Phone: 212 733 4045 | | | | | | | | | | | | | | | |
| | 24b. MFR CONTRO | OL NO. | | 25b. NA | ME AND ADDR | RESS O | F REPORTE | R | | | | | | | |
| | 2022000825 | | | | AND ADD | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOL | JRCE | | \dashv | | | | | | | | | | | |
| BY MANUFACTURER 17-JAN-2022 | STUDY | LITERATURE | | | | | | | | | | | | | |
| | HEALTH PROFESSION | | | _ | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYP | FOLLOWUP: | | | | | | | | | | | | | |
| - ' | | LOLLOWOP: | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: TREMOR (non-serious) with onset 28Sep2021, outcome "recovered" (03Nov2021), described as "tremor of extremities". The action taken for bosutinib was dosage not changed.

The reporter considered "tremor of extremities" not related to bosutinib.

Additional information: the event was reported as non-serious and rated grade 1.

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

Case Comment: Based on the information currently provided, the company deemed that there is not a reasonable possibility that the event tremor of extremities was related to Pfizer study drug BOSUTINIB.

| | | | | | | | CIOMS FORM |
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | |
| 000. 20 | I ADTENDE. | (LAOHOR IL.) | IXI | <u> </u> | | · | |
| | | | | | | | |
| | | L REΔ | CTION | INIEOR | MATION | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | | -6 REACTION ONSET | 8-12 CHECK ALL |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 74 Years | Male | 96.00 Day | | APPROPRIATE TO ADVERSE REACTION |
| Other Serious Crite Thoracic pain [Che | eria: Medically Sig est pain] | nificant | 38) | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| UNDER REAL-LIF | E CONDITIONS (| OF USE | | 47 | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | ort (Post Authorization | Sarety 5 | ituay) rec | ceived from a co | ontactable | |
| , ,,,,, | , · | | | (Cont | inued on Addition | al Information Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRU | G(S) IN | IFORMATIO | N | |
| | - | tablet | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) UNK | | | | | | N | YES NO NA |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from #1) Unknown | n/to) | | | | | | YES NO NA |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HIST | ORY | |
| PRIVACY FRANCE Does Provided to the Company of the | | | | | | | |
| | | | | · · | | | |
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| From/To Dates | ISTORY. (e.g. diagnostics, | | onth of period | | | | |
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| | | IV MANUE | | DED IN | | 1 | |
| | S OF MANUFACTURER | IV. IVIAINOI | ACTO | | | N . | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 | 1 UNITED STATES | 3 | | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NA | ME AND ADDRESS C | OF REPORTER | |
| | 2022000 | 83080 | | NAME | E AND ADDRES | S WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURES | | | | \neg | | | |
| 03-JUL-2023 | 1 — | ш | | | | | |
| SUSPECT ADVERSE REACTION REPORT I. REACTION INFORMATION | | | | | | | |

7+13. DESCRIBE REACTION(S) continued B1871047.

A 74-year-old male patient received bosutinib (BOSULIF). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: CHEST PAIN (medically significant) with onset Apr2021, outcome "recovered" (01Jun2021), described as "Thoracic pain"; CARDIAC FAILURE (non-serious) with onset Jun2021, outcome "not recovered", described as "Cardiac insufficiency". The patient underwent the following laboratory tests and procedures: Angiocardiogram: (17May2021) stenosis of interior intraventricular artery 2=40%, notes: and right coronary 50%. The action taken for bosutinib was dosage not changed.

Additional information: thoracic pain (effort angor): exploration coronarography on 07May2021: stenosis of Anterior intraventricular artery 2=40% and right coronary 50%. Multifactor cardiac insufficiency (ischemic and hypertension) leading to edema, hypertension arterial, fatigue and renal insufficiency. Thoracic pain was grade 3 and cardiac insufficiency was grade 2.

The investigator considered the events were not related to study drug or to concomitant treatments.

Follow-up (03Jul2023): This is a follow-up from a non-interventional study report received from the investigator via the CRO. Updated information included: updated patient's height.

Case Comment: In agreement with the reporter, the Company considers that the possibility that the suspect drug bosutinib may have caused the reported events chest pain and cardiac failure can be excluded.

| 13. Lab Data | ı | | | |
|--------------|-------------|---------------------------|--|-------------------|
| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
| 1 | 17-MAY-2021 | Angiocardiogram | stenosis of interior intraventricular artery 2=40% | |
| | | and right coronary 50% | r | |

| | | | CIOMS FORM |
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| | | | |
| SUSPECT A | DVERSE REACTION REPORT | | |
| | | | |
| | | | |
| | | ON INFORMATION | <u> </u> |
| (first, last) | RANCE Day Month Year 4 | AGE 3. SEX 3a. WEIGHT 4-6 REACTION ONSET 15 remale 95.00 Day Month 14 APR 2020 | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION |
| 7 + 13 DESCRIBE REACTION(S Event Verbatim [PREFERRED T POSITIONAL MYALGI | 6) (including relevant tests/lab data) ERM] (Related symptoms if any separated by commas) A [Myalgia] | | PATIENT DIED INVOLVED OR |
| Case Description: OBS UNDER REAL-LIFE C | | OF EFFICACY AND SAFETY OF BOSULIF | PROLONGED INPATIENT HOSPITALISATION INVOLVED PERSISTENT |
| | ional study report (Post Authorization Saf and Other HCP) for protocol B1871047. | ety Study) received from contactable | OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | (Continued on Additional Information Page) | LIFE THREATENING |
| | II. SUSPECT D | PRUG(S) INFORMATION | , |
| 14. SUSPECT DRUG(S) (include #1) Bosulif (BOSUTINIE | - | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) UNK | | 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | YES NO NA |
| 17. INDICATION(S) FOR USE #1) Unknown | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/to) #1) Ongoing | | 19. THERAPY DURATION #1) Unknown | YES NO NA |
| | III. CONCOMITAN | IT DRUG(S) AND HISTORY | |
| 22. CONCOMITANT DRUG(S) A | ND DATES OF ADMINISTRATION (exclude those used to t | treat reaction) | |
| | | | |
| | | | |
| 23. OTHER RELEVANT HISTOR From/To Dates | tY. (e.g. diagnostics, allergies, pregnancy with last month of Type of History / Notes | period, etc.) Description | |
| Unknown | | • | |
| | | | |
| | IV MANITEAC | TURER INFORMATION | |
| 24a. NAME AND ADDRESS OF | | 26. REMARKS | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard E New York, NY 10001 U Phone: 212 733 4045 | | | |
| | 24b. MFR CONTROL NO. | 25b. NAME AND ADDRESS OF REPORTER | |
| | 202200098625 | NAME AND ADDRESS WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE STUDY LITERATURE | NAME AND ADDRESS WITHHELD. | |
| 06-SEP-2023 | HEALTH PROFESSIONAL OTHER: | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYPE INITIAL FOLLOWUP: | | |

7+13. DESCRIBE REACTION(S) continued

A 45-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), (ongoing). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: MYALGIA (non-serious) with onset 14Apr2020, outcome "recovered" (2020), described as "POSITIONAL MYALGIA". The action taken for bosutinib was dosage not changed.

The reporter considered "positional myalgia" not related to bosutinib.

Additional information: Two events were assessed as non-serious and rated grade 1.

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

Amendment: This follow-up report is being submitted to amend previously reported information: The patient's gender was updated to female.

Follow-up (06Sep2023): This is a follow-up report from the investigator via CRO. New information received included: The event anxiety was removed.

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

Case Comment: The event "positional myalgia" is an intercurrent medical condition, not related to the suspect drug bosutinib.

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|--|--|--|-------------------|----------------------|-------------------------------|-----------|-----------|---------|-------------|---|-----|----------------------|----------------------------|------------|-------------|----|----|
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | |
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| | | | | | | | \square | | | | | | | | | | |
| | | I. REA | CTION II | NFORN | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | | | ACTIC | N ONS | SET Year | ┥. | | | CK ALL ROPRIA | TE T | 0 | | |
| PRIVACY | FRANCE | PRIVACY Year | 67 Years | emale | 74.00 Da 08 | | AU | | 201 | | | ADV | ERSE R | EAC | TION | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER Martial deficiency | | t tests/lab data) otoms if any separated by comma | as) | | | | | | | | | INVO | ENT DIE | DR | | | |
| | OBSERVATIONA FE CONDITIONS (| L STUDY - EVALUATIO OF USE | ON OF EFF | FICACY A | AND SAFETY | OF | BOS | ULIF | | PROLONGED INPATIENT HOSPITALISATION | | | | | | | |
| | ventional study repcian) for protocol B | oort (Post Authorization 1871047. | n Safety St | udy) rece | vived from a co | onta | ctabl | е | | OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | |
| | | | | (Contin | ued on Addition | nal Ir | ıforma | ation F | Page | , | | LIFE THRE | EATENII | NG | | | |
| | | II. SUSPEC | T DRITIC | | | | | | | <u>- 1</u> | | | | | | | _ |
| 14. SUSPECT DRUG(S) (#1) Bosulif (BOSU | include generic name) TINIB) Film-coated | | 71 DIXOC | <u> </u> | ORWATIO | 14 | | | | 20 | ABA | REAG ATE A UG? | CTION FTER S | TOP | PING | | |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/da | у | | | ROUTE(S) C | DF ADMINISTRATIO |)N | | | | | | YES | □ NC | > [| Z N∕ | Ą | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | 21 | REA | APPE. | CTION AR AFTI DDUCTI | | | | |
| 18. THERAPY DATES(froi #1) 16-DEC-2016 | · | | | THERAPY D) Unknow | | YES NO NA | | | | | | | | | | | |
| | | III. CONCOMIT | TANT DR | RUG(S) | AND HIST | OR | Υ | | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | sed to treat read | etion) | | | | | | | | | | | | | |
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| From/To Dates | HSTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| | | 1) / 840811 15 | -A OTI 101 | רם וגיר | | | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUF | ACTURI | 26. REMA | | ν | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | | |
| | 24h MED 00 | NITPOL NO | | OFh NAME | IE AND ADDRESS (|)E D' | -DODT | ED | | | | | | | | | |
| | 24b. MFR CC 2022001 | | | | E AND ADDRESS (AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | | | 1 | | | | | | | | | | | | | |
| 18-JAN-2022 | R STUDY | LITERATURE OTHER: | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 67-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), since 16Dec2016 (ongoing) at 300 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: IRON DEFICIENCY (non-serious) with onset 08Aug2019, outcome "not recovered", described as "Martial deficiency". The action taken for bosutinib was dosage not changed.

The reporter considered "martial deficiency" not related to bosutinib.

Additional information: Iron deficiency rated grade 2, non-serious. The event was unrelated to bosutinib and to any concomitant drug. The site reported: "known recurrent martial deficiency".

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

Case Comment: The event Iron deficiency was attributed to an intercurrent medical condition and unrelated to bosutinib.

| | | | | | | | CIOMS FORM |
|--|---|--------------------------------|------------------|---------|----------------|--------------|---------------------------------|
| SUSPECT ADVERSE REACTION REPORT I. REACTION INFORMATION I. PATIENT INITIALS (first, lists) | | | | | | | |
| SUSPEC | T ADVERSE I | REACTION REPO | RT | | | | |
| | | | | | | | |
| | | | | | | | |
| | | I. REA | CTION I | NFOR | MATION | | |
| | | | 1 1 | 3. SEX | _ | | APPROPRIATE TO |
| PRIVACY | TRANCE | | | Male | 1 70.00 | | ADVERSE REACTION |
| Other Serious Crit Arthrosis flare-up | eria: Medically Sig (grade 4) [Osteoal | nificant | as) | | | | INVOLVED OR PROLONGED INPATIENT |
| UNDER REAL-LIF | FE CONDITIONS | OF USE | | 47 | | | DISABILITY OR |
| | | DOIT (FOST AUTHORIZATION | i Salety St | | | | LIFE |
| | | | | - | | | THREATENING |
| 44 OLIOPEOT PRUO(0) (| :ld\ | II. SUSPEC | T DRUG | S(S) IN | IFORMATIC | <u>N</u> | OO DID DEACTION |
| #1) Bosulif (BOSU | TINIB) Film-coated | tablet | | | | | ABATE AFTER STOPPING |
| #1) UNK | | | #1 |) Unkno | own | ON | YES NO NA |
| #1) Unknown | USE | | | | | | REAPPEAR AFTER |
| #1) Unknown | m/to) | | #1 |) Unkno | own | | YES NO NA |
| , | | III. CONCOMIT | | | | ΓORY | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | ed to treat read | ction) | · | | |
| | | | | _ ` | | | |
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| | IISTORY. (e.g. diagnostics | | | | | | |
| Unknown | | | | | | | |
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| | | D. C. DA A DILLE | A OTUD | | | N.1 | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUF | ACTUR | | | N | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 | 1 UNITED STATES | 3 | | | | | |
| | 24b. MFR CC | ONTROL NO. | | 25b. NA | ME AND ADDRESS | OF REPORTER | |
| | 2022001 | 10342 | | NAMI | E AND ADDRES | SS WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURES | R 24d. REPOR | | | | | | |
| 18-JUL-2023 | I — | | | | | | |
| | l | _ | | | | | |

7+13. DESCRIBE REACTION(S) continued B1871047.

A 76-year-old male patient received bosutinib (BOSULIF); nilotinib (NILOTINIB), (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 05Nov2020, outcome "recovered" (04Feb2021), described as "DIARRHEA"; OSTEOARTHRITIS (hospitalization, medically significant) with onset 27Feb2021, outcome "recovered" (Feb2021), described as "Arthrosis flare-up (grade 4)". The action taken for bosutinib and nilotinib was dosage not changed.

The reporter considered "arthrosis flare-up (grade 4)" not related to bosutinib. The reporter considered "diarrhea" related to bosutinib.

Additional information: According to the investigator, the events were unrelated to concomitant medications.

Follow-up (05Jul2022): 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 (diarrhea).

Follow-up (18Jul2023): 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: event diarrhea was resolved on 04Feb2021.

Case Comment: There was not a reasonable possibility that the event "arthrosis flare-up (grade 4)" was related to suspect drug, bosutinib and is most likely due to the underlying disease of osteoarthritis. Based on the known drug safety profile, a causal association between bosutinib and the event diarrhea cannot be excluded. This case will be reassessed when further information is provided.

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|--|---|------------------|-------------------------|--------------|----------|--------------|--------------|------|--------|-----------------------------|------------|------|----|
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| SUSPECT ADV | ERSE REACTION REPOR | ? T | | | | | | | | | | | |
| OGGI EGI ADV | ENGL REAGIION REFO | `` | | | 1 1 | | | | | | | | |
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| | I DEAC | TION II | NFORMA | TION | | 7 | • | | | | | | |
| | DUNTRY 2. DATE OF BIRTH | | | | 4-6 REA | CTION | ONSET | 8-12 | CHE | CK ALL | | | |
| PRIVACY FRAI | NCE Day Month PRIVACY Year | 64 Years | emale 1 | | ay 26 | Month DEC | Year 2019 | 9 | | ROPRIA ERSE R | | N | |
| 7 + 13 DESCRIBE REACTION(S) (incl Event Verbatim [PREFERRED TERM] | luding relevant tests/lab data) (Related symptoms if any separated by commas | s) | | | | | | | PATI | ENT DIE | D | | |
| left eyelid lesion [Eyelid dis right iliac fossa pain [Abdo | - | | | | | | | 10 | PRC | OLVED O LONGE PITALIS | D INPAT | IENT | |
| | VATIONAL STUDY - EVALUATIO | N OF EFF | FICACY AN | SAFETY | OF E | BOSUI | LIF | _ | I INIV | OLVED F | EDEIET | ENIT | |
| UNDER REAL-LIFE COND | DITIONS OF USE | | | | | | | ╽╙ | OR S | SIGNIFIC ABILITY | CANT OR | EINI | |
| This is a non-interventiona protocol B1871047. | I study report received from conta | actable rep | oorter(s) (Ph | nysician an | nd Oth | er HC | P) for | | INC | APACITY | , | | |
| | | | (Continue | d on Additio | nal Inf | ormatio | on Page | | LIFE | EATENI | NG | | |
| | II. SUSPEC | T DRUG | (S) INFO | RMATIC | N | | | | | | | | |
| 14. SUSPECT DRUG(S) (include gene #1) Bosulif (BOSUTINIB) Fil | • | | | | | | | Al | BATE A | CTION AFTER S | TOPPIN | IG | _ |
| , 2004 (20002) | A seated topics | | (Continue | d on Additio | nal Inf | ormatio | on Page | | RUG? | | | | |
| 15. DAILY DOSE(S) #1) 100 mg, 1x/day | | | ROUTE(S) OF A) Unknown | DMINISTRATIO | ON | | | [| YES | S NO | | NA | |
| 17. INDICATION(S) FOR USE | | | | | | | | R | EAPPE | CTION AR AFT | | | |
| #1) Unknown | | | | | | | | RI | EINTR | ODUCTI | ON? | | |
| 18. THERAPY DATES(from/to) #1) 12-NOV-2018 / 18-NOV | 7-2018 | |) 7 days | ATION | | | | | YES | S NO | · 🛛 | NA | |
| | III. CONCOMIT | ANT DR | RUG(S) A | ND HIST | ΓOR` | ſ | | | | | | | |
| 22. CONCOMITANT DRUG(S) AND DA | ATES OF ADMINISTRATION (exclude those use | ed to treat reac | etion) | | | | | | | | | | |
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| | g. diagnostics, allergies, pregnancy with last mor | | | | | | | | | | | | |
| From/To Dates Unknown | Type of History / Notes | D | escription | | | | | | | | | | |
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| | | | | | | | | | | | | | |
| | IV. MANUFA | ACTURE | ER INFOI | RMATIO | N | | | | | | | | |
| 24a. NAME AND ADDRESS OF MANU Pfizer Inc | | | 26. REMARK | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard East | | | | | | | | | | | | | |
| New York, NY 10001 UNITE Phone: 212 733 4045 | ED STATES | | | | | | | | | | | | |
| 1 HOHE. 212 100 4040 | | | | | | | | | | | | | |
| | 24b. MFR CONTROL NO. | | | ND ADDRESS | | | _ | | | | | | |
| | 202200111284 | | | D ADDRES | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE STUDY LITERATURE | | NAME AN | D ADDRES | SS WI | IHHEL | ₋D. | | | | | | |
| 06-SEP-2023 | HEALTH PROFESSIONAL OTHER: | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYPE MINITIAL FOLLOWUP: | | 1 | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 64-year-old female patient received bosutinib (BOSULIF), first regimen from 12Nov2018 to 18Nov2018 at 100 mg 1x/day, second regimen from 19Nov2018 to 25Nov2018 at 200 mg 1x/day, third regimen from 26Nov2018 to 02Dec2018 at 300 mg 1x/day and fourth regimen since 03Dec2018 (ongoing) at 400 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: EYELID DISORDER (non-serious) with onset 26Dec2019, outcome "recovered" (2020), described as "left eyelid lesion"; ABDOMINAL PAIN LOWER (non-serious) with onset 2021, outcome "recovered" (May2021), described as "right iliac fossa pain". The action taken for bosutinib was dosage not changed.

The reporter considered "left eyelid lesion" and "right iliac fossa pain" not related to bosutinib.

Additional information: Left eyelid lesion was rated grade 1. Right iliac fossa pain was rated grade 2.

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

Follow-up (15May2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Other HCP) for protocol B1871047.

Updated information: new reporter (Other HCP).

Follow-up (06Sep2023): This is a non-interventional study follow-up report received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047.

Updated information includes: bosutinib therapy dates and regimens.

Case Comment: Events left eyelid lesion and right iliac fossa pain are most likely related to intercurrent or underlying conditions and unrelated to study drug BOSUTINIB.

14-19. SUSPECT DRUG(S) continued

| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(\$); 16. ROUTE(\$) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
|--|---|---------------------------|--|
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 200 mg, 1x/day; Unknown | Unknown | 19-NOV-2018 / |
| Regimen #2 | | | 25-NOV-2018; |
| | | | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, 1x/day; Unknown | Unknown | 26-NOV-2018 / |
| Regimen #3 | | | 02-DEC-2018; |
| | | | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg, 1x/day; Unknown | Unknown | 03-DEC-2018 / |
| Regimen #4 | | | Ongoing; |
| | | | Unknown |

| | | | | | | | | | | | | CI | O | VIS. | FO | RM |
|--|---|--------------------------------------|--------------------|---------------|----------------------------|------|--------|-----------|-------------------------------|---------------|------|-----------------------------|-------------|----------|------|----|
| | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | |
| | | | | | | Т | П | | П | Т | | П | Т | \top | Τ | Τ |
| | | | | | | | 14 | Ш | | | | Ш | \perp | 丄 | | |
| | FRANCE Day Month PRIVACY Year Year | | | | | _ | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | | Day Month Year | 77 | | 76.30 | Day | Month | | Year | 8-12 | AF | HECK AL PPROPR OVERSE | IATE | | N | |
| Event Verbatim [PREFERF Basedow's diseas | RED TERM] (Related symple [Graves' disease | ptoms if any separated by comn e] | nas) | | | | | | | 2 | | VOLVED ROLONG DSPITAL | OR SED I | INPAT | IENT | |
| | CACY | AND SAFET | Y OF | BOSL | JLIF | | [| OF DI: | VOLVED R SIGNIF SABILIT | FICAI Y OR | .NT | ENT | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | _ _ | IN: | CAPACIT | ΓY | | | | | |
| | | | | | | | | | | <u> </u> | J ;; | REATEN | NING | | | |
| | | II. SUSPEC | CT DRUG | (S) IN | FORMATI | ON | | | | T | | | | | | |
| #1) Bosulif (BOSU | • | tablet | | • | | _ | nforma | tion P | age) | | | EACTION E AFTER 1? | |)PPIN | G | |
| 15. DAILY DOSE(S) #1) 100 mg | | | | | | TION | | | | | YE | ES 🔲 | NO | | NA | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | | | 1 | REAP | EACTION PEAR AF RODUC | FTER | | | |
| 18. THERAPY DATES(fror #1) 10-NOV-2019 / | • | | | | | | | | | | ☐ YE | ES 🔲 | NO | X | NΑ | |
| | | | | $\overline{}$ |) AND HIS | TOF | RY | | | 1 | | | | | | |
| | ` ' | • | used to treat reac | tion) | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT H | ISTORY, (e.g. diagnostics. | allergies, pregnancy with last n | nonth of period, e | tc.) | | | | | | | | | _ | | | |
| From/To Dates Unknown to Ongo | | Type of History / Notes | D | escription | myeloid leuke | emia | (Chro | nic m | yelo | id le | ukae | mia) | | | | |
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| | | | | | | | | | | | | | | | | |
| | | IV. MANU | FACTURE | | | NC | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva | ard East 1 UNITED STATES | s | | 26. REM | MARKS | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | | | | | | | | | | | | | |
| | | | | | E AND ADDRE E AND ADDRE | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | 24d. REPOR | T SOURCE LITERATURE | | | E AND ADDRE | | | | | | | | | | | |
| 07-SEP-2023 | HEALTH PROFES | | | _ | | | | -2. | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE FOLLOWUP: | | | | | | | | | | | | | | |

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

A 77-year-old male patient received bosutinib (BOSULIF), first regimen from 10Nov2019 to 16Nov2019 at 100 mg, second regimen from 17Nov2019 to 23Nov2019 at 200 mg, third regimen from 24Nov2019 to 18Jan2020 at 300 mg and fourth regimen from 19Jan2020 to 16Jan2021 at 400 mg daily. The patient's relevant medical history included: "Chronic myeloid leukemia" (ongoing). Concomitant medication(s) included: NILOTINIB oral taken for chronic myeloid leukaemia, start date: 04Feb2021 (ongoing). The following information was reported: GRAVES' DISEASE (non-serious) with onset 20Nov2021, outcome "not recovered", described as "Basedow's disease"; ATRIAL FIBRILLATION (non-serious) with onset 02Dec2021, outcome "not recovered", described as "RAPID ATRIAL FIBRILLATION". Relevant laboratory tests and procedures are available in the appropriate section. Therapeutic measures were taken as a result of graves' disease.

The reporter considered "basedow's disease" and "rapid atrial fibrillation" not related to bosutinib.

Additional information: The patient then switched to Nilotinib from 04Feb2021 and ongoing, Both events occurred several months after Bosulif was stopped. For Basedow's disease, confirmation of diagnosis on 08Dec2021 associated symptomatology: loss of 8 kgs, tachycardia, quick reflexes, dyspnea on effort, lower TSH, increase in T4; treated by thiamazole (THYROZOL) from 17Dec2021. The event Basedow's disease was rated grade 2. Event reported as non-serious. The event Atrial fibrillation was rated grade 2. Event reported as non-serious. The investigator considered that the event was unrelated to study drug or to any concomitant drug.

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

Follow-up (07Sep2022): 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: lab data, new events (Basedow's disease and atrial fibrillation).

Follow-up (20Sep2022): 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: dyspnea and tachycardia are symptoms of Basedow's disease and therefore removed

Follow-up (18Jul2023): This is a non-interventional study follow up report received from the investigational site via the CRO. Updated information includes: Event RAPID ATRIAL FIBRILLATION onset date was changed to 02Dec2021.

Follow-up (07Sep2023 and 07Sep2023): This is a non-interventional study follow up report received from the clinical team in response to guery and investigational site via CRO.

Updated information includes: medical history added, dosage regimen, action taken of bosutinib added and Nilotinib information.

Case Comment: Based on "the patient switched to Nilotinib from 04Feb2021 and ongoing. Both events occurred several months after Bosulif was stopped", the Company concurs with the investigator that there is not a reasonable possibility that the events, Basedow's disease and atrial fibrillation, were related to bosutinib.

13. Lab Data

| 13. Lab Data | # Date Test / Assessing 1 08-DEC-2021 Blood thyroung 2 08-DEC-2021 Thyroxine 3 08-DEC-2021 Weight D. SUSPECT DRUG(S) continued (SPECT DRUG(S) (include generic name) Bosulif (BOSUTINIB) Film-coated tablet; men #2 | | | | |
|--|---|---|-------------------------|--------------|--|
| # | Date | C-2021 Thyroxine C-2021 Weight (S) continued (e) generic name) 15. DAILY DOSE(S): (f) ROUTE(S) OF ADMIN (IIB) Film-coated tablet; 200 mg; Unknown | ment / Notes | Results | Normal High / Low |
| 1 | 08-DEC-2021 | Blood thyre | oid stimulating hormone | lower | |
| 2 | 08-DEC-2021 | Thyroxine | | increase | |
| 3 | 08-DEC-2021 | Weight | | loss of 8 kg | |
| 1 08-DEC-2021 Blood thyroid stimulating hormone lower 2 08-DEC-2021 Thyroxine increase | | | | | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
| #1) Bosulif | (BOSUTINIB) Film-coa | ated tablet; | | | 17-NOV-2019 / 23-NOV-2019; 7 days |
| , | ` , | ated tablet; | 300 mg; Unknown | Unknown | 24-NOV-2019 / 18-JAN-2020; |

| 11-10 | CHEDECT | DDIIG(S) | continued |
|--------|---------|----------|-----------|
| 14-19. | SUSPECI | DKUGISI | 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 26 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg, daily; Unknown | Unknown | 19-JAN-2020 / |
| Regimen #4 | | | 16-JAN-2021; |
| | | | 11 months 29 days |

| | | | | | | | | | | | | CIO | DM | S F | OF | ₹M | | |
|--|----------------------------|---|--------------------|-----------------------|----------------------|---------|--------|-----------|---------------------------------|----------|--|------------------------------|----|------|----|----------|--|--|
| | | | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | | | |
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| | | | | | | | Ц | Ш | Ш | | | | L | | | <u> </u> | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | CTION II | | MATION 3a. WEIGHT | 4.0.00 | TACTIO | N ONC | | 1040 | | FOK ALL | | | | | | |
| (first, last) PRIVACY | FRANCE | | | | | | | | | | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION | | | | | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) VARICOSITIES OF THE LOWER LIMBS [Varicose vein] EROSION OF THE BUCCAL MUCOSA [Oral mucosa erosion] | | | | | | | | | - | | OLVED OLONGE | OR ED IN | | NT | | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | OR DIS | /OLVED I SIGNIFI SABILITY | CANT | SISTE T | NT | | | | | | |
| | | oort (Post Authorization P) for protocol B18710 | | ıdy) rece | eived from co | ontact | able | | | <u> </u> | INC | CAPACIT | Y | | | | | |
| | | | | (Contin | nued on Additi | onal Ir | forma | tion P | age) | <u> </u> | J ¦¦ | REATEN | NG | | | | | |
| 44 0U0DEGT BBUO(0) (| | II. SUSPEC | CT DRUG | (S) IN | FORMATI | NC | | | | I | 20.05 | 1071011 | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | | tablet | | | | | | | | ' / | | ACTION AFTER S | | PING | | | | |
| 15. DAILY DOSE(S) #1) UNK | | | |) Unknov | OF ADMINISTRAT WN | TON | | | | | YE | s 🔲 N | 0 | X N/ | Α. | | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | 4 | | | | | | 1 1 | REAPP | ACTION PEAR AFT RODUCT | | , | | | | |
| 18. THERAPY DATES(from #1) Ongoing | n/to) | | | THERAPY () Unknov | | | | | | | YE | s 🔲 N | 0 | X N | A | | | |
| | | III. CONCOMI | | | AND HIS | TOR | Υ | | | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | sed to treat react | tion) | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HI From/To Dates | STORY. (e.g. diagnostics, | allergies, pregnancy with last m Type of History / Notes | | tc.) escription | | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | FACTURE | R INF | ORMATIC | DN | | | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | rd East 1 UNITED STATES | 7 | | 26. REM/ | | | | | | | | | | | | | | |
| | 24b, MFR CO 2022001 | | | | E AND ADDRES | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | | LITERATURE | | NAME | AND ADDRE | SS W | /ITHH | ELD. | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | | - | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 66-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: ORAL MUCOSA EROSION (non-serious) with onset 10Dec2020, outcome "recovered" (Dec2020), described as "EROSION OF THE BUCCAL MUCOSA"; VARICOSE VEIN (non-serious) with onset 09Dec2021, outcome "not recovered", described as "VARICOSITIES OF THE LOWER LIMBS". The action taken for bosutinib was dosage not changed.

The reporter considered "varicosities of the lower limbs" and "erosion of the buccal mucosa" not related to bosutinib.

Additional information: Both events were grade 1, unrelated to study drug or concomitants. No follow-up attempts are possible. No further information is expected.

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

Case Comment: Based on the information provided, there is not a reasonable possibility that the events "varicosities of the lower limbs" and "erosion of the buccal mucosa" were related to bosutinib. Of note, the event "erosion of the buccal mucosa" resolved while treatment with bosutinib was ongoing without any change.



| | | | | | | | | | | | | CIC | MS | F | OR | M |
|--|--|--|-------------------------|---------------------|----------------------------|-----------|--------------|--------|-------|-----------|--------------|---------------------------|-----------------|------|----|---|
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| SUSPEC | T ADVERSE F | REACTION RE | PORT | | | | | | | | | | | | | |
| | | | | | | T | | П | | | Τ | | П | Τ | | _ |
| | | | | | | Ш, | 14 | Ш | | | | | Ш | | | _ |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. F | REACTION I | NFOR 3. SEX | MATION 3a. WEIGHT | 4-6 R | EACTION | LONSET | г [8- | ·12 C | CHEC | K ALL | | | | _ |
| (first, last) PRIVACY | FRANCE | | Year 76 Years | Male | 76.00 | Day 13 | Month JUN | Ye | ear | Α | APPR | OPRIA | TE TO EACTIO | ON | | |
| DYSPNEA [Dyspr | TION(S) (including relevant RED TERM] (Related symp noea] SION [Pleural effus | otoms if any separated by | commas) | | | | | | | | NVOL PROL | NT DIE VED O ONGEI | or D inpat | ΓΙΕΝ | т | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | OR SI | GNIFIC | OR | TENT | Г | | | |
| | ventional study repcian and Other HC | | | udy) rec | eived from c | ontac | table | | | | NCAF | PACITY | | | | |
| | | | | (Conti | nued on Addit | ional lı | nformat | ion Pa | ge) | <u> Н</u> | THRE | ATENIN | 1G | | | _ |
| 44 QUODEST PRUS (8) | · · · · · · | II. SUSF | PECT DRUG | S(S) IN | FORMATI | ON | | | Lac | D. DID F | 2540 | TION | | | | _ |
| #1) Bosulif (BOSU | (Include generic name) | tablet | | | | | | | | | TE AF | | TOPPIN | NG | | |
| 15. DAILY DOSE(S) #1) UNK | | | | ROUTE(S)) Unkno | OF ADMINISTRA WN | TION | | | | × | YES | NC | · 🗆 | NA | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | 21 | | PPEA | TION IR AFTE DUCTIO | | | | |
| 18. THERAPY DATES(fro #1) Unknown | m/to) | | | THERAPY) Unkno | DURATION WN | | | | | | YES | NC | | NA | | |
| | | | MITANT DE | |) AND HIS | TOF | RY | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude th | nose used to treat read | tion) | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT F From/To Dates | HSTORY. (e.g. diagnostics, | allergies, pregnancy with Type of History / N | | etc.) escription | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | |
| | | IV. MAI | NUFACTUR | ER INF | ORMATIO | NC | | | | | | | | | | _ |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Boulev New York, NY 1000 Phone: 212 733 40 | ard East 01 UNITED STATES | 5 | | 26. REM | IARKS | | | | | | | | | | | |
| | 24b. MFR CC 2022001 | | | | ME AND ADDRES AND ADDRE | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 18-JUL-2023 | R 24d. REPOR' STUDY HEALTH PROFES | LITERAT | | NAME | AND ADDRE | ESS W | /ITHHE | ELD. | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | VUP: | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 76-year-old male patient received bosutinib (BOSULIF). The patient's relevant medical history and concomitant medications were not reported. The following information was reported: DYSPNOEA (hospitalization) with onset 13Jun2020, outcome "recovered" (Sep2020), described as "DYSPNEA"; PLEURAL EFFUSION (non-serious) with onset 13Jul2020, outcome "recovered" (14Oct2020). The events dyspnea and pleural effusion were reported as grade 2. The action taken for bosutinib was dosage permanently withdrawn.

The investigator considered there was not a reasonable possibility that the event 'dyspnea' was related to bosutinib. The investigator considered there was a reasonable possibility that the event 'pleural effusion' was related to bosutinib.

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

Follow-up (05Jul2022): This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047 (Study alias BOSEVAL). Updated information includes: onset date of the event "Dyspnea" updated from 13Jul2020 to 13Jun2020.

Follow-up (18Jul2023): This is follow-up non-interventional study report received from the investigational site via CRO. Updated information includes: stop date of event Pleural effusion updated to 14Oct2020.

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

Case Comment: In agreement with the reporter, the Company considers the reported event dyspnoea as unrelated to the administration of bosutinib; conversely,the adverse event pleural effusion is considered related to bosutinib. The follow-up information received does not alter the previous company clinical evaluation.

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|--|----------------------------|--|-------------------|----------------------|-------------------------|-------------------|---------------|---|
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | |
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| | | | | | | | | |
| | | I. REA | CTION I | NFOR | MATION | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION ON | $\overline{}$ | 8-12 CHECK ALL APPROPRIATE TO |
| PRIVACY | FRANCE | Day PRIVACY Year | 76 Years | Male | | ay Month 5 JAN | Year 2021 | ADVERSE REACTION |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Pleural effusion [P | | tests/lab data) toms if any separated by comma | as) | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUATIO DF USE | ON OF EF | FICACY | AND SAFETY | OF BOSULI | F | HOSPITALISATION INVOLVED PERSISTENT |
| This is a non-interreporter(s) (Physic | | oort (Post Authorization 1871047. | n Safety St | udy) red | eived from a c | contactable | | OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | | | (Cont | nued on Additio | nal Information | ı Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATIC | ON | _ | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | ÷ . | tablet | | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | . ROUTE(S) | OF ADMINISTRATI WN | ON | | YES NO NA |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from #1) 24-OCT-2020 / | · | | | | DURATION ths 24 days | | | YES NO NA |
| | | III. CONCOMIT | TANT DE | RUG(S |) AND HIST | TORY | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | INISTRATION (exclude those us | sed to treat read | ction) | | | | |
| | | | | | | | | |
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| 23. OTHER RELEVANT H From/To Dates | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | |
| Unknown | | | | | | | | |
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| | | 1) / 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1/ 1 | ACTUD | | CONATIO | N.I. | | |
| 24a. NAME AND ADDRES | S OF MANUFACTURER | IV. MANUF | ACTUR | 26. REN | | N | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 5 | | | | | | |
| | 24b. MFR CC | NTROL NO. | | 25b. NA | ME AND ADDRESS | OF REPORTER | | |
| | 2022001 | 16528 | | NAME | AND ADDRES | SS WITHHELD |) . | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | SOURCE LITERATURE | | | | | | |
| 19-JAN-2022 | M HEALTH PROFES | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | TTYPE FOLLOWUP: | _ | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 76-year-old male patient received bosutinib (BOSULIF), from 24Oct2020 to 16Jan2021 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: PLEURAL EFFUSION (non-serious) with onset 15Jan2021, outcome "recovered" (04Feb2021). The action taken for bosutinib was temporarily withdrawn on 16Jan2021. Rechallenge of bosutinib was performed and "pleural effusion" reoccurred.

The reporter considered "pleural effusion" related to bosutinib.

Additional information: Event was grade 2. Study drug was temporarily withdrawn on 16Jan2021. Event recurred after the treatment was resumed. According to the investigator event was unrelated to concomitant treatments.

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported event Pleural effusion.

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| SUSPEC ⁻ | T ADVERSE I | REACTION REPO | ORT | | | | | | | | | | | | | | |
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| | | | | | | | | | | 1. | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | ⊣ । | 3. SEX Male | 3a. WEIGHT 76.30 kg | 4-6 R Day 14 | Mont | th | Yea | | Α | APPR | | - ATE TO REACTI | | | |
| Event Verbatim [PREFERR Diarrhea grade 1 [[| ED TERM] (Related sym Diarrhoea] | it tests/lab data) iptoms if any separated by comm | nas) | | | | | | | | | NVO | | | | NT | |
| | | | ION OF EF | FICACY | AND SAFE | TY OF | BOS | SULIF | F | | | OR SI | IGNIFI BILITY | OR | 1372 | NT | |
| | | | | tudy) red | eived from o | contac | table | | | | | | PACIT | Y | | | |
| | ### FRANCE Day PRIVACY Vear PAST Male 76.30 Ag 14 MoD 201 #### FRANCE Day PRIVACY Vear PAST Male 76.30 Ag 14 MoD 201 ################################### | | | | e) | <u></u> Н | JIFE THRE | EATENI | ING | _ | | | | | | | |
| | <u> </u> | II. SUSPE | CT DRUC | G(S) IN | FORMAT | ION | | | | 1 | | | | | | | |
| | | | | | | | | | | | | | CTION FTER S | STOPP | ING | | |
| 15. DAILY DOSE(S) #1) 100 mg, daily | | | | | | ATION | | | | | | | | ю 🔀 |] NA | \ | |
| 17. INDICATION(S) FOR U #1) Unknown | SE | | | | | | | | | 21 | | PPE/ | CTION AR AFT DDUCT | TER | | | |
| 18. THERAPY DATES(from #1) 10-NOV-2019 / | • | | | | | | _ | | _ | | П | YES | N | ю 🔀 |] NA | 4 | |
| | | III. CONCOM | ITANT DI | RUG(S |) AND HIS | STOF | —— ?Y | | | | | | | | | | |
| | | MINISTRATION (exclude those u | used to treat rea | | <i></i> | | | | | | | | | | | | |
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| 23. OTHER RELEVANT HIS From/To Dates 2011 to Ongoing DEC-2014 to Ongo | | Type of History / Notes Relevant Med H Relevant Med H | listory | Description Arterial h Atrial fibi | rillation (Atria | | | | | | | | | | | | |
| | | IV. MANU | FACT <u>UR</u> | ER IN | FORM <u>ATI</u> | ON_ | | | | | | | | | _ | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar | rd East 1 UNITED STATE | | | | | | | | | | | | | | | | |
| | | | | | | | | |). | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | RT SOURCE LITERATURE | <u> </u> | NAME | E AND ADDR | ESS V | VITHH | HELD |). | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | RT TYPE | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), first regimen from 10Nov2019 to 16Nov2019 at 100 mg daily, second regimen from 17Nov2019 to 23Nov2019 at 200 mg daily, third regimen from 24Nov2019 to 18Jan2020 at 300 mg daily and fourth regimen since 19Jan2020 (ongoing) at 400 mg daily. The patient's relevant medical history included: "ARTERIAL HYPERTENSION", start date: 2011 (ongoing); "cardiac arrhythmia by atrial fibrillation", start date: Dec2014 (ongoing), notes: cardiac arrhythmia by atrial fibrillation. Concomitant medication(s) included: XARELTO oral taken for atrial fibrillation, start date: Dec2014 (ongoing); IRBESARTAN oral taken for hypertension, start date: 2011 (ongoing).

The following information was reported: DIARRHOEA (non-serious) with onset 14Nov2019, outcome "recovered" (2020), described as "Diarrhea grade 1"; PHARYNGITIS (non-serious) with onset 29Nov2019, outcome "recovered" (Dec2019), described as "Pharyngitis grade 1". The action taken for bosutinib was dosage not changed.

The reporter considered "diarrhea grade 1" related to bosutinib. The reporter considered "pharyngitis grade 1" not related to bosutinib. Additional information: The events were unrelated to any concomitant drugs.

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

Follow-up (05Jul2022): This is a non- interventional study follow up report for protocol B1871047 received from investigational site via CRO.

Updated information: outcome of event diarrhea updated to recovered and recovery date provided.

Case Comment: Based on the information provided and known safety profile, there is a reasonable possibility that the reported diarrhea is related to bosutinib. The reported pharyngitis is likely an intercurrent medical condition and unrelated to bosutinib.

14-19. SUSPECT DRUG(S) continued

| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
|--|---|---------------------------|--|
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 200 mg, daily; Unknown | Unknown | 17-NOV-2019 / |
| Regimen #2 | | | 23-NOV-2019; |
| | | | 7 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, daily; Unknown | Unknown | 24-NOV-2019 / |
| Regimen #3 | | | 18-JAN-2020; |
| | | v | 1 month 26 days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 400 mg, daily; Unknown | Unknown | 19-JAN-2020 / |
| Regimen #4 | | | Ongoing; |
| | | | Unknown |

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|--|----------------------------------|---|------------------|----------------------|----------------|-------------|-----------|--------------|------|--------------|---|-------------|------|----|
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | |
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| | | I. REA | CTION I | NFOR | MATION | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | _ | CTION ONS | | 8-12 | CHEC | K ALL OPRIATI | F TO | | |
| PRIVACY | FRANCE | PRIVACY Year | 65 Years | Male | 95.00 kg | Day | Month 2 | Year 2019 | | | RSE RE | | | |
| | | tests/lab data) toms if any separated by comma DDE [Upper respiratory | | ction] | | | | | | INVOL | NT DIED VED OR ONGED | 1 | -NIT | |
| | OBSERVATIONAL FE CONDITIONS (| L STUDY - EVALUATIO OF USE | ON OF EFI | FICACY | AND SAFE | TY OF B | OSULIF | = | | HOSPI | ITALISA | TION | | |
| | | oort (Post Authorization P) for protocol B18710 | • | udy) red | eived from o | contactal | ble | | | OR SIG | VED PE GNIFICA ILITY OF PACITY | NT | NT | |
| | | | | (Cont | nued on Addi | tional Info | ormation | Page) | | LIFE THRE | ATENING | 3 | | |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMAT | ION | | | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | , | tablet | | (Cont | nued on Addi | tional Info | ormation | Page) | | | TION TER ST | OPPING | 3 | |
| 15. DAILY DOSE(S) #1) 300 mg | | | |) Unkno | OF ADMINISTRA | ATION | | | × | YES | NO | □ N | A | |
| 17. INDICATION(S) FOR U #1) Unknown | USE | | | | | | | | | APPEA | TION R AFTEI DUCTIO | | | |
| 18. THERAPY DATES(from #1) 04-JUN-2018 / | • | | | THERAPY) Unkno | DURATION WN | | | | | YES | NO | ⊠ N⁄ | A | |
| | | III. CONCOMIT | | $\overline{}$ |) AND HIS | STORY | / | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | ed to treat read | ction) | | | | | | | | | | |
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| | | | | | | | | | | | | | | |
| From/To Dates | IISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUF | ACTUR | 26. REN | | OIN | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 5 | | | | | | | | | | | | |
| | 24b. MFR CC | NTROL NO. | | 25b. NA | ME AND ADDRE | SS OF REP | ORTER | | | | | | | |
| | 2022001 | 48764 | | | AND ADDR | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | R 24d. REPOR | SOURCE LITERATURE | | NAME | AND ADDR | ESS WIT | THHELD. | - | | | | | | |
| 21-APR-2023 | M HEALTH PROFES | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | TTYPE FOLLOWUP: | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 65-year-old male patient received bosutinib (BOSULIF), first regimen since 04Jun2018 at 300 mg and second regimen till 19Feb2020. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: UPPER RESPIRATORY TRACT INFECTION (non-serious) with onset 2019, outcome "recovered" (2019), described as "UPPER AIRWAY INFECTION EPISODE". The action taken for bosutinib was dosage permanently withdrawn on 19Feb2020.

Additional information: Event was grade 2. It was reported that the last dosage before the onset of the event was 300 mg from 04Jun2018, bosutinib was ongoing when the event occurred. Bosutinib was permanently withdrawn on 19Feb2020.

The reporter considered "upper airway infection episode" not related to bosutinib.

Follow-up (13Apr2023): New information received from investigational site via CRO. Updated information included: patient's date of birth. Patient's age was added.

Follow-up (21Apr2023): New information received from the clinical team. Updated information included: suspect drug dosage regimen and action taken.

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

Case Comment: Based on the information provided, the event upper respiratory tract infection is most likely attributed to an intercurrent medical condition and unrelated to bosutinib. Of note, the event outcome was recovered but the action taken for bosutinib was dosage not changed.

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 tal | blet; UNK; Unknown | Unknown | Unknown / | |
| Regimen #2 | | | 19-FEB-2020; | |
| | | | Unknown | |

| | | | | | | | CIOMS FORM |
|--|---|--|-----------------|---------------------------|---|--------------|---|
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| SUSPECT | ADVERSE R | EACTION REPO | RT | | | | |
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| | | | | | | | |
| | | I. REA | CTION | INFOR | MATION | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT 4-6 REACTION | | 8-12 CHECK ALL APPROPRIATE TO |
| PRIVACY | FRANCE | PRIVACY Year | 72 Years | Male | 68.00 Day Month 10 JUN | Year 2021 | ADVERSE REACTION |
| 7 + 13 DESCRIBE REACTIC Event Verbatim [PREFERRE OEDEMA OF THE I INTESTINAL POLY | ED TERM] (Related sympt LOWER LIMBS [C | toms if any separated by comma Dedema peripheral] | as) | 4 | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| UNDER REAL-LIFE | E CONDITIONS O | OF USE | | | AND SAFETY OF BOSL | JLIF | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| This is a non-interve | entional study rep | ort (Post Authorization | ı Safety S | study) for | protocol B1871047. | | INCAPACII I |
| | | | | (Cont | inued on Additional Informat | ion Page) | LIFE THREATENING |
| | | U SUSPEC | T DRU | _ | IFORMATION | | |
| 14. SUSPECT DRUG(S) (inc | , | | T DICC | <u> </u> | INORMATION | | 20. DID REACTION ABATE AFTER STOPPING |
| #1) Bosulif (BOSUTI | NIB) Film-coated to | ablet | | | | | DRUG? |
| 15. DAILY DOSE(S) #1) 400 mg, daily | | | | 6. ROUTE(S) 41) Unkno | OF ADMINISTRATION OWN | | YES NO NA |
| 17. INDICATION(S) FOR US #1) Unknown | }E | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/t #1) 20-SEP-2018 / C | • | | | 9. THERAPY 41) Unkno | | | YES NO NA |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HISTORY | | |
| 22. CONCOMITANT DRUG(| S) AND DATES OF ADMI | INISTRATION (exclude those us | ed to treat rea | action) | | | |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| 23. OTHER RELEVANT HIS From/To Dates 2002 to 2018 2014 to 2014 | TORY. (e.g. diagnostics, a | allergies, pregnancy with last mo Type of History / Notes Relevant Med His Relevant Med His | story | Description Atrial fib | rillation (Atrial fibrillation) Cerebrovascular accident | :) | |
| | | IV. MANUF | ACTUF | R <u>ER IN</u> I | FORMATION | | |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4048 | d East UNITED STATES | 7 | | 26. REM | | | |
| | 24b. MFR CON | TROL NO. | | | ME AND ADDRESS OF REPORTER | | |
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| 26-JAN-2022 | HEALTH PROFESS | SIONAL OTHER: | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 72 year-old male patient received bosutinib (BOSULIF), since 20Sep2018 (ongoing) (Batch/Lot number: unknown) at 400 mg daily. Relevant medical history included: "Cardiac arrhythmia due to atrial fibrillation", start date: 2002, stop date: 2018; "stroke", start date: 2014, stop date: 2014. The patient's concomitant medications were not reported.

The following information was reported: OEDEMA PERIPHERAL (non-serious) with onset 10Jun2021, outcome "recovered" (Jun2021), described as "OEDEMA OF THE LOWER LIMBS"; INTESTINAL POLYP (non-serious) with onset 2021, outcome "recovered" (20May2021), described as "INTESTINAL POLYPS". The action taken for bosutinib was dosage not changed.

The investigator considered there was not a reasonable possibility that the events "oedema of the lower limbs" and "intestinal polyps" were related to bosutinib.

Additional information: the events were grade 2, non-serious, unrelated to bosutinib or to any concomitant drug.

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

Case Comment: Based on the available information, the company concurs with the reporting investigator that there was not a reasonable possibility that the events "oedema of the lower limbs" and "intestinal polyps" were related to bosutinib. The underlying cardiovascular and history of stroke may have played an important contributory role to the occurrence of the event.



| | | | | | | | | | | | CIO | MS I | FOF | RM |
|--|--|---|-------------------|---------------------------|----------------------------------|-----------|----------------|--------------|------|-------------------------|--|--------------|-----|----|
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| SUSPECT | ADVERSE F | REACTION REPO | RT | | | | | | | | | | | |
| 3031 201 | ADVENSE | CEACTION REFO | IX I | | | | TAT | | | | | | | |
| | | | | | | | | | | | | | | |
| | | I REA | CTION I | NEOR | MATION | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REA | CTION ONS | SET | 8-12 | CHEC | | | | |
| (first, last) PRIVACY | FRANCE | PRIVACY Year | 72 Years | Male | | | Month MAY 2 | Year 2021 | | | OPRIAT RSE RE | | I | |
| IRON DEFICIENCY | D TERM] (Related symptom) ANEMIA grade | tests/lab data) toms if any separated by comma 3 [Iron deficiency anae I grade 2 [Gastrointest | mia] | dysplasi | al | | | | | INVOL PROL | NT DIED VED OF ONGED VITALISA | R INPATII | ≣NT | |
| UNDER REAL-LIFE | CONDITIONS (| STUDY - EVALUATION OF USE OPPORT (Post Authorization | | | | | OSULIF | : | | OR SI | LVED PE GNIFICA BILITY O PACITY | ANT | :NT | |
| | | , | | | | | | | | LIFE | | | | |
| | | | | (Cont | nued on Additi | onal Info | rmation | Page) | | | ATENIN | G | | |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATI | ON | | | | | | | | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI | - | tablet | | | | | | | AB. | REAC SATE AF RUG? | TION TER ST | OPPINO | 6 | |
| 15. DAILY DOSE(S) #1) 400 mg, daily | | | | ROUTE(S)) Unkno | OF ADMINISTRAT WN | TION | | | | YES | NO | × | A | |
| 17. INDICATION(S) FOR US #1) Unknown | E | | | | | | | | | APPEA | TION AR AFTE DUCTIO | | | |
| 18. THERAPY DATES(from/t #1) 20-SEP-2018 / C | · | | | THERAPY) Unkno | DURATION WN | | | | | YES | NO | ×Ν | A | |
| | | III. CONCOMIT | TANT DE | RUG(S |) AND HIS | TORY | , | | | | | | | |
| 22. CONCOMITANT DRUG(S | S) AND DATES OF ADM | INISTRATION (exclude those us | sed to treat read | ction) | | | | | | | | | | |
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| | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIST From/To Dates 2002 to 2018 2014 to 2014 | TORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes Relevant Med His Relevant Med His | story A | escription Atrial fibu | illation (Atrial Cerebrovascu | | , | | | | | | | |
| | | IV. MANUF | ACTUR | FR INI | ORMATIC |)NI | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | 10.101/11401 | , (O I OIN | 26. REN | | -11 | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | UNITED STATES | | | | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | | ME AND ADDRES | | | | | | | | | |
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| 26-JAN-2022 | M HEALTH PROFES | SIONAL OTHER: | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 72 year-old male patient received bosutinib (BOSULIF), since 20Sep2018 (ongoing) (Batch/Lot number: unknown) at 400 mg daily. Relevant medical history included: "cardiac arrhythmia due to atrial fibrillation", start date: 2002, stop date: 2018; "STROKE", start date: 2014, stop date: 2014. The patient's concomitant medications were not reported.

The following information was reported: IRON DEFICIENCY ANAEMIA (hospitalization) with onset 19May2021, outcome "recovered" (21May2021), described as "IRON DEFICIENCY ANEMIA grade 3"; GASTROINTESTINAL ANGIODYSPLASIA (non-serious) with onset 20May2021, outcome "recovered" (26Jul2021), described as "ANGIODYSPLASIA OF THE COLON grade 2". The patient was hospitalized for iron deficiency anaemia (start date: 19May2021, discharge date: 21May2021, hospitalization duration: 2 day(s)). The action taken for bosutinib was dosage not changed.

Additional information: The patient was hospitalized for upper endoscopy and colonoscopy following persistent iron deficiency anemia from 19May2021 to 21May2021.

The investigator considered there was not a reasonable possibility that the events "iron deficiency anemia grade 3" and "angiodysplasia of the colon grade 2" were related to bosutinib nor any concomitant drug.

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

Case Comment: Based on the available information, the Company concurs with the investigator that there is not a reasonable possibility that the events "iron deficiency anemia grade 3" and "angiodysplasia of the colon grade 2" are related to bosutinib. The events are more likely inter-current medical conditions.

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| SUSPEC | T ADVERSE | REACTION REPO | ORT | | | | | | | | | | | | | | | _ |
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| | | | ACTION I | | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 2a. AGE 71 Years | 3. SEX Male | 3a. WEIGHT 68.00 kg | 4-6 F Day 19 | Moi FE | nth | | ear | 8-12 | AP | | DPRIA | TE TO | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Iron deficiency and Iron deficiency and | RED TERM] (Related symemia [Iron deficier | nptoms if any separated by comn ncy anaemia] | nas) | | | | , | | | | <u> </u> | | IVOL\ ROLC | | | | NT | |
| Case Description: UNDER REAL-LIF | | AL STUDY - EVALUATI OF USE | ION OF EFI | FICACY | AND SAFE | TY OI | F BO | SULI | IF | | ַ | ■ OF | R SIG | VED P SNIFIC | | TEN | ΙΤ | |
| This is a non-inter | ventional study re | port for protocol B187 | 1047. | 7 | | 4 | | | | | | | | ACITY | | | | |
| A 71 year-old male | patient received | bosutinib (BOSULIF), | since | (Cont | inued on Addi | tional | Inforn | nation | n Pa | ge) | | | FE HREA | ATENII | NG | | | |
| | | II. SUSPE | CT DRUG | S(S) IN | IFORMAT | ION | | | | | | | | | | | _ | _ |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | , | l tablet | | | | | | | | | , | DID RE ABATE DRUG | E AFT | | TOPPI | NG | _ | _ |
| 15. DAILY DOSE(S) #1) 400 mg, daily | | | | ROUTE(S | OF ADMINISTRA | ATION | | | | | | ☐ YE | ES [| NC | · 🛛 | NA | | |
| 17. INDICATION(S) FOR L #1) Unknown | JSE | | | | | | | | | | | DID RE REAPF REINT | PEAF | R AFT | | | | |
| 18. THERAPY DATES(from #1) 20-SEP-2018 / | · | | | . THERAPY | DURATION DWN | | | | | | | ☐ YE | ES [| NC | · 🛛 | NA | | |
| | | III. CONCOMI | ITANT DE | RUG(S |) AND HIS | STO | RY | | | | | | | | | | _ | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADI | MINISTRATION (exclude those to | used to treat read | ction) | · · | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT HI From/To Dates 2002 to 2018 | STORY. (e.g. diagnostics | s, allergies, pregnancy with last n Type of History / Notes Relevant Med H | | Description | rillation (Atria | al fibri | illatio | n) | | | | | | | | | | |
| 2014 to 2014 | | Relevant Med H | , | | Cerebrovaso | | | , | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | IV. MANU | FACTUR | ER IN | FORMATI | ON | | | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc | S OF MANUFACTURER | | 17.0.5. | 26. REI | | <u> </u> | | | | | | | | | | | _ | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATE | S | | | | | | | | | | | | | | | | |
| | 24b. MFR C | ONTROL NO. | | 25b. NA | ME AND ADDRE | SS OF F | REPOR | TER | | | | | | | | | | _ |
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| 24c. DATE RECEIVED BY MANUFACTURES | 24d. REPOR | | | NAM | E AND ADDR | ESS \ | WITH | HELD | Ο. | | | | | | | | | |
| 26-JAN-2022 | ₩ HEALTH PROFE | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

20Sep2018 (ongoing) (Batch/Lot number: unknown) at 400 mg daily. Relevant medical history included: "Atrial fibrillation", start date: 2002, stop date: 2018; "Stroke", start date: 2014, stop date: 2014. The patient's concomitant medications were not reported. The following information was reported: IRON DEFICIENCY ANAEMIA (hospitalization) with onset 19Feb2021, outcome "recovered" (22Feb2021), IRON DEFICIENCY ANAEMIA (hospitalization) with onset 15Jun2021, outcome "recovered" (29Jun2021) and all described as "Iron deficiency anemia". Both events were rated as grade 3. The action taken for bosutinib was dosage not changed.

The investigator considered there was not a reasonable possibility that the event "iron deficiency anemia" was related to bosutinib nor concomitant drug.

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

Case Comment: Both episodes of Iron deficiency anemia are deemed unrelated to the study drug, bosutinib.

| | | | | | | | | CIOMS FORM | | |
|---|-------------------------------|---|--|---------------------------|---------------------------------------|-----------------|--------------|--|--|--|
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| SUSPECT | ADVERSE RE | ACTION REPO | RT | | | | | | | |
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| | | I. REAC | CTION I | INFOR | MATION | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | DATE OF BIRTH Month Year | 2a. AGE | 3. SEX | · · · · · · · · · · · · · · · · · · · | 4-6 REACTION O | NSET Year | 8-12 CHECK ALL APPROPRIATE TO | | |
| PRIVACY | FRANCE De | PRIVACY | 71 Years | Male | 68.00 b | FEB | 2021 | ADVERSE REACTION | | |
| 7 + 13 DESCRIBE REACTION Event Verbatim [PREFERRED Gastritis burn [Reflux | | s/lab data) s if any separated by commas | s) | | | | | PATIENT DIED INVOLVED OR | | |
| Case Description: OI UNDER REAL-LIFE | | | N OF EFF | FICACY | AND SAFETY | OF BOSULI | F | PROLONGED INPATIENT HOSPITALISATION | | |
| This is a non-intervel reporter(s) (Physicial | ntional study report | (Post Authorization | Safety S | tudy) red | eived from a c | contactable | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | | |
| | | | | (Cont | inued on Additio | nal Information | n Page) | LIFE THREATENING | | |
| | | II. SUSPEC | T DRUC | G(S) IN | FORMATIC |)N | - | | | |
| 14. SUSPECT DRUG(S) (inclu#1) Bosutinib (BOSU | • | | | (-, | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | |
| 15. DAILY DOSE(S) #1) 400 mg, daily | | | 16. ROUTE(S) OF ADMINISTRATION #1) Unknown YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | |
| 18. THERAPY DATES(from/to #1) 20-SEP-2018 / Or | · | | | . THERAPY 1) Unkno | DURATION DWN | | | YES NO NA | | |
| | | III. CONCOMIT | ANT DI | RUG(S |) AND HIST | ORY | | | | |
| 22. CONCOMITANT DRUG(S |) AND DATES OF ADMINIS | | | _ | | | | | | |
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| 23. OTHER RELEVANT HISTOFOM/To Dates 2002 to 2018 2014 to 2014 | ORY. (e.g. diagnostics, aller | rgies, pregnancy with last mor Type of History / Notes Relevant Med His Relevant Med His | tory | Description Atrial fib | rillation (Atrial i | , | | | | |
| | | | , | · · · (- | 100.012.21 | do | | | | |
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| 24a. NAME AND ADDRESS O | OF MANUFACTURER | IV. MANUF | <u>ACTUR</u> | ER IN | | <u>N</u> | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | East UNITED STATES | | | | | | | | | |
| | 24b. MFR CONTR | OL NO. | | | ME AND ADDRESS | | | | | |
| | 2022001684 | 195 | | NAMI | E AND ADDRES | SS WITHHEL | D. | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SO | URCE LITERATURE | | | | | | | | |
| 26-JAN-2022 | HEALTH PROFESSION | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYF | PE FOLLOWUP: | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 71-year-old male patient received bosutinib (BOSUTINIB), since 20Sep2018 (ongoing) at 400 mg daily. The patient's relevant medical history included: "Atrial fibrillation", start date: 2002, stop date: 2018; "CVA (Cerebrovascular accident)", start date: 2014, stop date: 2014. The patient's concomitant medications were not reported.

The following information was reported: REFLUX GASTRITIS (non-serious) with onset Feb2021, outcome "recovering", described as "Gastritis burn". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed.

The reporter considered "gastritis burn" not related to bosutinib.

Additional information: Gastritis burn, grade 2, non-serious, unrelated to the study drug or concomitant medications. Ulcerative gastritis showed in fibroscopy on 20May2021.

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

Case Comment: Based on the information provided, the event Gastritis burn is assessed as unrelated to bosutinib. There is no known association between the event and the drug. Of note, the outcome of the event is recovering and the action taken for bosutinib was dosage not changed. The case will be re-evaluated if more information is available.

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|---------------------------|----------------------|-------------------|
| 1 | 20-MAY-2021 | Endoscopy | Ulcerative gastritis | <u> </u> |

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|--|---|---|--------------------|-----------|-----------------|---------|--------|--------|------|------|----------|-------------------------------------|--------|--------|------|----|
| | I. REACTION INFORMATION ITIALS 1a. COUNTRY PRIVACY Year 2a. AGE 3. SEX 3a. WEIGHT 4-6 REACTION ONSE PRANCE Day Month Year 71 PRIVACY Year Year 71 PRIVACY YEAR YEAR YEAR YEAR YEAR YEAR YEAR YEA | | | | | | | | | | | | | | | |
| SUSPEC | CT ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | |
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| | I. REACTION INFORMATION I. REACTION INFORMATION II. REACTION INFORMATION II. REACTION INFORMATION II. REACTION INFORMATION III. REACTION III. RE | | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | | | | | 4-6 RE | ACTIO | N ONSE | ET | 8-1: | | HECK | | | | |
| PRIVACY | FRANCE | | 71 Years | emale | | | | | | | | PPROF DVERS | | | N | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER | TION(S) (including relevant RED TERM] (Related symp | tests/lab data) otoms if any separated by comm | mas) | • | | | | 7 | | 1 | □ PA | ATIENT | DIE | D | | |
| Anxiety [Anxiety] Scalp pruritus [Pre | uritus] | | | | | | | | | ſ | ┛ PF | IVOLVE ROLON | NGED | INPAT | ΓΙΕΝ | Т |
| Case Description: | OBSERVATIONA | L STUDY - EVALUAT | ION OF EFF | ICACY A | AND SAFET | Y OF | BOS | ULIF | | | | OSPITA | | | | |
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| | | | | ıdy) rece | eived from co | ntact | able | | | | IIN | CAPA | JII Y | | | |
| | | | | (Contin | nued on Additio | onal In | ıforma | tion P | age) | , [| 그 # | FE HREAT | ENIN | IG | | |
| | | II. SUSPE | CT DRUG | (S) INF | ORMATIC | NC | | | | | | | | | | |
| | | tablet | | | | | | | | 20. | | EACTION OF THE STREET | | ГОРРІІ | ١G | |
| 15. DAILY DOSE(S) | | | 16 | ROLITE(S) | OF ADMINISTRATI | ION | Þ | | | - | | | | | | |
| #1) 400 mg, daily | | | | | | 1011 | | | | | YI | ES | NO | | NA | |
| 17. INDICATION(S) FOR #1) Chronic Myelo | | ic myeloid leukaemia) | | 47 | | | | | | 21. | REAP | EACTIOPEAR TRODU | AFTE | | | |
| 18. THERAPY DATES(fro #1) 18-MAR-2019 | TREET BRITIALS (Incl. List) FRANCE Day Description FRANCE Day Description Description To Human To | | | | | | | | | Y | ES [|] ио | | NA | | |
| | | III. CONCOM | ITANT DR | UG(S) | AND HIS | TOR | Υ | | | | | | | | | |
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| 23. OTHER RELEVANT H | HISTORY, (e.g. diagnostics. | allergies, pregnancy with last n | month of period, e | tc.) | | | | | | | | | | | | |
| From/To Dates Unknown | (| | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANU | FACTURE | | |)IN | | | | | | | | | | |
| Stella Pietrafesa | ard East | | | | | | | | | | | | | | | |
| New York, NY 1000 Phone: 212 733 40 | | S | | | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | 25b. NAM | ME AND ADDRESS | S OF RE | PORTE | R | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | | | NAME | AND ADDRE | SS W | ΉΗ | ĿLĎ. | | | | | | | | |
| 16-MAY-2023 | HEALTH PROFES | | | 1 | | | | | | | | | | | | |
| 27-FEB-2024 | l | <u></u> | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 71-year-old female patient received bosutinib (BOSULIF), from 18Mar2019 to 30Apr2019 at 400 mg daily for chronic myeloid leukaemia. The patient's relevant medical history was not reported. Concomitant medication(s) included: TASIGNA oral taken for chronic myeloid leukaemia, start date: 27May2019 (ongoing).

The following information was reported: ANXIETY (non-serious) with onset 27May2019, outcome "recovered" (29Jun2019); PRURITUS (non-serious) with onset 11Jun2019, outcome "not recovered", described as "Scalp pruritus".

Additional information: Anxiety and Itchy scalp were reported as non-serious with grade 1. Action taken for event Anxiety was reported as not applicable for Bosulif and dose not changed for Tasigna. Action taken for event Itchy scalp was reported as Dose reduced for Tasigna.

According to the investigator, the events anxiety and Itchy scalp were unrelated to study drug and unrelated to concomitant drugs.

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

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: added concomitant drug TASIGNA, added event Itchy scalp.

Case Comment: Event ANXIETY represents an intercurrent medical condition and unrelated to bosutinib. Based on available information and known safety profile of the suspect product the reasonable possibility that bosutinib played a contributory role toward the reported itchy scalp cannot be excluded.

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| | SUSPECT ADVERSE REACTION REPORT | | | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | | | |
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| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION 2a. AGE | INFOR 3. SEX | MATION 3a. WEIGHT | 1 6 DE | ACTIC | NI ONIC | NET. | 8-1 | 12 (| | CK AL | _ | | | | | | |
| PRIVACY | FRANCE | Day Month Year PRIVACY | 58 Years | Male | 70.00 Da 0' | ıy | Mont JAN | h | Year 202 | 1 | A | APPI | ROPRI ERSE | IATE | | N | | | | |
| Urinary tract infe | CTION(S) (including relevant RRED TERM] (Related symp ction [Urinary tract in ction [Urinary tract in | • | s) | | | | | | | 1 | | INVC PRO | ENT D DLVED LONG PITAL | OR SED | t Inpat | IENT | | | | |
| | n: OBSERVATIONAL IFE CONDITIONS (| _ STUDY - EVALUATIO DF USE | N OF EF | FICACY | AND SAFETY | OF | BOS | ULIF | : | ו | □ <u>"</u> | INVO | OLVED SIGNIF ABILITY | PE FICA Y OF | RSIST | ENT | | | | |
| | | oort (Post Authorization P) for protocol B187104 | | study) rec | eived from con | itact | able | | | | | | APACIT | ΓY | | | | | | |
| | | | | (Conti | nued on Addition | nal In | forma | tion I | Page |) [| | THR | EATEN | NINC | 3 | | | | | |
| [auaaaaaaaaaa | II. SUSPECT DRUG(S) INFORMATION SUSPECT DRUG(S) (include generic name) | | | | | | | | | | | | T., .,, .,, .,, | | | | | | | |
| | SUSPECT DRUG(S) (include generic name)) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | |
| 15. DAILY DOSE(S) #1) 400 mg, 1x/da | ay | | | 6. ROUTE(S) 1) Unkno | | | | | YES | · 🗆 | NO | × | NA | | | | | | | |
| 17. INDICATION(S) FOR #1) Chronic myeld | | c myeloid leukaemia) | | | 21. | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | |
| 18. THERAPY DATES(fr #1) 22-JAN-2019 | · | | | 19. THERAPY DURATION #1) Unknown | | | | | | | | | | NA | | | | | | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND HIST | OR | Υ | | | | | | | | | | | | | |
| 22. CONCOMITANT DR | UG(S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat rea | action) | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| 23 OTHER RELEVANT | HISTORY (e.g. diagnostics | allergies, pregnancy with last mo | nth of period | etc) | | | | | | | | | | _ | | | | | | |
| From/To Dates Unknown | Thorotti. (e.g. diagnosiics, | Type of History / Notes | nur or period | Description | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | _ | | | | | | |
| IV. MANUFACTURER INFORMATION 24a. NAME AND ADDRESS OF MANUFACTURER 26. REMARKS | | | | | | | | | | | | | | _ | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouley | vard East 001 UNITED STATES | 3 | | 20. KEW | IANNO | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2022001 | | | | ME AND ADDRESS (| | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTUR | 24d. REPORT | | | NAME | AND ADDRES | s w | 'ITHH | ELD. | • | | | | | | | | | | | |
| 20-JUL-2023 | STUDY HEALTH | | | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | T 25a. REPORT ☑ INITIAL | | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 58-year-old male patient received bosutinib (BOSULIF), since 22Jan2019 (ongoing) at 400 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: URINARY TRACT INFECTION (non-serious) with onset 01Jan2021, outcome "recovered" (14Jan2021), URINARY TRACT INFECTION (non-serious) with onset 16Aug2021, outcome "recovered" (Mar2022) and all described as "Urinary tract infection". The action taken for bosutinib was dosage not changed.

Additional information: urinary tract infection grade 2 and recovered, unrelated to study drug or concomitant. According to the investigator, the event was non-serious and not related to study drug or concomitant medication.

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

Follow-up (28Jul2022): This is a follow-up report from an investigational site via CRO. Updated information: clinical course of events.

Follow-up(23Feb2023): New information received from investigational site via CRO included: second epidose of urinary infection from 16Aug2021 to Mar2022, unreated to treatment, non-serious, grade 2, dose of bosulif not changed in response to the event

Follow-up (20Jul2023 and 21Jul2023): This is a follow-up report from an investigational site via CRO. Updated information: Onset of bosulif changed to 22Jan2019.

Case Comment: The reported two episodes of urinary tract infection likely represent intercurrent medical conditions and are considered unrelated to bosutinib.

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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | | И | | | | | | | | | | | |
| | | I. REA | CTION II | NFORM | IATION | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | | Ba. WEIGHT | - | EACTIO | | | 8-12 | | ECK ALL | | го | | | | |
| PRIVACY | FRANCE | PRIVACY Year | 35 Years F | emale | 59.00 kg | Day 20 | JUI | | Year 2019 | | | VERSE I | | | | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFER Night sweats [Night | | tests/lab data) troms if any separated by comm | as) | | | | | | | 2 | | TIENT DI | OR | | | | | |
| • | OBSERVATIONAL FE CONDITIONS (| L STUDY - EVALUATION OF USE | ON OF EFF | FICACY A | ND SAFET | ΓY OF | BOS | SULIF | | | НО | OLONGE SPITALI: OLVED | SATIO | ON | | | | |
| | | oort (Post Authorization P) for protocol B18710 | | udy) recei | ved from c | ontac | table | | | - | OR DIS | SIGNIFI SABILITY CAPACIT | CAN | T | | | | |
| | | | | (Continu | ued on Addit | ional I | nforma | ation F | Page) | , _ | ן הא | E REATEN | ING | | | | | |
| | (Continued on Additional Information Page II. SUSPECT DRUG(S) INFORMATION | | | | | | | | <u> </u> | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION 4. SUSPECT DRUG(S) (include generic name) \$1) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | 1 | | ACTION AFTER | | PPING | | | | |
| 15. DAILY DOSE(S) #1) 400 mg, 1x/da | | | | | | | | | | | YE | s 🔲 N | ю [| X N | A | | | |
| 17. INDICATION(S) FOR #1) Chronic myelo | 400 mg, 1x/day #1) Unknown | | | | | | | | | | REAPP | ACTION EAR AF RODUCT | | , | | | | |
| 18. THERAPY DATES(fro #1) 05-MAR-2019 | · | | | THERAPY DU | | | | | | YES NO NA | | | | | | | | |
| | | III. CONCOMI | TANT DR | RUG(S) | AND HIS | STOF | RY | | | | | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | IINISTRATION (exclude those us | sed to treat react | tion) | | | | | | | | | | | | | | |
| | | | | 7 | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 23 OTHER RELEVANT H | HSTORY (e.g. diagnostics | allergies, pregnancy with last m | onth of period e | itc.) | | | | | | | | | | | | _ | | |
| From/To Dates Unknown | no ronni, (e.g. diagnositos, | Type of History / Notes | | escription | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | W. MANUEL OF UPER WERDLINES | | | | | | | | | | | | | | | | | |
| | IV. MANUFACTURER INFORMATION 24a. NAME AND ADDRESS OF MANUFACTURER 26. REMARKS | | | | | | | | | | | | | | | \neg | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NAME | E AND ADDRES | SS OF R | EPORT | ER | | | | | | | | \dashv | | |
| | 2022001 | 73959 | | | AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPORT | SOURCE | | NAME A | AND ADDRE | ESS V | VITHE | iELD. | | | | | | | | | | |
| 16-MAY-2023 | HEALTH PROFES | SSIONAL OTHER: | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 35-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 05Mar2019 to 20Jun2019 at 400 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: NIGHT SWEATS (non-serious) with onset 20Jun2019, outcome "recovered" (02Sep2021). The action taken for bosutinib was dosage not changed.

The reporter considered "night sweats" not related to bosutinib.

Additional information: The event was grade 2, non-serious. As per the investigator, the event was unrelated to study drug and concomitant treatments.

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

Follow-up (16May2023): This is a follow-up report received from the CRO. Updated information included: The event's grade was changed from grade 1 to grade 2.

Case Comment: Event night sweats represents an intercurrent medical condition and unrelated to bosutinib .

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| SUSPEC | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | |
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| | | | | =25 | | | | Ш | | | | Ш | | L | <u>L</u> | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION 2a. AGE | 3. SEX | MATION 3a. WEIGHT | 4-6 R | EACTION | ONSE | т | 8-12 | СН | ECK ALI | | _ | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 65 Years | Male | 95.00 kg | Day | Month DEC | Y | /ear 019 | U | AP | PROPRI VERSE | ATE T | | 1 | |
| | CTION(S) (including relevant RRED TERM] (Related symp [Nasopharyngitis] | t tests/lab data) ptoms if any separated by comma | 15) | | | | | | | | J IN\ J PR | TIENT D OLVED OLONG SPITALI | OR ED INI | | ENT | |
| | : OBSERVATIONA IFE CONDITIONS (| L STUDY - EVALUATIC OF USE | ON OF EF | FICACY | AND SAFET | ΓY OF | BOSU | JLIF | | | ■ OR | OLVED SIGNIF | ICAN 1 | SISTE T | ≣NT | |
| | | port (Post Authorization P) for protocol B187104 | | itudy) rec | eived from c | ontac | table | | | | | CAPACIT | | | | |
| | | | | (Conti | nued on Addit | ional l | nformat | ion Pa | age) | |] LIF | E REATEN | IING | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMATI | ON | | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION 14. SUSPECT DRUG(S) (include generic name) #1) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | P | | ACTION AFTER | | PINO | 3 | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | | | TION | | | | ſ | YE | :s 🔲 1 | 10 | X N | .A | |
| 17. INDICATION(S) FOR #1) Unknown | #1) 300 mg, daily #1) Unknown 7. INDICATION(S) FOR USE | | | | | | | | | | | ACTION PEAR AF RODUCT | TER | | | |
| 18. THERAPY DATES(fro #1) 04-JUN-2018 | • | | | 9. THERAPY £1) Unkno | | | | | | [| YE | :s 🔲 1 | 10 | ⊠ ⋈ | ıA | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HIS | TOF | RY | | | | | _ | | | | |
| #1) VALSARTAN | (VALSARTAN) ; | 7 | ed to treat rea | action) | _ | _ | _ | _ | | _ | _ | _ | _ | - | _ | - |
| | DL (BISOPROLOL) ATIN (ROSUVASTA | ; 2005 / Ongoing ATIN) ; 2005 / Ongoing | 3 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| From/To Dates | | , allergies, pregnancy with last mo | | Description | !! vo.n | - 4 , / | موجاء الا | ! | :ام | | 04 | . A | | | | |
| Unknown to Ongo Unknown to Ongo | | Relevant Med His Relevant Med His | , | | cardiomyop (Gastritis) | atny (| ISChae | emic c | carui | ОПІ | ′0раі | iny) | | | | |
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| | | | | | | | | | | | | | | | _ | _ |
| 24a. NAME AND ADDRE | ESS OF MANUFACTURER | IV. MANUF | ACTUR | 26. REM | | NC | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | | ME AND ADDRES | | | | | | | | | | | |
| | 2022001 | | | | AND ADDRI | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | Mariabi | LITERATURE | | | | -00 . | | | | | | | | | | |
| 13-APR-2023 DATE OF THIS REPORT | HEALTH PROFES 25a. REPOR | | | 4 | | | | | | | | | | | | |
| 27-FEB-2024 | INITIAL | FOLLOWUP: | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 65-year-old male patient received bosutinib (BOSULIF), since 04Jun2018 (ongoing) at 300 mg daily. The patient's relevant medical history included: "Ischemic cardiomyopathy" (ongoing); "GASTRITIS" (ongoing). Concomitant medication(s) included: VALSARTAN oral taken for ischaemic cardiomyopathy, start date: 2005 (ongoing); BISOPROLOL oral, start date: 2005 (ongoing); ROSUVASTATIN oral, start date: 2005 (ongoing).

The following information was reported: NASOPHARYNGITIS (non-serious) with onset Dec2019, outcome "recovered" (Dec2019), described as "Rhinopharyngitis"; INFLUENZA (non-serious) with onset 2020, outcome "recovered" (2020), described as "Flu". Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed.

The reporter considered "rhinopharyngitis" and "flu" not related to bosutinib.

Additional information: The events "rhinopharyngitis" and "flu" were rated non-serious with grade 1. According to the investigator, both events were unrelated to the study drug bosutinib and unrelated to concomitant drugs.

Follow-up (13Apr2023): This is a follow-up report received from the CRO. Updated information included: Reporter information, bosutinib start date.

Case Comment: Based on the information provided, the events "rhinopharyngitis" and "flu" are more likely attributed to intercurrent medical conditions and unrelated to bosutinib.

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| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|-------|-------------|----------------------------------|-----------|-------------------|
| 1 | 11-APR-2018 | Endoscopy upper gastrointestinal | GASTRITIS | _ |
| | | tract | | |

| | | | | CIOMS FORM |
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| SUSPECT | ADVERSE REACTION | ON REPORT | | |
| | | | | |
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| | | I. REACTIO | N INFORMATION | |
| 1. PATIENT INITIALS (first, last) | | OF BIRTH 2a. AGE | 3. SEX 3a. WEIGHT 4-6 REACTION ONSET | 8-12 CHECK ALL APPROPRIATE TO |
| PRIVACY | | onth IVACY Year 69 Years | Female $\begin{bmatrix} 58.00 \\ kg \end{bmatrix}$ Day Month 2016 | ADVEDCE DEACTION |
| 7 + 13 DESCRIBE REACTION Event Verbatim [PREFERRE | DN(S) (including relevant tests/lab data) D TERM] (Related symptoms if any sep | parated by commas) | | PATIENT DIED |
| Cough [Cough] Anorexia [Decrease | | | | INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| | | - EVALUATION OF | EFFICACY AND SAFETY OF BOSULIF | INVOLVED DEDELETENT |
| UNDER REAL-LIFE | CONDITIONS OF USE | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR |
| | entional study report (Post A an) for protocol B1871047. | Authorization Safety | Study) received from a contactable | INCAPACITY |
| | | 4 | (Continued on Additional Information Page) | LIFE THREATENING |
| | II. | SUSPECT DR | UG(S) INFORMATION | |
| 14. SUSPECT DRUG(S) (inc #1) Bosulif (BOSUTI | clude generic name) NIB) Film-coated tablet | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | YES NO NA |
| 17. INDICATION(S) FOR US #1) Unknown | E | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from/r #1) 24-FEB-2016 / 0 | | | 19. THERAPY DURATION #1) 9 days | YES NO NA |
| | III. Ç | ONCOMITANT | DRUG(S) AND HISTORY | |
| 22. CONCOMITANT DRUG(| S) AND DATES OF ADMINISTRATION | (exclude those used to treat | reaction) | |
| | | | | |
| | | | | |
| | | | | |
| From/To Dates | TORY. (e.g. diagnostics, allergies, preg Type of | nancy with last month of per f History / Notes | od, etc.) Description | |
| Unknown | | | | |
| | | | | |
| | | | | |
| | | \ | IDED INCODMATION | |
| 24a. NAME AND ADDRESS | | v. IVIANUFACTU | JRER INFORMATION 26. REMARKS | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 | UNITED STATES | | | |
| Phone: 212 733 4045 | | | | |
| | 24b, MFR CONTROL NO. 202200178643 | | 25b. NAME AND ADDRESS OF REPORTER NAME AND ADDRESS WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE | | | |
| 31-JAN-2022 | STUDY HEALTH PROFESSIONAL | LITERATURE OTHER: | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TYPE | FOLLOWUP: | | |

7+13. DESCRIBE REACTION(S) continued

A 69-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 24Feb2016 to 03Mar2016 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: DECREASED APPETITE (non-serious) with onset Oct2016, outcome "not recovered", described as "Anorexia"; COUGH (non-serious) with onset Oct2016, outcome "recovered" (Oct2016). The action taken for bosutinib was unknown.

The reporter considered "cough" and "anorexia" not related to bosutinib.

Additional information: The events cough and anorexia were reported as non-serious with grade 1. According to the investigator, the events were unrelated to study drug and unrelated to concomitant drugs.

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

Case Comment: The Company agrees with the assessment of the investigator and reasonably does not attribute the events to study drugs and concomitant drugs. Events are likely intercurrent medical conditions associated with the underlying malignancy.

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|---|----------------------------|--|-------------|---------------------------|-------------------|------------------|---|-----|
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| SUSPECT | Γ ADVERSE F | REACTION REPO | RT | | | | | |
| 000. 20 | ADVENCE. | (LAOHOR IL.) | IX I | | | | | |
| | | | | | | | | |
| | | I DEA | CTION | INIEOD | MATION | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. KEA | 2a. AGE | 3. SEX | | 4-6 REACTION ONS | | |
| (first, last) PRIVACY | FRANCE | Day PRIVACY Year | 68 Years | Female | 58.00 Da 0 | | APPROPRIATE TO ADVERSE REACTION | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERRI Nocturnal pollakiuri Burning mouth (gra | ia (grade 1) [Polla | • | is) | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | т |
| UNDER REAL-LIFE | E CONDITIONS (| | | | | | F INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | ī |
| reporter(s) (Physici | | oort (Post Authorization 1871047. | Sarety S | tudy) rec | eived from a c | ontactable | | |
| | | | | (Cont | nued on Addition | nal Information | Page) LIFE THREATENING | |
| | | II. SUSPEC | | | | | | |
| 14. SUSPECT DRUG(S) (in #1) Bosulif (BOSUT | - | | TDRO | 3(U) 114 | FORWINITE | 714 | 20. DID REACTION ABATE AFTER STOPPING DRUG? | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | 3. ROUTE(S) 1) Unkno | OF ADMINISTRATION | ON | YES NO NA | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | |
| 18. THERAPY DATES(from. #1) 23-FEB-2016 / (| • | | | THERAPY | | | YES NO NA | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HIST | ORY | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | IINISTRATION (exclude those us | | | , | | | |
| | | | | | | | | |
| | | | | 7 | | | | |
| | | | | | | | | |
| | STORY. (e.g. diagnostics, | allergies, pregnancy with last mo | | | | | | |
| From/To Dates Unknown to Ongoir | ng | Type of History / Notes Relevant Med His | | Description Arterial h | ypertension (F | Hypertension) | | |
| | | | | | | | | |
| | | D/ MANUE | | | | | | |
| 24a. NAME AND ADDRESS | OF MANUFACTURER | IV. MANUF | ACTUR | 26. REN | | N | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | rd East I UNITED STATES | 3 | | | | | | |
| | 24b. MFR CO | NTROL NO. | | | ME AND ADDRESS | | | |
| | 2022001 | 78772 | | NAIVIE | AND ADDRES | SS WITHHELD. |). | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE LITERATURE | | | | | | |
| 31-JAN-2022 | ₩ HEALTH PROFES | SSIONAL OTHER: | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TTYPE FOLLOWUP: | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 68-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 23Feb2016 to 01Mar2016 at 300 mg daily. The patient's relevant medical history included: "Arterial hypertension" (ongoing). The patient's concomitant medications were not reported.

The following information was reported: POLLAKIURIA (non-serious) with onset 04Apr2016, outcome "recovered" (05Apr2016), described as "Nocturnal pollakiuria (grade 1)"; ORAL DISCOMFORT (non-serious) with onset 06Oct2016, outcome "recovered" (Oct2016), described as "Burning mouth (grade 1)".

The reporter considered "nocturnal pollakiuria (grade 1)" and "burning mouth (grade 1)" not related to bosutinib.

Additional information: The events nocturnal pollakiuria and burning mouth were reported as non-serious grade 1. According to the investigator, the events were unrelated to study drug and unrelated to concomitant drugs.

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

Case Comment: Based on the available information, the Company considers both events are unrelated to suspect drug bosutinib but more likely inter-current medical conditions.

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|---|--------------------------|---|------------------|-------------------------|-------------|----------|-----------|--------------|---|--------------------------|--|---------------|------|--|--|--|
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| SUSPECT A | DVEDSE D | EACTION DEDO | DT | | | | | | | | | | | | | |
| SUSPECTA | DVERSE R | EACTION REPO | KI | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | I. REA | CTION | INFOR | MATION | | | | | | | | | | | |
| (first, last) | a. COUNTRY | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 F | Month | NSET Year | 8-12 | | CK ALL ROPRIAT | E TO | | | | |
| PRIVACY F | RANCE | PRIVACY | Unk | Female | Unk | 02 | SEP | 2019 | | ADVE | RSE RE | ACTIO | ٧ | | | |
| 7 + 13 DESCRIBE REACTION(S Event Verbatim [PREFERRED T Other Serious Criteria: Cervicalgia [Neck pain | Medically Sign | | as) | | | | | | 00 | INVO PROI | ENT DIE | R) INPATI | ENT | | | |
| Case Description: OBS UNDER REAL-LIFE C This is a non-intervent | ONDITIONS O | F USE | | | | | | lF | | OR S DISA | LVED PI IGNIFIC BILITY C PACITY | ANT | ENT | | | |
| | 5.00) 10pc | | , O | | , | | , - | | | | | | | | | |
| | | | | (Conti | nued on Add | ditional | nformatio | n Page) | | LIFE THRE | EATENIN | IG | | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMA | TION | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include #1) Bosutinib (BOSUTII | | | | - (-) | | | | | AE | D REAG BATE A RUG? | CTION FTER ST | OPPING | 3 | | | |
| 15. DAILY DOSE(S) #1) 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | | | | NO | | IA | | | |
| 17. INDICATION(S) FOR USE | #1) Unknown | | | | | | | | | | | | | | | |
| #1) Unknown | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(from/to) #1) Unknown | | | | o. THERAPY 1) Unkno | | YES | NO | | IA | | | | | | | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND H | ISTOI | RY | | • | | | | | | | |
| 22. CONCOMITANT DRUG(S) A | ND DATES OF ADMIN | NISTRATION (exclude those us | sed to treat rea | action) | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTOR From/To Dates Unknown | RY. (e.g. diagnostics, a | llergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTUR | ER INF | ORMAT | ION | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard E New York, NY 10001 U Phone: 212 733 4045 | ast | | | 26. REM | | | | | | | | | | | | |
| | 24b. MFR CON | TROL NO. | | | ME AND ADDR | | | | | | | | | | | |
| | 20220017 | 9047 | | NAME | AND ADD | RESS \ | VITHHEL | D. | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT S | | | | | | | | | | | | | | | |
| 28-JAN-2022 | STUDY HEALTH PROFESS | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT 1 | TYPE FOLLOWUP: | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A female patient (unknown if pregnant) received bosutinib (BOSUTINIB) (Batch/Lot number: unknown). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: NECK PAIN (medically significant) with onset 02Sep2019, outcome "unknown", described as "Cervicalgia". It was described as that on 02Sep2019 asthenia, nausea, episodes of malaise related to a cervical discomfort. On 24Sep2019, she went to the emergency room for headache, fever, neck pain, dizziness, vomiting, nausea and was finally diagnosed with cervicalgia. The action taken for bosutinib was unknown. The patient discontinued bosutinib due to unspecified reason and was treated with nilotinib hydrochloride (TASIGNA) from an unspecified date.

The reporter's assessment of the causal relationship of the "cervicalgia" 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.

Case Comment: The event Cervicalgia is serious and unrelated to the suspect drug, bosutinib (BOSUTINIB). This case will be reassessed when further information is provided.

| | | | | | CIOMS FORM |
|---|---|--|-----------------|--|---|
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| SUSPEC | T ADVERSE R | REACTION REPOR | RT | | |
| 333. 23 | .,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | | | |
| | | | | | |
| | | I. REA(| CTION | INFORMATION | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX 3a. WEIGHT 4-6 REACTION ONSET | 8-12 CHECK ALL APPROPRIATE TO |
| PRIVACY | FRANCE | PRIVACY Year | 69 Years | Female $\begin{bmatrix} 58.00 \\ kg \end{bmatrix}$ $\begin{bmatrix} Day \\ 14 \end{bmatrix}$ $\begin{bmatrix} Month \\ DEC \end{bmatrix}$ $\begin{bmatrix} Year \\ 2016 \end{bmatrix}$ | ADVEDSE DEACTION |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR LEFT LOWER LIM | | tests/lab data) toms if any separated by commas EER [Skin ulcer] | s) | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT |
| Case Description: UNDER REAL-LIF | | | N OF EF | FICACY AND SAFETY OF BOSULIF | HOSPITALISATION INVOLVED PERSISTENT |
| | | • | • | tudy) for protocol B1871047. | OR SIGNIFICANT DISABILITY OR INCAPACITY |
| A 69 year-old fema | ale patient received | d bosutinib (BOSULIF), | from | | |
| | | | | (Continued on Additional Information Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRU | G(S) INFORMATION | . |
| 14. SUSPECT DRUG(S) (ir #1) Bosulif (BOSUT | - · | ablet | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | S. ROUTE(S) OF ADMINISTRATION 1) Unknown | YES NO NA |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from #1) 24-FEB-2016 / | • | | | 9. THERAPY DURATION 1) 9 days | YES NO NA |
| | | III. CONCOMIT | ANT D | RUG(S) AND HISTORY | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat rea | action) | |
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| | | | | | |
| From/To Dates | STORY. (e.g. diagnostics, | allergies, pregnancy with last mor Type of History / Notes | | etc.) Description | |
| Unknown | | | | | |
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| | | D/ MANUE | ^ OTLIE | TED INICODMATION | |
| 24a. NAME AND ADDRESS | S OF MANUFACTURER | IV. IVIAINUE | ACTUR | ER INFORMATION 26. REMARKS | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATES | | | | |
| | 24b. MFR CO | NTROL NO. | | 25b. NAME AND ADDRESS OF REPORTER | |
| | 20220018 | | | NAME AND ADDRESS WITHHELD. | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | SOURCE | | NAME AND ADDRESS WITHHELD. | |
| 09-MAR-2023 | STUDY HEALTH PROFES | ш | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | |

7+13. DESCRIBE REACTION(S) continued

24Feb2016 (Batch/Lot number: unknown) to 03Mar2016 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: SKIN ULCER (hospitalization) with onset 14Dec2016, outcome "not recovered", described as "LEFT LOWER LIMB ARTERIAL ULCER". The patient was hospitalized for skin ulcer (start date: 14Dec2016, discharge date: 23Dec2016, hospitalization duration: 9 day(s)).

The investigator considered there was not a reasonable possibility that the event "left lower limb arterial ulcer" was related to bosutinib.

Additional information: The event left lower limb arterial ulcer was rated serious with grade 3.

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

Follow-up (07Feb2022): This is a non-interventional study follow up report (Post Authorization Safety Study) for protocol B1871047 received from study site via CRO.

Updated information: Event grade was updated to grade 3.

Case Comment: There is not a reasonable possibility that the event LEFT LOWER LIMB ARTERIAL ULCER was related to bosutinib. The onset of the event was 9-month post therapy.

| | | | | | | | | | | | | CIC | MS | FO | RM | | | | |
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| SUSPECT | ADVEDSE | | TION DEDO | DT | - | | | | | | | | | | | | | | |
| SUSPECT | PRIVACY FRANCE Day Month PRIVACY Year 68 Years Female 58.00 kg Day Month OCT 2 | | | | | | | | | | | | | | | | | | |
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| | | | I. REA | CTION | INFOR | MATION | _ | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | | | | 1 60 | | | | | 1 | 8-12 | APP | CK ALL ROPRIA | | | | | | | |
| PRIVACY | FRANCE | | | Years | Female | | 1 | | | 5 | ADV | ERSE R | EACTIC | N | | | | | |
| 7 + 13 DESCRIBE REACTION Event Verbatim [PREFERRED | N(S) (including relevan | t tests/lab o | lata) | 26) | • | | 7 | | | 1 | 1 PATI | ENT DIE | D | | | | | | |
| DRY MOUTH [Dry m | outh] | ptomo ii an | y sopulated by comme | 10) | | | | | | | I I INVO | OLVED C |)R | | | | | | |
| DYSPNEA [Dyspnoe | ea] | | | | | | | | | | PRO | LONGE PITALIS | D INPAT | IENT | | | | | |
| Case Description: Of | | | | ON OF E | FFICACY | AND SAF | ETY (| OF BOSU | JLIF | l _ | | | | | | | | | |
| UNDER REAL-LIFE | CONDITIONS | OF USE | | | | | | | | ╽┖ | ORS | OLVED F SIGNIFIC ABILITY | CANT | ENT | | | | | |
| This is a non-interver | | | | Safety | Study) red | eived from | n conta | actable re | eporters | | | APACITY | | | | | | | |
| (Physician and Other | r HCP) for proto | col B18 | 3/1047. | | | | | 7 | | | _ | | | | | | | | |
| | | | | | (Cont | nued on Ad | lditiona | I Informat | ion Page) | ⊥⊏ | LIFE | EATENI | NG | | | | | | |
| | | | II. SUSPEC | T DRI | JG(S) IN | FORMA | JION | J | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (inclu | | | 5551 20 | . 5110 | · • (•) 11 (| | 7 | - | | | | CTION FTER S | TODDI | ıc | | | | | |
| #1) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | | | AFIER S | TOPPIN | IG | | | | | |
| 15. DAILY DOSE(S) | 5. DAILY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | | _ | | | | | | |
| #1) 300 mg, daily | | | | | | | | | | | | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR USE |) 300 mg, daily #1) Unknown INDICATION(S) FOR USE | | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER | | | | | | | |
| #1) Unknown | | | | | | | | | | R | EAPPE | ODUCTI | ER ON? | | | | | | |
| 18. THERAPY DATES(from/to | | | | | 19. THERAPY | | | | | ١, | _ | _ | | | | | | | |
| #1)24-FEB-2016/03 | 3-MAR-2016 | | | | #1) 9 days | 5 | | | | | YES | N | · X | NA | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 22. CONCOMITANT DRUG(S | AND DATES OF ADA | | CONCOMIT | | |) AND H | IISTC | DRY | | | | | | | | | | | |
| 22. CONCOMITANT DRUG(5) |) AND DATES OF ADI | MINISTRAI | ION (exclude those us | sed to treat i | eaction) | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTO | ORY. (e.g. diagnostics | , allergies, | pregnancy with last mo | onth of perio | d, etc.) | | | | | | | | | | | | | | |
| From/To Dates Unknown | | | pe of History / Notes | | Description | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRESS O | DE MANILICA CTUBES | | IV. MANUF | ACTU | RER INI | | ΓΙΟΝ | | | | | | | | | | | | |
| Pfizer Inc | OF MANUFACTURER | 47 | | | 26. KEN | IARNS | | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard | | 0 | | | | | | | | | | | | | | | | | |
| New York, NY 10001 Phone: 212 733 4045 | | 8 | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC | | O | | | ME AND ADDE | | | | | | | | | | | | | |
| | 2022001 | 88354 | | | | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | | LITERATURE | | INAIVIE | . AND ADL | √NE33 | VVII ME | .LD. | | | | | | | | | | |
| 31-JAN-2022 | ₩ HEALTH | | OTHER: | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT | 25a. REPOR | | | | \dashv | | | | | | | | | | | | | | |
| 27-FEB-2024 | ⊠ INITIAL | | FOLLOWUP: | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 68-year-old female patient received bosutinib (BOSULIF), from 24Feb2016 to 03Mar2016 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: DRY MOUTH (non-serious) with onset Oct2016, outcome "recovered" (Oct2016); DYSPNOEA (non-serious) with onset Oct2016, outcome "recovered" (Nov2016), described as "DYSPNEA". The action taken for bosutinib was dosage not changed.

The reporter considered "dry mouth" and "dyspnea" not related to bosutinib.

Additional information: Both events were rated non-serious with grade 1.

The action taken in response to both events for the study drug bosutinib was dosage not changed. According to the investigator both events were unrelated to the study drug bosutinib and unrelated to concomitant drug.

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

Case Comment: Based on the information provided, there is no temporal relationship between the events dyspnea and dry mouth and the administration of bosutinib. Events occurred 7 months after the last dose of bosutinib. Events are likely intercurrent medical condition in this 68-year-old female patient.

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|--|--|---|------------------------------------|------------------------|--------------------------|---------------------|----------|--------|----------|------------|---|----------|--------------|-------------------------------------|---------------|------------|-----|----|--|--|
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| SUSPEC | T ADVERSE | REACTIO | N REPO | RT | | | | | | | | | _ | | | _ | | _ | | |
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| | | | | 1 | | MATION | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | Day Mont | th Year | 2a. AGE 69 Years | 3. SEX Male | 3a. WEIGHT 86.00 kg | Day | Мо | | Yea 202 | ar | Α | APPI | CK ALL ROPRIA ERSE F | ATE TO | | | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFER Rectorrhagia [Rec Hiatal hernia [Hiat | RED TERM] (Related sym tal haemorrhage] | t tests/lab data) ptoms if any separ | rated by comma | as) | | | | | | | | | NVC | ENT DI DLVED LONGE PITALIS | OR ED INF | | :NT | | | |
| Case Description: UNDER REAL-LIF | | | EVALUATIO | ON OF EF | FICACY | AND SAFE | TY O | F BO | SULIF | F | | | OR S | OLVED SIGNIFI ABILITY | ICANT ' OR | ISTE | NT | | | |
| This is a non-interreporter(s) (Physic | | | ıthorizatior | า Safety S | Study) red | ceived from | a con | tactal | ole | | | | | APACIT' | Y | | | | | |
| | | | | | (Cont | inued on Add | litional | Inforn | nation | Pag | je) | | LIFE THRI | EATEN | ING | | | | | |
| | | II. S | SUSPEC | T DRU | G(S) IN | IFORMAT | ΓΙΟΝ | | | | <u> </u> | | | | | | | _ | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | - | tablet | | | | | | | <u> </u> | | 20 | | TE A | CTION AFTER S | | PING | i | | | |
| 15. DAILY DOSE(S) #1) 400 mg, 1x/day | | | | | | | | | | | | <u>`</u> | YES | : | 10 [2 | 3 № | A | | | |
| 17. INDICATION(S) FOR U #1) Unknown | 1) 400 mg, 1x/day #1) Unknown INDICATION(S) FOR USE | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | |
| 18. THERAPY DATES(fror #1) 15-JAN-2019 / | • | | | | 9. THERAPY #1) Unkno | | _ | _ | _ | | | | YES | : | 10 [2 | ₫N | Ą | | | |
| | | III. CC | NCOMI ⁻ | TANT D | RUG(S |) AND HI | STO | RY | | | | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADI | $\overline{}$ | | | $\overline{}$ |) | | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT H From/To Dates Unknown | ISTORY. (e.g. diagnostics | | ncy with last mo istory / Notes | onth of period | l, etc.) Description | | | | | | | | | | | | | | | |
| UTIKTIOWIT | | | | | | | | | | | | | | | | | | | | |
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| | | IV. | MANUF | -ACTUF | RER IN | FORMAT | ION | | | _ | | | | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | ard East 1 UNITED STATE | 7 | | | 26. REM | MARKS | | | | | | | | | | | | | | |
| | 24b. MFR CO | ONTROL NO. | | | 25b. NA | ME AND ADDRE | ESS OF | REPOR | TER | | | | | | | | | _ | | |
| | 2022001 | 93649 | | | NAME | E AND ADDF | RESS | WITH | HELD |). | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | 24d. REPOR | | LITERATURE | | | | | | | | | | | | | | | | | |
| 16-MAR-2023 | ₩ HEALTH PROFE | | OTHER: | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | FOLLOWUP: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 69-year-old male patient received bosutinib (BOSULIF), since 15Jan2019 (ongoing) at 400 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: RECTAL HAEMORRHAGE (non-serious) with onset Mar2021, outcome 'recovered' (2021), described as 'Rectorrhagia'; HIATUS HERNIA (non-serious) with onset Jun2021, outcome 'not recovered', described as 'Hiatal hernia'. Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed.

The reporter considered 'rectorrhagia' and 'hiatal hernia' not related to bosutinib.

Additional information: Additional information: during the consultation of 08Mar2021 and 15Sep2021, blood in stool was reported. During the consultation of 07Jun2021, it was noted subject underwent digestive examinations revealing hiatal hernia and coloscopy revealing a lesion of bottom low caecal which was bleeding. Both rectorrhagia and Hiatal hernia were grade 1 assessed as non-serious. Lesion of bottom low caecal was not reported as adverse event.

Follow-up (07Feb2022). This a non-interventional study follow-up report from the investigational site via CRO. Updated information: patient's demographics, bosutinib dosage details updated, and deleted event 'Lesion of bottom low caecal which was bleeding', reporter causality Added

Follow-up (16Mar2023): This a non-interventional study follow-up report from clinical team.

Update information includes: lesion of bottom low caecal from 08Mar2021 to Sep2021 (not reported as adverse event in the E-CRF)

Case Comment: The events grade 1 'rectorrhagia' and 'hiatal hernia' which was bleeding are assessed as unrelated to bosutinib. Details regarding the drug-event temporal relationship, clinical course of the events, patient's medical history and concomitant medications are not reported. The case will be re-evaluated if more information is available.

13. Lab Data

| # Date | Test / Assessment / Notes | Results | Normal High / Low |
|--------|------------------------------|--|-------------------|
| 1 | Colonoscopy | lesion of bottom low caecal which was bleeding | |
| 2 | Gastrointestinal examination | hiatal hernia | |

| | | | | | | | | | | | | CIC | MS | FOR | RM | | |
|--|---|---|-----------------|-------------------------|------------|--------|----------|----------|--------------|---|--|---|--|-----|----|--|--|
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| CHEDECT AL | DVEDSE DE | | | | | | | | | | | | | | | | |
| SUSPECTAL | DVERSE RE | ACTION REPO | | | | | | | | | | | | | | | |
| | I. REACTION INFORMATION I. PATIENT INITIALS (first, last) PRIVACY I. REACTION INFORMATION 2. DATE OF BIRTH 2a. AGE | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | I. REA | CTION | INFOR | MATIO | N_ | | | | | | | | | | | |
| (first, last) | <u> </u> | | 1 1 | 3. SEX | | - | | | ISET Year | 8-12 | | CK ALL ROPRIA | TE TO | | | | |
| PRIVACY F | RANCE | ' <u>- .</u> | | Male | | | | | 2020 | | ADV | ERSE RI | EACTIO | N | | | |
| Other Serious Criteria: Worsening of sub-mucc malignancy] Worsening of sub-mucc tumour] Case Description: OBS | Medically Signifosal gastric nodu esal gastric nodu esal gastric nodu ERVATIONAL S | icant ule (GIST tumor type ule (GIST tumor type STUDY - EVALUATIO | on biops | sy of 26M | ar2021) [| [Gast | rointes | tinal st | | 00 0 | INVO PROI HOSI INVO OR S DISA | ENT DIE DLVED O LONGEI PITALIS, DLVED P BIGNIFIC BILITY (PACITY | PR D INPAT ATION ERSIST CANT DR | | | | |
| UNDER REAL-LIFE CO | INDITIONS OF | USE | | (Cont | nued on A | dditio | nal Info | rmation | Page) | _ | LIFE THRE | EATENIN | NG | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | - | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION 14. SUSPECT DRUG(S) (include generic name) #1) Bosutinib (BOSUTINIB) Unknown | | | | | | | | | | AE | | CTION FTER S | TOPPIN | G | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily 16. ROUTE(S) OF ADMINISTRATION #1) Unknown | | | | | | | | | | | YES | NC | | NA | | | |
| #1) 500 mg, daily #1) Unknown 17. INDICATION(S) FOR USE #1) Chronic lymphoid leukemia (Chronic lymphocytic leukaemia) | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(from/to) #1) 14-DEC-2017 / Ongo | oing | | | 9. THERAPY 1) Unkno | | | | | | YES NO NA | | | | | | | |
| | | III. CONCOMIT | ANT D | RUG(S |) AND I | HIST | ORY | | | | | | | | | | |
| 22. CONCOMITANT DRUG(S) AN | ID DATES OF ADMINIS | STRATION (exclude those use | ed to treat rea | action) | | | | | | | | | | | | | |
| 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 Adenoma (Adenoma benign) | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTUR | RER INI | FORMA | ATIO | N | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF MANUFACTURER Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 24b. MFR CONTROL NO. 25b. NAME AND ADDRESS OF REPORTER | | | | | | | | | | | | | | | | | |
| | 24b. MFR CONTR | | | | ME AND ADD | | | |). | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SO | DURCE | | | | | | | | | | | | | | | |
| 07-MAR-2023 | STUDY HEALTH PROFESSIO | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT TY | PE FOLLOWUP: | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

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

A 68-year-old male subject received bosutinib (BOSUTINIB), since 14Dec2017 (ongoing) at 500 mg daily for chronic lymphoid leukemia. The patient's relevant medical history included: "adenomatous polyps" (unspecified if ongoing). The subject's concomitant medications were not reported.

The following information was reported: SECOND PRIMARY MALIGNANCY (medically significant), GASTROINTESTINAL STROMAL TUMOUR (medically significant) all with onset 16Oct2020, outcome "recovered" (Jul2021) and all described as "Worsening of sub-mucosal gastric nodule (GIST tumor type on biopsy of 26Mar2021)". Gastroscopy was performed on 16Oct2020 showing a big sub-mucosal gastric nodule, which increased of size. On 05Feb2021, high echo endoscopy was performed and showed sub-mucosal tumour of 5 cm of the fourth layer hypoechogenous evoking a gastrointestinal stromal tumor. The finding date of the gastric nodule was on 26Mar2021, date on which the biopsy was performed, whether 28 days after the visit M36, not considered as an adverse event according to protocol. Surgery with removal of the gastrointestinal stromal tumor was performed on 15Jul2021, then gastric decompensation at the end of Jul2021 and favorable outcome. The event Worsening of sub-mucosal gastric nodule (GIST tumor type on biopsy of 26Mar2021) was reported as serious (medically significant) with grade 3. The action taken for bosutinib was dosage not changed.

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

Follow-up (21Mar2022 and 28Mar2022): New information received from the investigational site investigator via the CRO. Updated information: patient details (date of birth, height, and weight), medical history, lab data, event details (onset and stop date), reaction data (new event: Condition aggravated was added) outcome of event, causality and seriousness. This case was upgraded to serious.

Follow-up (16May2022): This is a non-interventional study follow-up report received from the investigational site via CRO. Updated information includes: study drug dosage regimen and therapy date.

Follow-up (27Jun2022): new information received from the investigational site. Updated information: Bosutinib indication.

Follow-up (07Mar2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from study site for protocol B1871047.

Updated information: lab data dated on 26Mar2021 updated, event verbatim updated from worsening of sub-mucosal gastric nodule to Worsening of sub-mucosal gastric nodule (GIST tumor type on biopsy of 26Mar2021).

Case Comment: Based on the available information, there was not reasonable possibility that the event "Worsening of sub-mucosal gastric nodule (GIST tumor type on biopsy)" as second primary malignancy was related to bosutinib.

13 Lab Data

| is. Lab Dala | | | | |
|--------------|-------------|---|----------------------------------|-------------------|
| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
| 1 | 26-MAR-2021 | Biopsy | Gastric nodule | _ |
| | | GIST tumor type | | |
| 2 | 16-OCT-2020 | Endoscopy upper gastrointestinal tract | a big sub-mucosal gastric nodule | |
| | | which increased of size. | | |
| 3 | 05-FEB-2021 | Endoscopy upper gastrointestinal tract | sub-mucosal tumour | |
| | | 5 cm of the fourth layer hypoechogenous evoking a gastrointestinal stromal tumor. | | |

| | | | | | | | | CIOMS FORM |
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| SUSPEC | T ADVERSE F | REACTION REPO | RT | | | | | |
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| | | | | | | $\perp 1/4$ | | |
| | | I DEA | CTION I | NEOD | MATION | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | 4-6 REACTION | ONSET | 8-12 CHECK ALL |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | Unk | Unk | | | Year 2019 | APPROPRIATE TO ADVERSE REACTION |
| Pain in face [Facial Cramps [Muscle s | al pain] spasms] | | as) | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| UNDER REAL-LIF | FE CONDITIONS (| OF USE | | 47 | | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| | | oort (Post Authorization | Safety St | udy) rec | eived from a | contactable | ! | <u> </u> |
| 1000.12.(2) | Jian, 15. p. 2 | | | (Conti | nued on Addition | onal Informat | ion Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATIO | ON | | |
| #1) Bosulif (BOSU | TINIB) Film-coated | | | | | | _ | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) #2) | | | #1 |) Unkno | wn | TION | | YES NO NA |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | USE | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(from #1) Unknown #2) Unknown | m/to) | | #1 |) Unkno | wn | | | YES NO NA |
| | | III. CONCOMIT | | | | TORY | | 1 |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | | | | , | | | |
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| | | | | | | | | |
| | IISTORY. (e.g. diagnostics, | | | | | | | |
| From/To Dates Unknown | | Type of History / Notes | | escription | | | | |
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| | 1 UNITED STATES | 3 | | | | | | |
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| 24c. DATE RECEIVED | | | | = | | | | |
| 28-JAN-2022 | THE SECOND STATES AND A CONTRACT OF THE SECOND STATES OF ADMINISTRATION (exclude present on the state) of the state of the | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | ГТҮРЕ | | | | | | |

7+13. DESCRIBE REACTION(S) continued B1871047.

A patient (no qualifiers provided) received bosutinib (BOSULIF); nilotinib hydrochloride (TASIGNA). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: MUSCLE SPASMS (non-serious) with onset 25Jun2019, outcome "unknown", described as "Cramps"; BLOOD MAGNESIUM DECREASED (non-serious) with onset 25Jun2019, outcome "unknown", described as "Magnesium decreased"; FACIAL PAIN (non-serious) with onset 25Jun2019, outcome "unknown", described as "Pain in face". The action taken for nilotinib hydrochloride was dosage reduced.

Additional information: The patient had discontinued bosutininb as required by protocol and was under nilotinib hydrochloride (TASIGNA) from an unspecified date. As of 24Sep2019 the patient experienced pain in face (TASIGNA discontinued then dose reduced), cramps and magnesium decreased.

The reporter's assessment of the causal relationship of "pain in face", "cramps" and "magnesium decreased" 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.

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

Case Comment: The information currently available is limited. Bosutinib administration dates, indication for use, medical history and concomitant medications were not reported. At this time there are no sufficient details supporting a causative role of bosutinib for the reported events.

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| SUSPEC | I ADVERSE F | REACTION REPO | RI | | | | | | | | | | | |
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| PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 3a. WEIGHT | _ | CTION O | NSET Year | 8-12 | APP | CK ALL ROPRIA | | | |
| PRIVACY | FRANCE | PRIVACY | Unk F | emale | Olik | | JAN | 2019 | | ΑDv | ÆRSE K | EACTIO | N | |
| 7 + 13 DESCRIBE REACT | TION(S) (including relevant RED TERM] (Related symp | t tests/lab data) otoms if any separated by comma | as) | | | | | | | PAT | IENT DIE | ED. | | |
| a few episodes of | bronchial superinfe | | , | | | | | | | | OLVED (| | - | |
| dysphonia [Dysph dyspnea [Dyspnoe | - | | | | | | | | | | DLONGE SPITALIS | D INPATI SATION | ENT | |
| infectious episode | [Infection] | nial or pseudo flu) [Infed | otion1 | | | | | | _ | 1 INV | OI VED F | PERSISTI | FNT | |
| depressive syndro | , | lial or pseudo na) [micc | Juonj | 47 | | | | | - | OR : | SIGNIFIO ABILITY | CANT OR | | |
| Case Description: | ORSERVATIONAL | L STUDY - EVALUATIO | ON OF FFI | FICACY | AND SAFFT | Y OF B | IUSUI | IF | | INC | APACITY | , | | |
| | FE CONDITIONS (| | | | | | | | _ | l LIFE | | | | |
| | | | | (Conti | nued on Additi | onal Info | ormation | n Page |) | THR | REATENI | NG | | |
| | | II. SUSPEC | T DRUG | S(S) IN | FORMATION | ON | | | Į. | | | | | |
| 14. SUSPECT DRUG(S) (#1) Bosutinib (BOS | , | _ | _ | | | | | _ | A | BATE A | ACTION AFTER S | TOPPING | G | |
| , , | SATINIB MONOHY | DRATE) | | | | | | |] " | RUG? | | | | |
| 15. DAILY DOSE(S) #1) UNK | | | | ROUTE(S)) Unkno | OF ADMINISTRAT | TION | | |] [| YES | s 🔲 N | ⊃ ⊠ ⊳ | ۸A | |
| #2) UNK | | | |) Unkno | | | | | <u> </u> | | | | | |
| 17. INDICATION(S) FOR I #1) Unknown #2) Unknown | USE | | | | | | | | R | EAPPE | CTION EAR AFT ODUCTI | | | |
| 18. THERAPY DATES(from | · | | | THERAPY | | | | | ┨, | ¬ _{v=} | . \square_{N} | > ⊠ ∧ | | |
| #1) Unknown / 25- #2) Unknown | OC1-2018 | | | Unkno' (Unkno' (: | | | | | | | ° LJ '`` | , (2) | IA. | |
| | | III. CONCOMIT | TANT DF | RUG(S) | AND HIS | TORY | , | | | | | | | |
| 22. CONCOMITANT DRU | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | | | | | | | | | | | | |
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| From/To Dates | HSTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRES | SO OF MANUFACTURER | IV. MANUF | ACTURI | ER INF | | DN | | | | | | | | |
| Pfizer Inc Stella Pietrafesa | 55 OF IMANOPACTORER | | | ZU. INLIVI | AKNO | | | | | | | | | |
| 66 Hudson Bouleva | | | | | | | | | | | | | | |
| Phone: 212 733 40 | 01 UNITED STATES 45 | • | | | | | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURE | R 24d. REPORT | T SOURCE LITERATURE | | | | | | | | | | | | |
| 14-NOV-2023 | HEALTH PROFES | SSIONAL OTHER: | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | _ | | 7 | | | | | | | | | | |
| 21-FED-2024 | I INITIAL | FOLLOWUP: | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

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

A female patient (unknown if pregnant) received bosutinib (BOSUTINIB), till 25Oct2018; dasatinib monohydrate (SPRYCEL), (Batch/Lot number: unknown). The patient's relevant medical history and concomitant medications were not reported. The following information was reported: INFECTION (non-serious) with onset Jan2019, outcome "unknown", described as "another infectious syndrome (bronchial or pseudo flu)"; INFECTION (non-serious) with onset 2019, outcome "unknown", described as "infectious episode"; BRONCHITIS (non-serious) with onset Jan2020, outcome "unknown", described as "a few episodes of bronchial superinfection"; DYSPHONIA (non-serious), outcome "unknown"; DYSPNOEA (non-serious), outcome "not recovered", described as "dyspnea"; DEPRESSION (non-serious), outcome "unknown", described as "depressive syndrome". The action taken for dasatinib monohydrate was unknown.

The reporter's assessment of the causal relationship of "a few episodes of bronchial superinfection", "dysphonia", "dysphonia", "infectious episode", "another infectious syndrome (bronchial or pseudo flu)" and "depressive syndrome" 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.

Additional information: The patient was treated with SPRYCEL. At the specialist consultation on 02Jan2019, dysphonia and dyspnoea were reported. On 21Jan2019, dyspnea was still present, and an infectious episode was reported at the end of the year. Another infectious syndrome (bronchial or pseudo flu) was reported at the end of Jan2019. On 06Jan2020, a few episodes of bronchial superinfection and a depressive syndrome were reported. As of 26Sep2023, it was reported that the long term events are not reported by the center. The patient stopped Bosutinib and the last administration was on 25Oct2018. The long term events related to an infection were notified spontaneously during monitoring and will not be registered in the eCRF: Infectious syndrome in Jan2019 and bronchial superinfection in Jan2020. As of 14Nov2023, Comment for event a few episodes of bronchial superinfection: A history of current pneumonia before entering the study. A fungal infection after stopping bosutinib and not reported by the counter because long term follow-up. Reconcile with discrepancy. Site refuse to report AE after 28 days post bosutinib treatment. Comment for the events dyspnea; dysphonia; depressive syndrome; another infectious syndrome (bronchial or pseudo flu) and infectious episode: Reconcile with discrepancy. Site refuse to report AE after 28 days post bosutinib treatment.

Follow-up (26Sep2023): Updated information included a clarification received from the clinical team following a request regarding the event "Another infectious syndrome (bronchial or pseudo flu)".

Follow-up (14Nov2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from a contactable reporter(s) (Physician) for protocol B1871047. Updated information included: Event comment added.

Case Comment: All of the events are assessed as non serious and unrelated except for the event "a few episodes of bronchial superinfection" which is assessed as related. The unrelated events are most likely intercurrent medical conditions, unrelated to the suspect drug, bosutinib (BOSUTINIB). This case will be reassessed when further information is provided.

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| | | I RFAC | | INIFOR | MATION | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | | 1-6 REACTION O | ONSET | 8-12 CHECK ALL |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 69 Years | Female | 57.00 Da | | Year 2019 | APPROPRIATE TO ADVERSE REACTION |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Chest pain [Chest Osteoporosis [Ost pain on the right si | pain] eoporosis] | tests/lab data) stoms if any separated by commas Imonary pain] | s) | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION |
| UNDER REAL-LIF | E CONDITIONS (| | | 47 | | | LIF | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY |
| This is a non-interreporter(s) (Physic | | oort (Post Authorization P) | Safety St | tudy) rec | eived from cor | itactable | | |
| Τοροποιίο, (, | Jan ana 54.5 | | | (Conti | nued on Addition | nal Informatio | on Page) | LIFE THREATENING |
| | | II. SUSPEC | T DRUC | G(S) IN | FORMATIO | N | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | , | | | _ | | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | i. ROUTE(S) 1) Unkno | OF ADMINISTRATION | DN | | YES NO NA |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? |
| 18. THERAPY DATES(fror #1) 07-MAR-2018 | • | | | . THERAPY 1)3 mon | DURATION ths 29 days | | | YES NO NA |
| | | III. CONCOMIT | ANT DE | RUG(S |) AND HIST | ORY | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | INISTRATION (exclude those use | | | | | | |
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| 23. OTHER RELEVANT H From/To Dates Unknown | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last mor Type of History / Notes | | etc.) Description | | | | |
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| | <u> </u> | IV. MANUF | ^CTUR | | | NI | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. IVIAINUI | ACTOR | 26. REM | | <u> </u> | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | |
| | 24b. MFR CO | NTROL NO. | | | ME AND ADDRESS | | _ | |
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| 01-FEB-2022 | HEALTH PROFES | SSIONAL OTHER: | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TTYPE FOLLOWUP: | | | | | | |

7+13. DESCRIBE REACTION(S) continued

for protocol B1871047.

A 69-year-old female patient received bosutinib (BOSULIF), from 07Mar2018 to 05Jul2018 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: CHEST PAIN (non-serious) with onset 12Sep2019, outcome "recovered" (2020); OSTEOPOROSIS (non-serious) with onset 18Sep2019, outcome "not recovered"; PULMONARY PAIN (non-serious) with onset Oct2020, outcome "recovered" (Oct2020), described as "pain on the right side of the lung".

The reporter considered "chest pain", "osteoporosis" and "pain on the right side of the lung" not related to bosutinib.

Additional information: The patient was no longer on bosutinib and without any treatment, some vague chest pains were reported on 12Sep2019, an osteoporosis problem on 18Sep2019 and pain on the right side of the lung end of Oct2020. All the events were rated non serious and grade 1. According to the investigator, these events were unrelated to the study drug bosutinib and unrelated to concomitant drug.

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

Case Comment: There is no temporal relationship between the events and administration of bosutinib. Bosutinib were discontinued for almost a year prior to the onset of the events in this report. The Company therefore considered that there was not a reasonable possibility that the events are associated with the study product or concomitant drugs.

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| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | CTION II | NFOR 3. SEX | MATION 3a. WEIGHT | 4-6 RF | ACTION OF | NSFT | 8-12 C | HECK AI | | | |
| (first, last) PRIVACY | | Day Month Year PRIVACY | 77 | emale | H- | Day | Month | Year 2020 | A | PPROPE DVERSE | RIATE TO | | |
| | | sts/lab data) ns if any separated by comma | as) | | | | | | Q P | ATIENT [| DIED | | |
| Left hip pain [Arthi Anemia [Anaemia] | • - | | | | | | | | | NVOLVEI ROLONO IOSPITAL | SED INF | | NT |
| | OBSERVATIONAL S | STUDY - EVALUATION | ON OF EFF | FICACY | AND SAFET | Y OF I | BOSUL | IF | _ " | NVOLVE |) PERS | ISTEN | IT |
| | | rt (Post Authorization | Safety Sti | ıdv) for | protocol B18 | 71047 | | | | OR SIGNII DISABILIT NCAPACI | Y OR | • | |
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| | | II. SUSPEC | T DRUG | (S) IN | FORMATI | ON | | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | include generic name) TINIB) Film-coated tal | plet | | | | | | | 20. DID R ABAT DRUG | EAFTER | | PING | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day | / | | | ROUTE(S)) Unkno | OF ADMINISTRA WN | TION | | | | res 🔲 | NO [| NA 🔼 | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | | | REACTION PPEAR A TRODUC | FTER | | |
| 18. THERAPY DATES(fror #1) 12-APR-2018 / | • | | | | DURATION ths 9 days | | | | | res 🔲 | NO [| NA 🔼 | |
| | | III. CONCOMIT | | |) AND HIS | STOR | Y | | ı | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADMINI | STRATION (exclude those us | sed to treat reac | tion) | | | | | | | | | |
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| 00 OTHER RELEVANTURE | IOTODY (a. a. diamandia a all | ide to de | | 4-1 | | | | | | | | | |
| From/To Dates Unknown | is fort, (e.g. diagnostics, all | ergies, pregnancy with last mo Type of History / Notes | | escription | | | | | | | | | |
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| | | IV. MANUF | ACTURE | | | NC | | | | | | | |
| 24a. NAME AND ADDRES Pfizer Inc Stella Pietrafesa | SS OF MANUFACTURER | | | 26. REM | IARKS | | | | | | | | |
| 66 Hudson Bouleva | ard East 1 UNITED STATES | | | | | | | | | | | | |
| Phone: 212 733 40 | | | | | | | | | | | | | |
| | 24b. MFR CONT | ROL NO. | | | ME AND ADDRES | | | | | | | | |
| | 202200208 | | | NAME | AND ADDRE | ss Wi | IHHEL | J. | | | | | |
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| 03-FEB-2022 | HEALTH PROFESSION | | | 1 | | | | | | | | | |
| 27-FEB-2024 | 25a. REPORT T | YPE FOLLOWUP: | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 77 year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 12Apr2018 (Batch/Lot number: unknown) to 20Jun2018 at 200 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported. The following information was reported: ARTHRALGIA (hospitalization) with onset Jan2020, outcome "recovered" (04Aug2020), described as "Left hip pain"; ANAEMIA (non-serious) with onset 09Jun2020, outcome "recovered" (09Jun2020), described as "Anemia". Therapeutic measures were taken as a result of arthralgia, anaemia.

Additional information: events were rated as grade 3. For event "left hip pain", in Jan2020 hospitalization was required with hip prosthesis placement on 09Jun2020, no hip pain reported during the consultation of 04Aug2020. Report of hospitalization not available. For event "anemia", following of a hemorrhagic hip prosthesis, transfusional management of 3 erythrocyte concentrates in Jun2020.

The investigator considered the events were not related to study drug and concomitant drug.

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

Case Comment: Based on the available information, the Company concurs with the investigator that there is not a reasonable possibility that the reported events Left hip pain, Anemia are related to the bosutinib. The events are more likely inter-current medical conditions.



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| | | I. REA | CTION II | NFOR | MATION | | | | | | | | | | | | |
| PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE | 3. SEX | 3a. WEIGHT Da | | ACTIC | n ons | SET Yea | _ | 12 | APP | CK ALL | ATE 1 | | | |
| PRIVACY | TRANCE | PRIVACY | Years F | emale | kg kg | | OC | T 2 | 202 | 20 | | ADV | ERSE F | (EAC | SHON | I | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERI Left hip pain [Arthi | | tests/lab data) otoms if any separated by comma | s) | | | | | | | | | INVO | ENT DI | OR | | | |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUATIO DF USE | ON OF EFF | FICACY | AND SAFETY | OF | BOS | ULIF | : | | _ | HOS | LONGE PITALIS | SATIO | ON | | |
| | | port (Post Authorization | | | protocol B187 | 1047 | 7. | | | | Ш | OR S | SIGNIFI ABILITY APACIT | CAN | T | .IVI | |
| A 77-year-old fema | ale patient (unkno | wn if pregnant) received | d bosutinib | | | | | | | | _ | LIFE | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION ECT DRUG(S) (include generic name) | | | | | | | | | | | | | | | | |
| | CT DRUG(S) (include generic name) ulif (BOSUTINIB) Film-coated tablet DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | | | | | | |
| | II. SUSPECT DRUG(S) INFORMATION SPECT DRUG(S) (include generic name) Bosulif (BOSUTINIB) Film-coated tablet LY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION | | | | | | | | | | | | | | PPING | 6 | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day | SPECT DRUG(S) (include generic name) Bosulif (BOSUTINIB) Film-coated tablet ILY DOSE(S) 16. ROUTE(S) OF ADMINISTRATION 200 mg, 1x/day ICATION(S) FOR USE | | | | | | | | | | | | | 0 | ×Σ | A | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | 21 | RE/ | APPE | CTION AR AF ODUCT | | ? | | | | |
| 18. THERAPY DATES(from #1) 12-APR-2018 / | • | | | | DURATION ths 9 days | | | | | | | YES | : <u>П</u> и | 0 | ×Σ | A | |
| | | III. CONCOMIT | TANT DR | UG(S |) AND HIST | OR | Υ | | | • | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those use | ed to treat reac | tion) | | | | | | | | | | | | | |
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| From/To Dates | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | tc.) escription | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| | | 1// МАЛИТ | ACTI IDI | ED IVID | | NI | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANUF | ACTURE | 26. REM | | N | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | | |
| | | NITROL NO | | 05/ 11/ | ME AND ADDRESS | 05.5 | -000- | | | | | | | | | | |
| | 24b. MFR CC 2022002 | | | | ME AND ADDRESS (AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTUREI | 24d. REPOR | | | | | | | | | | | | | | | | |
| 03-FEB-2022 | STUDY | SSIONAL OTHER: | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

(BOSULIF), from 12Apr2018 (Batch/Lot number: unknown) to 20Jun2018 at 200 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: ARTHRALGIA (non-serious) with onset Oct2020, outcome "recovered" (Jan2021), described as "Left hip pain".

Additional information: Left hip pain, non-serious, grade 1. Loss of molecular response non-serious, grade 2. Events were unrelated to any concomitant drug

The investigator considered there was not a reasonable possibility that the events "left hip pain" and "loss of molecular response" were related to bosutinib.

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

Case Comment: Based on the information provided, the reported hip pain is likely an intercurrent medical condition in this 77 year old female patient and unrelated to bosutinib.

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| 4. DATIENT INITIAL C | 4- COUNTRY | | | | | 4.0.0 | FACTION | N ONO | | 8-12 | | IECK AL | | | | |
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| | | | | (Conti | nued on Addit | ional I | nforma | tion P | age) | |] LIF | E REATE | NING | 3 | | |
| | | II. SUSPEC | T DRUC | G(S) IN | FORMAT | ION | | | | | | | | | | |
| #1) Bosulif (BOSU | JTINIB) Film-coated | tablet | | | | | | | | | | ACTION AFTER ? | | OPPIN | G | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/da #2) | ау | | # | 1) Unkno | wn | TION | | | | | YE | s 🔲 | NO | | NA | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | USE | | | | | | | | | l | REAP | ACTION PEAR AF RODUC | FTER | | | |
| 18. THERAPY DATES(fro #1) 12-APR-2018 #2) Unknown | · | | # | 1) 2 mon | hs 9 days | | | | | | YE | s 🔲 | NO | | NA | |
| | | III. CONCOMIT | TANT DI | RUG(S | AND HIS | STOF | RY | | | | | | | | | |
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| DATE OF THIS REPORT 27-FEB-2024 | 1 | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 77-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 12Apr2018 to 20Jun2018 at 200 mg 1x/day; imatinib mesilate (GLIVEC). The patient's relevant medical history was not reported. Concomitant medication(s) included: ESIDREX, stop date: Apr2019.

The following information was reported: OEDEMA PERIPHERAL (non-serious) with onset Apr2019, outcome "recovered" (Sep2019), described as "Lower limbs edema"; PRURITUS (non-serious) with onset Sep2019, outcome "recovered" (Jan2020), described as "Generalized pruritus". The action taken for imatinib mesilate was dosage permanently withdrawn.

The reporter considered "lower limbs edema" and "generalized pruritus" not related to bosutinib.

Additional information: Lower limbs edema occurred following the withdrawal of diuretics (ESIDREX sopped in Apr2019), grade 2, non-serious, unrelated to the study drug bosulif or to a concomitant medication. Generalized pruritus, grade 2, non-serious, unrelated to the study drug, related to concomitant GLIVEC.

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

Case Comment: There is no temporal relationship between the events edema peripheral and pruritus and the administration of bosutinib. Bosutinib last dose was approximately 285 days prior to the onset of the events in this report. The Company therefore considered that there was not a reasonable possibility that the events edema peripheral and pruritus are associated with the study product, bosutinib.

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| | | | I. RE | EACT | TION | INFOR | MATIO | N_ | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. Day | DATE OF BIRTH Month Yes | _ | 2a. AGE 45 | 3. SEX | 3a. WEIGH | | | Mon | _ | NSET Ye | \dashv | 8-12 | AP | PPRO | | ATE TO | | | |
| PRIVACY | | | PRIVACY | Y | ears/ | Male | kg | 1 | 2 | JUI | N | 20 | 17 | | AD | 7V E F | NOE N | LACT | ION | | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR | RED TERM] (Related sym | nt tests/lab nptoms if ar | data) ny separated by cor | ommas) | | | | | | | | ₹ | | E |] PA | TIEN | NT DIE | ΞD | | | |
| Weight loss [Weigh weight gain [Weigh | • | | | | | | | | | | | | | Ę | ┛ PR | ROLO | | OR ED INPA SATION | | NT | |
| Case Description: | OBSERVATIONA | L STU | Y - EVALUA | NOITA | OF EF | FICACY | AND SA | FETY | OF | BOS | SULI | F | | _ | | | 7 | | | _ | |
| UNDER REAL-LIF | E CONDITIONS | OF USI | Ē | | | | | | | | | | | | OR DIS | R SIC | GNIFIC | OR | STE | NΤ | |
| This is a non-interview reporter(s) (Physic | | | | tion S | afety S | tudy) red | ceived fro | m a c | onta | ctab | le | | | | INC | CAP | ACITY | ſ | | | |
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| | | | II CHCDI | ГОТ | | | | 7 | | | ation | u | 967 | | | IIXL | VI EIVII | 140 | | | |
| 14. SUSPECT DRUG(S) (ir | nclude generic name) | | II. SUSPE | ECT | DRU | ۱۱ (۵) ق | IFORM. | ATIC |)N | | | | Т | | DID RE | | | | | | |
| #1) Bosulif (BOSUT | ΓΙΝΙΒ) Film-coated | l tablet | | | | | | | | | | | | | ABATE DRUGʻ | | TER S | STOPP | ING | | |
| 15. DAILY DOSE(S) | | | | | | S. ROUTE(S |) OF ADMINIS | STRATIO | ON | V | | | ᅥ | ſ | □YE | FS (| Пм | 。 区 | 7 N/ | | |
| #1) 200 mg, daily | | | | | # | 1) OTKIR | DWII | | | | | | 4 | | | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | ISE | | | | | | | | | | | | | R | DID RE REAPF REINT | PEA | R AFT | | | | |
| 18. THERAPY DATES(from | n/to) | | | | | | DURATION | | | | | | \dashv | | _ | | _ | _ | , | | |
| #1) 12-DEC-2016 / | 02-MAR-2017 | | | | # | 1) 2 mor | iths 19 da | iys | | | | | | L | YE | ES [| NO | o X | N/ | ١ | |
| | | | CONCO | MITA | NT D | RUG(S | a) AND I | HIST | OR | Υ | | | | | | | | | | | |
| 22. CONCOMITANT DRUG | | MINISTRA | ΓΙΟΝ (exclude thos | se used t | to treat rea | action) |) | | <u> </u> | • | | | | | | | | | | | |
| #1) SPRYCEL (DA | ASATINIB MONO | HYDK | (TE) ; 19-AF | PR-20 | 117 / Or | igoing | | | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT HIS | STORY. (e.g. diagnostics | | pregnancy with las | | | etc.) Description | | | | | | | | | | | | | | | |
| Unknown | | | | | | · | | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRESS | S OF MANUFACTURER | | IV. MANI | UFA | CIUR | 26. REI | | 1110 | IN | | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva | rd Fast | 7 | | | | | | | | | | | | | | | | | | | |
| New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATE | S | | | | | | | | | | | | | | | | | | | |
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| 27-FEB-2024 | ⊠ INITIAL | | FOLLOWU | JP: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 45-year-old male patient received bosutinib (BOSULIF), from 12Dec2016 to 02Mar2017 at 200 mg daily. The patient's relevant medical history was not reported. Concomitant medication(s) included: SPRYCEL oral taken for chronic myeloid leukaemia, start date: 19Apr2017 (ongoing).

The following information was reported: WEIGHT INCREASED (non-serious) with onset 12Jun2017, outcome "recovered" (07May2018), described as "weight gain"; WEIGHT DECREASED (non-serious) with onset 2017, outcome "recovered" (02Mar2017), described as "Weight loss". The action taken for bosutinib was dosage not changed.

The reporter considered "weight loss" and "weight gain" not related to bosutinib.

Additional information: Weight loss was rated grade 2. Weight gain was rated grade 3. According to the investigator, the events were unrelated to study drug and to concomitant drug.

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

Case Comment: Based on the information provided, the reported events are likely intercurrent medical conditions and unrelated to the bosutinib.

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| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | |
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| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | ACTION II | | MATION 3a. WEIGHT | 4-6 RE | ACTION | N ONSE | тТ | 8-12 | CHE | ECK ALL | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 76 Years | | _ | Day | Month | Ye | ear 020 | 0 .2 | APP | PROPRIA /ERSE R | | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERI Lower limb oedem Eyelid edema [Eye | RED TERM] (Related symples Na [Oedema periph | otoms if any separated by comm | nas) | | | | | | | | I INV | OLVED COLONGEI | OR D INP | | NT | |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUATI DF USE | ON OF EFF | FICACY P | AND SAFET | Y OF | BOSI | JLIF | | | OR DIS | OLVED P SIGNIFIC ABILITY (APACITY | CANT OR | STEN | ΝΤ | |
| | | oort (Post Authorization P) for protocol B18710 | | udy) rece | ived from co | ntact | able | | | | INC. | | | | | |
| | | | | (Contin | ued on Addition | onal In | forma | tion Pa | ige) | | THR | REATENII | NG | | | |
| | | II. SUSPEC | CT DRUG | (S) INF | ORMATIC | NC | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | - | tablet | | | ued on Additio | $\overline{}$ | forma | tion Pa | | Al | | ACTION AFTER S | TOPF | PING | | |
| 15. DAILY DOSE(S) #1) 200 mg, 1x/day | У | | | ROUTE(S) C) Unknow | OF ADMINISTRATI VN | ION | | | | | YES | S NO | > E | NA | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | 47 | | | | | | RI | EAPPE | ACTION EAR AFT ODUCTION | | | | |
| 18. THERAPY DATES(from #1) 03-MAY-2019 / | | | | THERAPY D) 2 month | uration ns 30 days | | | | | | YES | S NO | > ∑ | N A | | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | TOR | Υ | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those u | ised to treat react | tion) | | | | | | | | | | | | |
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| 23. OTHER RELEVANT H | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last m Type of History / Notes | | tc.) | | | | | | | | | | | | |
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| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. WIMINUT | | 26. REMA | | /1 N | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURE! | 24d. REPOR | T SOURCE | | NAME | AND ADDRE | SS W | ITHHI | ELD. | | | | | | | | |
| 04-FEB-2022 | STUDY HEALTH PROFES | SSIONAL DOTHER: | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | | 1 | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 76-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), first regimen from 03May2019 to 01Aug2019 at 200 mg 1x/day, second regimen from 02Aug2019 to 22Oct2020 at 300 mg 1x/day and third regimen since 23Oct2020 (ongoing) at 200 mg 1x/day. The patient had no relevant medical history. The patient's concomitant medications were not reported. The following information was reported: OEDEMA PERIPHERAL (non-serious) with onset Jun2020, outcome "recovered" (Aug2021), described as "Lower limb oedema"; EYELID OEDEMA (non-serious) with onset 29Jun2021, outcome "recovered" (Aug2021), described as "Eyelid edema". The action taken for bosutinib was dosage not changed.

The reporter considered "lower limb oedema" not related to bosutinib. The reporter considered "eyelid edema" related to bosutinib. Additional information: the events lower limb oedema and eyelid edema were rated grade 1.

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

Case Comment: Based on the information provided and known safety profile, there is a reasonable possibility that the reported events are 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, 1x/day; Unknown | Unknown | 02-AUG-2019 / 22-OCT-2020; 1 year 2 months 21 |
| WAY Provide (POOLITINIE) Film on the late | 000 vv 4/4 v 11/4 v 4 | | days |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 200 mg, 1x/day; Unknown | Unknown | 23-OCT-2020 / |
| Regimen #3 | | | Ongoing; |
| | | | Unknown |

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| SUSPEC | T ADVERSE F | REACTION REP | PORT | | | | | | | | | | | | | | |
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| | | I. RE | ACTION | INFOR | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day Month Yea | 2a. AGE | 3. SEX | - | | ACTIO | _ | SET Yea | _ | -12 | | CK ALL ROPRIA | | го | | |
| PRIVACY | FRANCE | PRIVACY Year | 45 Years | Male | 110.00 Da | | MAI | | 201 | | | ADV | ERSE R | EAC | TION | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Renal failure degra Dermatitis grade 1 | RED TERM] (Related symports) Red TERM] (Related symports) | otoms if any separated by cor | mmas) | | | | | | | | | INVO PRO | OLVED O DLONGE SPITALIS | DR D IN | | :NT | |
| Case Description: UNDER REAL-LIF | | L STUDY - EVALUA OF USE | TION OF EF | FICACY | AND SAFETY | OF | BOS | ULIF | : | | | OR S | OLVED F SIGNIFIC ABILITY | CAN' OR | | NT | |
| This is a non-inter | ventional study rep | oort (Post Authorizat | ion Safety S | tudy) for | protocol B187 | 1047 | 7. | | | | | INC | APACITY | ′ | | | |
| | | | | (Cont | inued on Addition | nal In | ıforma | ntion F | Pan | e) | | LIFE | E EATENI | NG | | | |
| | | II CHODE | CT DDL | | | | | | ug | <u>" </u> | | | CEATER | | | | |
| 14. SUSPECT DRUG(S) (i | nclude generic name) | II. 505PE | CIDRU | J(S) IIV | IFORMATIO | IN | | | | 20 | | | CTION | | | | |
| #1) Bosulif (BOSU | TINIB) Film-coated | tablet | | | | | | | | | | RUG? | AFTER S | STOP | PPING | i | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | 1) Unkno | OF ADMINISTRATION | ON | | | | | | YES | S NO | 0 | X N | Α | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | | | | 21 | RE | APPE | CTION EAR AFT ODUCTI | | · | | |
| 18. THERAPY DATES(fror #1) 12-DEC-2016 / | • | | | | DURATION oths 19 days | | | | | | | YES | S NO | 0 [| X N | A | |
| | | III. CONCON | | _ |) AND HIST | OR | Υ | | | | | | | | | | |
| | ` ' | INISTRATION (exclude those HYDRATE) ; 19-AP | | - | | | | | | | | | | | | | |
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| From/To Dates | ISTORY. (e.g. diagnostics, | allergies, pregnancy with las Type of History / Note | | etc.) Description | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| 24a. NAME AND ADDRES | S OF MANUFACTURER | I V. IVIMIV | 217.0101 | 26. RE | | • | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 40 | 1 UNITED STATES | 3 | | | | | | | | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURES | 24d. REPOR | SOURCE LITERATUR | ?F | | | | | | | | | | | | | | |
| 04-FEB-2022 | STUDY STUDY HEALTH | ш | ` | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | P: | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 45 year-old male patient received bosutinib (BOSULIF), from 12Dec2016 (Batch/Lot number: unknown) to 02Mar2017 at 200 mg daily. The patient's relevant medical history was not reported. Concomitant medication(s) included: SPRYCEL taken for chronic myeloid leukaemia, start date: 19Apr2017 (ongoing).

The following information was reported: RENAL FAILURE (non-serious) with onset 17Mar2017, outcome "not recovered", described as "Renal failure degradation grade 2"; DERMATITIS (non-serious) with onset Nov2017, outcome "recovered" (Jan2018), described as "Dermatitis grade 1".

The investigator considered there was not a reasonable possibility that the events "renal failure degradation grade 2" and "dermatitis grade 1" were related to bosutinib nor concomitant medication.

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

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| | · · · · – | 2. DATE OF B | IRTH | 2a. AGE | 3. SEX | | Т 4-6 | | 1 | 8-12 | | ECK ALL | TE TO | | |
| PRIVACY FR | ANCE | | Year | 65 Years | Female | 50.00 kg | Day | | | | | VERSE F | | NC | |
| 7 + 13 DESCRIBE REACTION(S) (Event Verbatim [PREFERRED TER Voice disorder [Dysphor | | sts/lab data) ms if any separated | by commas | ;) | | | | • | | 3 | I INV | TIENT DII OLVED (OLONGE | DR. | FIENT | |
| | | | ALUATIO | N OF EF | FICACY | AND SAF | ETY C | OF BOS | ULIF | | HO INV | SPITALIS | ERSIS | | |
| This is a non-interventio B1871047. | nal study repo | ort received fro | om a con | itactable | reporter | s) (Physic | cian) fo | or proto | col | <u>ן</u> ' | DIS | SIGNIFI SABILITY CAPACITY | OR | | |
| A 65-year-old female pa | I. REACTION INFORMATION IT INITIALS In COUNTRY PRANCE De De BRITT FRANCE De De De BRITT FRANCE De De De De BRITT FRANCE De DE DE BRITT FRANCE DE DE BRITT DE DE BRITT DE DE BRITT DE DE DE BRITT DE DE DE BRITT DE DE DE BRITT DE DE DE BRITT DE DE DE BRITT DE DE DE BRITT DE D | | ation Pag | _{le)} [| | E REATENI | NG | | | | | | | | |
| | | II. SU | SPECT | Γ DRU | G(S) IN | FORMA | ATION | 1 | | | | | | | |
| | • | blet | | | | | | | , | 20. | | ACTION AFTER S | TOPPI | NG | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | | | | | TRATION | | | | YE | s N | · X | NA | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | | REAPP | ACTION EAR AFT RODUCT | ER ON? | | |
| 18. THERAPY DATES(from/to) #1) 13-FEB-2019 / 02-MA | AR-2019 | | | | | | | | | | YE | s 🔲 N | · 🛛 | NA | |
| | | III. CON | COMIT | ANT D | RUG(S |) AND F | HISTO | RY | | | | | | | |
| 22. CONCOMITANT DRUG(S) AND | D DATES OF ADMIN | IISTRATION (exclu | de those use | d to treat rea | action) | | | | | | | | | | |
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| | I. REACTION INFORMATION II. A COUNTRY Department of BRITH 1 and 2 AGE SEX SEX SEX SEX SEX SEX SEX SEX SEX SE | | | | | | | | | | | | | | |
| | I. REACTION INFORMATION INTINITIALS II. COUNTRY III. BASEACTION OF BIRTH III. SUSPECT DRUG (S) SEX AND SAFETY OF BOSULIF REAL-LIFE CONDITIONS OF USE III. SUSPECT DRUG (S) INFORMATION III. SUSPECT DRUG (S) AND HISTORY III. CONCOMITANT DRUG (S) AND | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTORY. From/To Dates APR-2020 to APR-2020 | ENTINITIALS IN COUNTRY RANCE Day PROVED YEAR 65 BIRTH STRANCE DAY DATE OF BIRTH STRANCE DAY DAY DATE OF BIRTH STRAN | | d nodule | remo | val) | | | | | | | | | | |
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| Pfizer Inc | I. REACTION INFORMATION I. S. ADEL S. ADEL S. A. SER. S. S. D. | | | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard Eas New York, NY 10001 UNI Phone: 212 733 4045 | I. REACTION INFORMATION I. REACTION INFORMATION INFORMATION I. REACTION INFORMATION INFORMATION I. REACTION INFORMATION INFORMATION INFORMATION INFORMATION INFORMATIO | | | | | | | | | | | | | | |
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| 24c. DATE RECEIVED BY MANUFACTURER | I. REACTION INFORMATION II. COUNTRY Description: Descri | | | | | | | | | | | | | | |
| 07-MAR-2023 | ı | ш | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 1 | | LOWUP: | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

13Feb2019 to 02Mar2019 at 300 mg daily. The patient's relevant medical history included: "thyroid nodule surgery", start date: Apr2020, stop date: Apr2020. The patient's concomitant medications were not reported.

The following information was reported: DYSPHONIA (non-serious) with onset Oct2020, outcome "recovered" (Dec2020), described as "Voice disorder".

Additional information: The patient was on long-term follow-up and on TASIGNA. Operated thyroid nodule in Apr2020, having caused voice disorders in Oct2020. The event voice disorder was rated as grade 1, assessed as non-serious.

The reporter considered "voice disorder" not related to bosutinib.

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

Follow-up (30May2022): This is a follow-up to a non-interventional study report for protocol B1871047:

Updated information: Reaction data (new event Epigastric pain added), relevant medical history (Intermittent epigastric pain removed).

Follow-up (07Mar2023). This is a non-interventional study report received from a contactable reporter(s) (Physician) for protocol

Updated information included: Bosutinib start date updated to 13Feb2019 and event 'Epigastric pain' deleted.

Case Comment: Based on the information currently available and in concurrence with reporting investigator, the reported 'voice disorder' is deemed unrelated to study drug bosutinib. Event is likely due to an intercurrent condition; the mentioned surgery on thyroid nodule may provide alternative explanation.

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| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE 34 | 3. SEX | | Day | Mont | th | Year | 8-12 | Al | PPR | K ALL OPRIAT RSE RE | | ON | | |
| PRIVACY | | PRIVACY | Years | Male | kg | 23 | DE | C 2 | 2021 | - | | | | | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER COVID-19 [COVI | | tests/lab data) otoms if any separated by comma | as) | | | | | | | 5 | _ _ ⊾ | NVOL | NT DIE | ıR | | | |
| | : OBSERVATIONAL | L STUDY - EVALUATION | ON OF EF | FICACY | AND SAFET | Y OF | BOS | SULIF | : | | Н | IOSPI | ONGEI ITALISA | ATION | | | |
| | rventional study repician) for protocol B | oort (Post Authorization 1871047. | Safety S | Study) red | eived from a | conta | actabl | le | | | – 0 | OR SIGNISAB | VED PI GNIFIC BILITY C PACITY | ANT OR | TEN | Т | |
| | | | | | | | | | | ۱, | | IFE_ | ATENIN | | | | |
| | (Continued on Additional Information Page) II. SUSPECT DRUG(S) INFORMATION CT DRUG(S) (include generic name) ulif (BOSUTINIB) Film-coated tablet | | | | | | | | | | | | | | | | |
| | | | G(3) IIV | INCKIVIATI | OIN | | | | | DID R | | TION TER S | TOPPI | NG. | | | |
| #1) Bosulif (BOSU | JTINIB) Film-coated | tablet | | ۹ | | , | | | DRUG | | IEK S | IOPPII | NG | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/da | ay | | | 6. ROUTE(S) 11) Unkno | OF ADMINISTRA OWN | TION | | | | | ШΥ | res | NC | , X | NA | | |
| 17. INDICATION(S) FOR #1) Chronic myeld | | c myeloid leukaemia) | | | | | | | | 1 | | PPEA | TION R AFTE DUCTIO | | | | |
| 18. THERAPY DATES(fro #1) 09-SEP-2019 | | | | 9. THERAPY 11) Unkno | | | | | | | ΠY | res | NC | , X | NA | | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND HIS | TOF | RY | | | | | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | IINISTRATION (exclude those us | ed to treat rea | action) | | | | | | | | | | | | | |
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| From/To Dates 23-DEC-2021 to Unknown | | allergies, pregnancy with last mo Type of History / Notes Relevant Med His Past Drug Event 2 injections receiv | story | Description | myeloid leuk | emia | (Chro | nic m | nyelo | id le | ukae | emia | a) | | | | |
| | | ,00 | | | | | | | | | | | | | | | |
| | | | | | | | | (Con | ntinue | ed on | Addi | ition | al Info | ormat | ion | Paç | je) |
| 240 NAME AND ADDRE | SS OF MANUFACTURER | IV. MANUF | ACTUR | RER INI | | NC | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | vard East 01 UNITED STATES | 3 | | 20. KL | iinii No | | | | | | | | | | | | |
| | 24b. MFR CO | INTROL NO. | | 25h NA | ME AND ADDRES | S OF P | EPORT | ER | | | | | | | | | _ |
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| 24c. DATE RECEIVED BY MANUFACTURE | ER 24d. REPORT | SOURCE LITERATURE | | 7 | | | | | | | | | | | | | |
| 10-FEB-2022 | ₩ HEALTH PROFES | Ш | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TTYPE FOLLOWUP: | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 34-year-old male patient received bosutinib (BOSULIF), since 09Sep2019 (ongoing) at 500 mg 1x/day for chronic myeloid leukaemia. The patient's relevant medical history included: "Chronic myeloid leukemia", start date: 23Dec2021 (ongoing). The patient's concomitant medications were not reported. Past drug history included: Covid-19 vaccine for COVID-19 immunization, notes: 2 injections received.

The following information was reported: COVID-19 (non-serious) with onset 23Dec2021, outcome "recovered" (27Dec2021). The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of covid-19.

The reporter considered "covid-19" not related to bosutinib.

Additional information: COVID-19 contracted despite vaccination up to date (2 injection of vaccine). COVID-19 grade 2. Oral DOLIPRANE was received from 23Dec2021 to 27Dec2021 for fever. According to the investigator, the event was not related to study drug or concomitant medication.

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

Case Comment: In concurrence with the reporting investigator, the Company considers the reported COVID-19 is unrelated to suspect drug bosutinib administration. The patient contracted COVID-19 amid coronavirus pandemic.

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|---|
| Unknown | Past Drug Event | COVID-19 vaccine (COVID-19 VACCINE); Drug Indication: COVID-19 immunization (COVID-19 immunisation) |
| | 2 injections received | |

| | | | | | | | | | | | | CI | ON | /IS | FO | RM | |
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| 1. PATIENT INITIALS | 1a. COUNTRY | I. REA | ACTION IN | | JATION 3a. WEIGHT | 1-6 P | EACTIO | NO NA | :FT | 8-12 | 2 CL | HECK AL | 1 | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | ⊣ । | | 50.00 kg | Day 16 | Mont SEI | h | Year 2019 | 1 | AF | PROPR | IATE | | ٧ | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERI Asthenia [Asthenia Asthenia [Asthenia | RED TÉRM] (Related symp a] | tests/lab data) otoms if any separated by comr | mas) | | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | [| OF DI: | VOLVED R SIGNIF SABILIT | FICAI Y OR | NT | ≣NT | | |
| This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | | _ ا | IN: | CAPACIT | ΓY | | | | | |
| | | | | (Contin | ued on Addit | ional I | nforma | ation P | Page) | <u> L</u> | <u> </u> | IREATE | NING | i | | | |
| 14 CHOPEOT DDUGG: 1 | ingludo gozzaia a | II. SUSPE | CT DRUG | (S) INF | FORMATI | ION | | | | Tan | DID 55 | EACTION | | | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | | tablet | | | | | | | | | | AFTER | | PPIN | 3 | | |
| 15. DAILY DOSE(S) #1) 300 mg, daily | | | |) Unknow | OF ADMINISTRA VN | TION | | | | | YE | s 🔲 | NO | ×۵ | IA | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE . | | | | | | | | | 21. | REAP | EACTION PEAR AF RODUC | TER | | | | |
| 18. THERAPY DATES(from #1) 13-FEB-2019 / | • | | | THERAPY D | | | | | | YES NO NA | | | | | | | |
| | | III. CONCOM | | | AND HIS | STOF | RY | | | | | | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | IINISTRATION (exclude those | used to treat react | tion) | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT H From/To Dates Unknown | ISTORY. (e.g. diagnostics, | allergies, pregnancy with last r Type of History / Notes | | tc.) escription | | | | | | | | | | | | | |
| | | IV MANUI | EACTUDE | ED INE | | ON. | | | | | | | | | | | |
| 24a. NAME AND ADDRES | SS OF MANUFACTURER | IV. MANU | rau i UKE | 26. REM | | JIN | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva | 1 UNITED STATES | 3 | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2022002 | | | | E AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE! | R 24d. REPORT STUDY HEALTH PROFES | LITERATURE | : | NAME | AND ADDRI | ESS V | VITHH | IELD. | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 Z5a. REPORT TYPE Zinitial Followup: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 64-year-old female patient (unknown if pregnant) received bosutinib (BOSULIF), from 13Feb2019 to 02Mar2019 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: ASTHENIA (non-serious) with onset 16Sep2019, outcome "recovered" (Oct2019), ASTHENIA (non-serious) with onset 22Apr2020, outcome "recovered" (Jun2020) and all described as "Asthenia".

The reporter considered "asthenia" not related to bosutinib.

Additional information: Both episodes of asthenia were grade 1. Causality assessment was unrelated to study drug and concomitant treatments for both episodes of asthenia.

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

Follow-up (07Mar2023): 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: start date of bosutinib updated.

Follow-up (09Mar2023): 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: onset date of first episode of asthenia (updated from "16Mar2019" to "16Sep2019").

Case Comment: Based on temporal association, the episodes of asthenia are deemed unrelated to bosutinib as the events occurred 6 months 15 days and 1 year 1 month 21 days from the last dose of bosutinib.

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| SUSPECT | ADVERSE F | REACTION R | EPORT | | | | | | | | | | | | | | |
| | | | | | | Т | | | Т | <u> </u> | Т | | | $\overline{}$ | Т | Ι | _ |
| | | | | | | | Δ | | | | | | | | | | |
| | | 1. 1 | REACTION | N INFOR | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRT | | 3. SEX | | | ACTIC | N ONS | | — | -12 | | CK ALL | | го | | |
| PRIVACY | FRANCE | PRIVACY | , Year 73 Years | Female | 86.00 Da kg | ay | Wont | | Yea 202 | | | | ERSE R | | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) MYCOSIS OF THE INGUINAL FOLDS [Fungal infection] PAROXYSTIC ATRIAL FIBRILLATION [Atrial fibrillation] | | | | | | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | OR S | OLVED F SIGNIFIC ABILITY | CAN | | NT | | | |
| This is a non-interve | ntional study rep | oort (Post Authori | zation Safety | Study) for | protocol B1871 | 1047 | 7. | | | | | | APACITY | | | | |
| | | | 4 | (0 | | | • | | . | | П | LIFE | | | | | |
| | | | | | inued on Addition | | iforma | ation I | Pag | je) | _ | THR | EATENI | NG | | | |
| 14. SUSPECT DRUG(S) (incl | ude generic name) | II. SUS | PECT DRI | JG(S) IN | IFORMATIO | N | | | | 12 | 0. DIE |) REA | CTION | — | | | |
| #1) Bosulif (BOSUTII | | tablet | | | | | | , | | | AB | | AFTER S | STOP | PPING | i | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | #1) Unkno | OF ADMINISTRATION | ON | | | | | | YES | S N | o [| X N | Α | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | 2 | RE | APPE | CTION EAR AFT ODUCT | | , | | |
| 18. THERAPY DATES(from/to #1) 09-DEC-2019 / D | • | | | 19. THERAPY #1) Unkno | | | | | | YES NO NA | | | | | | | |
| | | III. CONC | OMITANT I | DRUG(S |) AND HIST | OR | Υ | | | , | | | | | | | |
| 22. CONCOMITANT DRUG(S #1) BISOPROLOL (#2) LEVOTHYROX #3) FLECAINE (FLE #4) IMODIUM (LOP | BISOPROLOL) (LEVOTHYROX ECAINIDE ACET | ; MAR-2020 / O (INE SODIUM) ; (ATE) ; MAR-20 | ngoing ; DEC-1999 / 14 / Ongoing | Ongoing | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIST From/To Dates Unknown | ORY. (e.g. diagnostics, | allergies, pregnancy with Type of History / | | od, etc.) Description | | | | | | | | | | | | | |
| | | IV. MA | NUFACTU | RER IN | ORMATION | N | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 | | | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2022002 | | | NAMI | ME AND ADDRESS (EAND ADDRES | s w | 'ITHH | IELD. | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 14-FEB-2022 | 24d. REPORT STUDY HEALTH PROFES | LITERA SIONAL OTHER | | NAMI | E AND ADDRES | ss W | 'ITHH | IELD. | - | | | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 DINITIAL FOLLOWUP: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 73 year-old female patient received bosutinib (BOSULIF), from 09Dec2019 (Batch/Lot number: unknown) to Dec2020 at 200 mg daily. The patient's relevant medical history was not reported. Concomitant medication(s) included: BISOPROLOL taken for hypertension, start date: Mar2020 (ongoing); LEVOTHYROX taken for hypothyroidism, start date: Dec1999 (ongoing); FLECAINE taken for heart rate abnormal, start date: Mar2014 (ongoing); IMODIUM taken for diarrhoea, start date: Jan2016 (ongoing). The following information was reported: FUNGAL INFECTION (non-serious) with onset Jan2021, outcome "recovered" (2021), described as "MYCOSIS OF THE INGUINAL FOLDS"; ATRIAL FIBRILLATION (non-serious) with onset 2020, outcome "recovered" (Jan2021), described as "PAROXYSTIC ATRIAL FIBRILLATION".

Additional information: The event "mycosis of the inguinal folds" was rated non-serious with grade 1 and the event "paroxystic atrial fibrillation" was rated non-serious with grade 2.

According to the investigator, both events were unrelated to the study drug bosutinib and unrelated to concomitant drugs.

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

Case Comment: There is insufficient information to attribute the causality of events, Atrial fibrillation and Fungal infection, to the suspect drug Bosutinib malate. Medical history was not provided, however, the Subject is on concomitant medications for hypertension, hypothyroidism and abnormal heart rate, suggestive of medical conditions which may provide a plausible alternative cause for Atrial fibrillation.

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| SUSPEC | T ADVERSE I | REACTI | ON REPO | ORT | | | | | | | | | | | | | | | _ |
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| | | | | | | | | | | | | | | | | Ш | \Box | | Ш |
| | | | | | INFOR | | | | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | Day N | Month Year | 2a. AGE 74 Years | 3. SEX Female | 3a. WEIGHT 86.00 kg | Day 14 | Мо | | <u> </u> | ar | 8-12 | AP | | PRIA | TE TO | | | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF POLYPS [Polyp] INCREASE OF AT | RED TERM] (Related sym | nptoms if any se | eparated by comm | nas) | | | | | | | | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | |
| 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 | | | | | | | | | OF DIS | | NIFIC | | STEN | ۱T | | | | | |
| reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | | | 1 LIF | FE | | | | | | | | |
| | | | | | | nued on Addi | | Inforn | nation | Pag | ge) | | J TH | HREA | ΓEΝΙΙ | NG | _ | | _ |
| 14. SUSPECT DRUG(S) (i | include generic name) | | . SUSPEC | CT DRU | JG(S) IN | FORMAT | ION | | | | | 20, [| DID RE | ACT | ION | | _ | | _ |
| #1) Bosulif (BOSU | - | tablet | | | | | | | | | | / | | AFT | | TOPPI | NG | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | | 16. ROUTE(S) #1) Unkno | OF ADMINISTRA WN | ATION | | | | | 1 | YE | ES [|] NO | · X | NA | | |
| 17. INDICATION(S) FOR U #1) Unknown | JSE | | | | | | 7 | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | |
| 18. THERAPY DATES(fror #1) 09-DEC-2019 / | • | | | | 19. THERAPY #1) Unkno | | | | | | | 1 | YE | ES [|] NO | · X | NA | ı | |
| | | III. Ç | CONCOMI | TANT ! | DRUG(S |) AND HIS | STO | RY | | | | | | | | | | | |
| 22. CONCOMITANT DRUG #1) NILOTINIB (N #2) ELIQUIS (API #3) LEVOTHYRO #4) ASPIRINE (AI | IILOTINIB) ; Ong IXABAN) ; Ongo IX (LEVOTHYRO) | MINISTRATION going ing XINE SOD | N (exclude those u | used to treat | | , | _ | | | | | | | | | | | | |
| 23. OTHER RELEVANT H From/To Dates Unknown | ISTORY. (e.g. diagnostics | | gnancy with last m of History / Notes | | od, etc.) Description | | | | | | | | | | | | | | |
| | | | | | יסבס ואונ | | | | | | | | | | | | | | |
| 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 | | | | | | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURES | 2022002 24d. REPOR | T SOURCE | | | NAME | ME AND ADDRE | ESS | WITH | HELD | | | | | | | | | | |
| D7-SEP-2022 STUDY LITERATURE D'OTHER: OTHER: | | | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 74 year-old female patient received bosutinib (BOSULIF), from 09Dec2019 (Batch/Lot number: unknown) to Dec2020 at 200 mg daily. The patient's relevant medical history was not reported. Concomitant medication(s) included: NILOTINIB (ongoing); ELIQUIS (ongoing); LEVOTHYROX (ongoing); ASPIRINE (ongoing).

The following information was reported: POLYP (hospitalization) with onset 11Sep2021, outcome "recovered" (06Jan2022), described as "POLYPS"; ARTERIOSCLEROSIS (medically significant) with onset 14Jun2021, outcome "not recovered", described as "INCREASE OF ATHEROMA PLAQUES". The patient underwent the following laboratory tests and procedures: colonoscopy: (11Sep2021) discovery of two polyps. The action taken in response to these events for the study drug bosutinib was not applicable. Additional information: it was reported "discovery during a colonoscopy on 11Sep2021 of two polyps, the first of which was removed on the same day and the second polyp was removed during the hospitalization of 06Jan2022". The event polyps was rated serious (hospitalization) with grade 3 and the event "increase of atheroma plaques" was rated non-serious with grade 4. In follow-up information received on 04Apr2022, it was reported there is no severity criterion noted in the hospital file and in the CRF (Case Report Form). The increase in atheroma plaques was seen only on the ultrasound of 14Jun2021. According to the investigator, both events were unrelated to the study drug bosutinib and unrelated to concomitant drugs. In follow-up dated 07Sep2022, was reported that increase of atheroma plaques was rated grade 2.

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

Follow-up (04Apr2022): New information was received in response to a query reporting information regarding event severity and that atheroma plaques was seen only on the ultrasound of 14Jun2021.

Follow-up (07Sep2022): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the CRO for protocol B1871047. Updated information: grade of one event.

Case Comment: The company deemed that there is not a reasonable possibility that the events POLYPS and INCREASE OF ATHEROMA PLAQUES were related to Pfizer study drug BOSUTINIB. The event mostly represented an intercurrent condition in this patient.

13. Lab Data

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|-------|-------------|---------------------------|------------------------------|-------------------|
| 1 | 11-SEP-2021 | Colonoscopy | Discovery of two polyps | |
| 2 | 14-JUN-2021 | Ultrasound scan | Increase in atheroma plaques | |

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|---|---|---|------------------|--------------------------|----------------------|----------|------------|---------|--------------|--|--------------|---------------|--------------------------|-------|------------|------|----------|
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| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | |
| | | | | | | | П | | | | | Т | Τ | T | T | | |
| | | | | | | | И | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a, COUNTRY | I. REA | CTION 2a, AGE | INFOR 3. SEX | MATION 3a, WEIGHT | 1-6 P | EACTIO | NI ONS | :FT | 8-12 | 2 (| THE | CK ALL | | | | |
| PRIVACY | FRANCE | Day Month Year PRIVACY | 71 Years | Male | 114.00 kg | Day | Moni NO | h | Year 2021 | 1 | Δ | APPF | ROPRIA ERSE R | ATE : | | | |
| DYSPNEA ON E | CTION(S) (including relevant RRED TERM] (Related symp FFORT [Dyspnoea Pain in extremity] | | | | | | | 0 | _ □ ¦ | NVO PROI | ENT DIE | OR D IN | | ENT | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | _ _ | OR S DISA | LVED FIGNIFIC | CAN OR | SISTE | NT | | |
| | | oort (Post Authorization P) for protocol B18710 | | tudy) rec | eived from c | ontac | table | | | | | | PACIT) | Y | | | |
| | | | | (Conti | nued on Addit | tional I | nform | ation F | Page) | <u>, </u> | | LIFE THRE | EATENI | ING | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMATI | ION | | | | _ | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) JTINIB) Film-coated | tablet | | | | | | , | | 20. | | TE A | CTION FTER S | STOF | PPING | 3 | |
| 15. DAILY DOSE(S) #1) 300 mg, 1x/da | ау | | | s. ROUTE(S) 1) Unkno | OF ADMINISTRA WN | ATION | | | | | □ | YES | N | 0 | X N | A | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | | | | | | | 1 | REAF | PPE | CTION AR AFT DDUCT | | ? | | |
| 18. THERAPY DATES(fro #1) 12-NOV-2020 | | | | . THERAPY 1) Unkno | | | | | | | | YES | N | 0 | X N | A | |
| | | III. CONCOMIT | rant di | RUG(S |) AND HIS | STOF | RY | | | | | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | TINISTRATION (exclude those us | ed to treat rea | action) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23 OTHER RELEVANT | HISTORY (e.g. diagnostics | allergies, pregnancy with last mo | onth of period | etc.) | | | | | | | | | | | | | \dashv |
| From/To Dates Unknown | THOTOTAL (e.g. diagnostics, | Type of History / Notes Past Drug Event Dyspnea on 05No | • | Description | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | (Con | tinue | ed on | Add | litio | nal Inf | forn | natio | n Pa | ge) |
| | | IV. MANUF | ACTUR | ER IN | ORMATIO | ON | | | | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | 01 UNITED STATES | | 26. REMARKS | | | | | | | | | | | | | | |
| | 24b. MFR CO | | | | ME AND ADDRES | | | | | | | | | | | | |
| 24c DATE RECEIVED | 2022002 24d. REPORT | | | | AND ADDRI | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE 26-OCT-2023 | Marion | LITERATURE | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 Minitial Followup: | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 71-year-old male patient received bosutinib (BOSULIF), since 12Nov2020 (ongoing) at 300 mg 1x/day. The patient's relevant medical history and concomitant medications were not reported. Past drug history included: Dasatinib, reaction(s): "Dyspnea", notes: Dyspnea on 05Nov2020.

The following information was reported: DYSPNOEA EXERTIONAL (non-serious) with onset Nov2021, outcome "not recovered", described as "DYSPNEA ON EFFORT"; PAIN IN EXTREMITY (non-serious) with onset Nov2021, outcome "not recovered", described as "Lower limb pain". The action taken for bosutinib was dosage not changed.

The reporter considered "dyspnea on effort" and "lower limb pain" not related to bosutinib.

Additional information: The events dyspnoea on effort and lower limb pain were rated grade 1. Action taken with bosutinib in response to both events was dose not changed. Events reported as non-serious. The investigator considered that the event was unrelated to any concomitant drug.

Follow-up (15Sep2022): This is a non-interventional study report (Post Authorization Safety Study) received from CRO for protocol B1871047.

Updated information: primary reporter details updated, new reporter added, patient details (DOB, weight and height) added, dosage of bosutinib added, event verbatim changed from dyspnoea to dyspnoea on effort, start date of events dyspnoea on effort and lower limb pain updated to Nov2020 and outcome updated as not recovered (previously unknown), and causality for both events updated as unrelated (previously not reported).

Amendment: This follow-up report is being submitted to amend previous information: onset date for both events corrected to Nov2021.

Case Comment: Based on the available information, the Company considers the reported events "dyspnea on effort" and "lower limb pain" are unrelated to suspect drug bosutinib but more likely due to underlying or inter-current medical conditions.

23. OTHER RELEVANT HISTORY continued

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|--|
| Unknown | Past Drug Event | DASATINIB (DASATINIB); Drug Reaction: Dyspnea (Dyspnoea) |
| | Dyspnea on 05Nov2020 | |

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| SUSPEC | CT ADVERSE I | REACTION RE | PORT | | | | | | | | | | | | | _ | |
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| | | I. R | EACTION II | NFOR | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day Month Y | | 3. SEX | 3a. WEIGHT | 4-6 RE | ACTIO Month | N ONSE | T ⁄ear | 8-12 | API | ECK ALL PROPRIA | ATE TO | | | | |
| PRIVACY | FRANCE | PRIVACY | | Male | 78.80 kg | Day | JUN | | 020 | | ΑD | VERSE F | ₹EACT | ΓΙΟΝ | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER | TION(S) (including relevan RED TERM] (Related sym | t tests/lab data) ptoms if any separated by c | ommas) | | | | | | | E | PAT | TENT DI | ED | | | | |
| Digestive disorder [Gastrointestinal disorder] Diastasis [Diastasis recti abdominis] | | | | | | | | | | C |] INV | OLVED (| OR ED INF | ATIE | NT | | |
| Back pain, low dorsalgia on discopathy MODIC 1 (T6-T7-T8) [Back pain] Scalp infection [Skin infection] | | | | | | | | | | | SPITALIS | | | | | | |
| Dyspnea [Dyspnoea] | | | | | | | | | | OR | OLVED I SIGNIFI | CANT | ISTE | ١T | | | |
| Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF | | | | | | | | | | | | ABILITY APACIT | | | | | |
| UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | _ | | _ | | | | | |
| | | | | (Cont | inued on Additi | onal Ir | forma | tion Pa | age) | L | THE | E REATENI | ING | | | | |
| | | II. SUSP | ECT DRUG | (S) IN | FORMATION | NC | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU | (include generic name) | tablet | | | | | | | | Α. | | ACTION AFTER S | | PING | | | |
| | | | | | | | | | | | KUG | | | | | | |
| 15. DAILY DOSE(S) #1) UNK | | | |) Unkno | OF ADMINISTRAT | ION | | | | [| YE | s 🔲 N | o [| N A | | | |
| 17. INDICATION(S) FOR | USE | | | | | | | | | | | ACTION | _ | | | _ | |
| #1) Unknown | | | | | | | | | | | | EAR AFT RODUCT | | | | | |
| 18. THERAPY DATES(fro | m/to) | | | THERAPY | DURATION | | | | | TYES NO NA | | | | | | | |
| #1) Olikilowii | | | #1 |) OTIKITO | , , , , , , , , , , , , , , , , , , , | | | | | L. | | | | | | | |
| | | III. CONCO | MITANT DR | RUG(S |) AND HIS | TOR | Υ | | | | | | | | | | |
| 22. CONCOMITANT DRU | IG(S) AND DATES OF ADM | MINISTRATION (exclude the | | | | | | | | | | | | | | | |
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| 23. OTHER RELEVANT F | HISTORY. (e.g. diagnostics | , allergies, pregnancy with la Type of History / No | | tc.) | | | | | | | | | | | | _ | |
| Unknown | | Type of Filetoly / The | | compaci | | | | | | | | | | | | | |
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| 243 NAME AND ADDRES | SS OF MANUFACTURER | IV. MAN | <u>IUFACTURI</u> | ER INI | | <u>N</u> | | | | | | | | | | _ | |
| Pfizer Inc Stella Pietrafesa | | | | | | | | | | | | | | | | | |
| 66 Hudson Bouleva | ard East 01 UNITED STATE: | S | | | | | | | | | | | | | | | |
| Phone: 212 733 40 | | 7 | | | | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | 25b. NA | ME AND ADDRESS | S OF RE | PORTE | ĒR | | | | | | | | _ | |
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| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | T SOURCE | JRE | NAME | AND ADDRE | SS W | 'ITHH | ELD. | | | | | | | | | |
| 07-SEP-2022 | HEALTH PROFES | ш | - - | | | | | | | | | | | | | | |
| DATE OF THIS REPORT | | | | 1 | | | | | | | | | | | | | |
| 27-FEB-2024 NIITIAL FOLLOWUP: | | | | | | | | | | | | | | | | | |

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 77-year-old male patient received bosutinib (BOSULIF). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: BACK PAIN (non-serious) with onset Jun2020, outcome "recovering"; described as "Back pain, low dorsalgia on discopathy MODIC 1 (T6-T7-T8)"; DIASTASIS RECTI ABDOMINIS (non-serious) with onset Dec2020, outcome "unknown", described as "Diastasis"; GASTROINTESTINAL DISORDER (non-serious) with onset Dec2020, outcome "recovered" (May2021), described as "Digestive disorder"; SKIN INFECTION (non-serious) with onset 06Nov2021, outcome "recovered" (18Nov2021), described as "Scalp infection"; DYSPNOEA (non-serious) with onset 21Mar2022, outcome "recovering", described as "Dyspnea". The action taken for bosutinib was dosage not changed.

Additional information: The patient was on bosutinib. It was noted digestive disorders from Dec2020 to May2021, in Dec2020 back pain for 6 months and diastasis. Scalp infection was grade 1 from 06Nov2021 to 18Nov2021. Event dyspnea on 21Mar2022 was grade 1.

The reporter considered "digestive disorder" related to bosutinib. The reporter considered "back pain, low dorsalgia on discopathy modic 1 (t6-t7-t8) ", "scalp infection" and "dyspnea" not related to bosutinib or to concomitant treatment.

The reporter's assessment of the causal relationship of "diastasis" 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 (02Jun2022). This follow-up is received from the investigational site via CRO. Updated information included: patient's details, details on 'scalp infection', new event (dyspnea). Causality for some events.

Follow-up (07Sep2022). This is a follow-up received from the CRO. This is a non-interventional study follow-up report (Post Authorization Safety Study) for protocol B1871047.

Updated information includes: patient weight updated; updated start date for the event low back pain (from 2020 to Jun2020) and updated outcome (from unknown to recovering), investigator causality assessment for digestive disorder and lower back pain, updated description of the event back pain.

Case Comment: Based on available information, a possible contributory role of the subject drug BOSUTINIB cannot be excluded for the reported events Digestive disorder and diastasis. The events back pain, scalp infection and dyspnea were not related to bosutinib. This case will be re-assessed should additional information become available.

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| | | | | | MATION | | | 1 | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE 76 . | 3. SEX | | 4-6 REACTION Mont | h Year | d AF | HECK ALL PPROPRIAT OVERSE RE | | |
| PRIVACY | | PRIVACY | Years F | emale | kg | 04 MAI | R 2021 | <u> </u> | , , , , , , , , , , , , , , , , , , , | .,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | |
| | | tests/lab data) otoms if any separated by comma | as) | | | | | □ P [#] | TIENT DIE | D | |
| diarrhea [Diarrhoea Cephalgia [Headac | • | | | | | | | | VOLVED O | | NT |
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| UNDER REAL-LIFE | | L STUDY - EVALUATIO DF USE | ON OF EF | FICACY | AND SAFET | Y OF BOS | ULIF | | VOLVED PI | | NT |
| This is a non-interv | entional study rer | port (Post Authorization | Safety St | udy) rec | eived from co | ntactable | | DI | SABILITY C CAPACITY | | |
| | | P) for protocol B18710 | | ady) iec | S.VOG HOIII GC | doiable | | | | | |
| | | | | (Cont | nued on Addition | onal Informa | ntion Page) | | FE IREATENIN | IG | |
| | | II CHICDEO | T DDUC | | | | - , | | | | |
| 14. SUSPECT DRUG(S) (in | clude generic name) | II. SUSPEC | 1 DRUG | i(S) IN | FORMATIO | ON | | 20. DID RI | EACTION | | |
| #1) Bosulif (BOSUT | - | tablet | | | | | | ABATI DRUG | AFTER ST | FOPPING | |
| 15. DAILY DOSE(S) | | | 16 | | OF ADMINISTRAT | $\overline{}$ | ition Page) | 4 | | | |
| #1) 200 mg, daily | | | |) Unkno | | ION | | | ES NO | □ N/ | A |
| 17. INDICATION(S) FOR US | SE | | | | | 7 | | 21. DID RI | | <u> </u> | |
| #1) Unknown | | | | | | | | | PEAR AFTE RODUCTIO | | |
| 18. THERAPY DATES(from | • | | | | DURATION | | | 1 | ES N O | | ^ |
| #1) 17-DEC-2020 / (| 07-APR-2021 | | #1 |) 3 mon | ths 22 days | | | "" | _3 | ' | • |
| | | III. CONCOMIT | ΓΔΝΤ DE | RIIG(S |) AND HIS | TORV | | • | | | |
| 22. CONCOMITANT DRUG | (S) AND DATES OF ADM | IINISTRATION (exclude those us | | |) AND THO | TOICI | | | | | |
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| From/To Dates | STORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | |
| Unknown | | | | | | | | | | | |
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| | 05.14441115; 07:15== | IV. MANUF | ACTUR | | | DN | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc | OF MANUFACTURER | | | 26. REN | IARKS | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevar | | | | | | | | | | | |
| New York, NY 10001 Phone: 212 733 404 | | | | | | | | | | | |
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| | 24b. MFR CC 2022002 | | | | ME AND ADDRESS AND ADDRE | | | | | | |
| 24c DATE RECEIVED | | | | NAME | AND ADDRE | SS WITHH | ELD. | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | Z4d. REPOR STUDY | LITERATURE | | | | | | | | | |
| 30-NOV-2023 | ⊠ HEALTH PROFES | | | 4 | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | 「TYPE ☐ FOLLOWUP: | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 76-year-old female patient received bosutinib (BOSULIF), first regimen from 17Dec2020 to 07Apr2021 at 200 mg daily and second regimen from 08Apr2021 to 30Jun2022 at 300 mg daily. The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: HEADACHE (non-serious) with onset 04Mar2021, outcome "recovered" (Apr2021), described as "Cephalgia"; DIARRHOEA (non-serious) with onset Sep2021, outcome "recovered" (Jul2022), described as "diarrhea". The action taken for bosutinib was dosage permanently withdrawn on 30Jun2022.

The reporter considered "diarrhea" related to bosutinib. The reporter considered "cephalgia" not related to bosutinib.

Additional information: Bosutinib has not been reintroduced.

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

Follow-up (05Jul2022): New information received from the CRO.
Updated information included: The event cephalgia resolved in Apr2021.

Follow-up (06Sep2022): This is a follow-up Non-Interventional Study report (Post Authorization Safety Study) for protocol B1871047. Updated information received from the CRO includes event outcome for diarrhea and headache and action taken for bosutinib.

Follow-up (10May2023): This is a follow-up Non-Interventional Study report (Post Authorization Safety Study) for protocol B1871047. Updated information received from the CRO included: The event headache resolved in Apr2021.

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

Amendment: This follow-up report is being submitted to amend previously reported information: date of Birth was corrected (the patient's age was therefore 76 years old).

Follow-up (18Jul2023): This is a follow-up Non-Interventional Study report received from investigational site via CRO included: Update information: Bosulif from 08Apr2021 at 300mg daily.

Follow-up (07Sep2023, 07Sep2023): This is a follow-up Non-Interventional Study report received from investigational site via CRO and a follow-up Non-Interventional Study report received from clinical team :

Update information: new reporter (slide 2), dosage regimen for Bosulif (new first regimen). stop date for second regimen for Bosulif.

Follow-up (30Nov2023): This is a follow-up Non-Interventional Study report received from investigational site via CRO. Updated information: clinical course.

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

Case Comment: Based on the information currently available and known product safety profile, a causal association between the study drug bosutinib and the reported events 'diarrhea' and 'cephalgia' cannot be completely excluded. The follow-up information received does not alter the previous company clinical evaluation.

14-19. SUSPECT DRUG(S) continued

| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
|--|---|---------------------------|--|
| #1) Bosulif (BOSUTINIB) Film-coated tablet; | 300 mg, daily; Unknown | Unknown | 08-APR-2021 / |
| Regimen #2 | | | 30-JUN-2022; |
| | | | 1 year 2 months 23 |
| | | | days |

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| | | | | NFORMATION | 1 | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 77 | 3. SEX 3a. WEIGHT 4-6 REACTION ONSET 52.10 Day Month Year 2021 | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION | | | | | | | |
| | | sts/lab data) ms if any separated by comma pain) [Pain in extremi | | | PATIENT DIED INVOLVED OR | | | | | | | |
| Case Description: C UNDER REAL-LIFE | | | N OF EFF | FICACY AND SAFETY OF BOSULIF | PROLONGED INPATIENT HOSPITALISATION INVOLVED PERSISTENT | | | | | | | |
| This is a non-interverse reporter(s) (Physicial | OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | | | | | |
| | reporter(s) (Physician and Other HCP) for protocol B1871047. (Continued on Additional Information Page) | | | | | | | | | | | |
| | | II. SUSPEC | T DRUG | S(S) INFORMATION | | | | | | | | |
| 14. SUSPECT DRUG(S) (ind #1) Bosutinib (BOSU | , | tablet | | | 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | |
| 15. DAILY DOSE(S) #1) | | | | ROUTE(S) OF ADMINISTRATION) Unknown | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR US #1) Unknown | SE | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(from/ #1) Unknown | /to) | | | THERAPY DURATION) Unknown | YES NO NA | | | | | | | |
| | | | | RUG(S) AND HISTORY | | | | | | | | |
| 22. CONCOMITANT DRUG(| (S) AND DATES OF ADMIN | IISTRATION (exclude those use | ed to treat reac | tion) | | | | | | | | |
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| 23. OTHER RELEVANT HIS From/To Dates | STORY. (e.g. diagnostics, al | lergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | |
| Unknown | | , , , , , , , , , , , , , , , , , , , | | | | | | | | | | |
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| | | \ | A CTLID! | ED INICODMATION | | | | | | | | |
| 24a. NAME AND ADDRESS | OF MANUFACTURER | IV. WANUE | ACTURE | ER INFORMATION 26. REMARKS | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevar New York, NY 10001 Phone: 212 733 404 | UNITED STATES | | | | | | | | | | | |
| | 24b. MFR CON | FROL NO. | | 25b. NAME AND ADDRESS OF REPORTER | | | | | | | | |
| | 202200282 | | | NAME AND ADDRESS WITHHELD. | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT S | OURCE LITERATURE | | NAME AND ADDRESS WITHHELD. | | | | | | | | |
| 02-JUN-2022 | HEALTH PROFESS | | | | | | | | | | | |
| DATE OF THIS REPORT 25a. REPORT TYPE 27-FEB-2024 Initial Followup: | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 77-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: PAIN IN EXTREMITY (non-serious) with onset Sep2021, outcome "unknown", described as "Numerous functional complaints (limb pain)".

The reporter considered "numerous functional complaints (limb pain)" not related to bosutinib. Follow-up attempts are completed. No further information is expected.

Additional information: The event was assessed as non-serious and rated as grade 2. According to the reporter, the event was not related to study drug or concomitant medication.

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

Amendment: This follow-up report is being submitted to amend previously reported information: patient's year of birth updated and accordingly patient's age updated from 27-year-old, and patient's height updated.

Case Comment: Event numerous functional complaints (limb pain) represents an intercurrent medical condition and unrelated to bosutinib.

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| | | | CTION | INFOR | MATION | 4 | | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | DATE OF BIRTH Day Month Year | 2a. AGE 73 | 3. SEX | 3a. WEIGHT Da | | Monti | 1 | Year | 8-12 | Al | HECK A PPROF DVERS | PRIAT | |)N | | |
| PRIVACY | | PRIVACY | Years | Female | kg | | DEC | 2 | 020 | 2 | ,,, | DVLIKE | | 7,0110 | ,,, | | |
| HYPOTENSION | 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) HYPOTENSION [Hypotension] FATIGUE [Fatigue] Case Description: OBSERVATIONAL STUDY- EVALUATION OF EFFICACY AND SAFETY OF BOSULIF | | | | | | | | | | | ATIENT IVOLVE ROLON OSPITA | ED OF | R) INPAT | TEN | т | |
| Case Description UNDER REAL-LI | AND SAFETY | OF I | BOSL | JLIF | | [| - 0 | IVOLVE R SIGN ISABIL | NIFIC/ | ANT | ENT | г | | | | | |
| | This is a non-interventional study report (Post Authorization Safety Study) received from reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | | | IN | ICAPA | | | | | |
| | | | | (Conti | nued on Addition | nal In | forma | tion F | Page) | 1 | | FE HREAT | ENIN | IG | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMATIO | N | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosutinib (BO #2) PERINDOPRI | SUTINIB) Unknown | | | | | | | | | 20. | | EACTION E AFTE | | OPPIN | IG | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily #2) UNK | | | # | s. ROUTE(S) 1) Unkno 2) Unkno | | ON | | | | | ПΥ | ES [|]NO | × | NA | | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | USE | | | | | | | | | 1 | REAP | EACTION PEAR TRODU | AFTE | | | | |
| 18. THERAPY DATES(fro #1) 09-DEC-2019 #2) Unknown | | | # | 9. THERAPY 1) Unkno 2) Unkno | wn | | | | | | ΠΥ | ES [|]NO | × | NA | | |
| | | III. CONCOMIT | ANT DI | RUG(S) | AND HIST | OR | Υ | | | | | | | | | | |
| | JG(S) AND DATES OF ADM NILOTINIB) ; Unki | MINISTRATION (exclude those use nown | ed to treat rea | action) | | | | | | | | | | | | | |
| | FLECAINIDE ACET | TATE) ;Unknown (INE SODIUM) ;Unkn | iown | | | | | | | | | | | | | | |
| | DL (BISOPROLOL) | | | | | | | | | | | | | | | | |
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| From/To Dates | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes | | etc.) Description | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| | | IV. MANUF. | ACTUR | RER INF | ORMATIO | N | | | | | | | | | | | |
| Pfizer Inc | SS OF MANUFACTURER | | | 26. REM | ARKS | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES | | | | | | | | | | | | | | | | | |
| Phone: 212 733 40 | | 9 | | | | | | | | | | | | | | | |
| | 24b. MFR CO | INTROL NO. | | 25b. NAI | ME AND ADDRESS | OF RE | PORTI | ER. | | | | | | | | | _ |
| | 2022002 | | | | AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | ER 24d. REPORT | | NAME | AND ADDRES | SS W | 'ITHH | ELD. | | | | | | | | | | |
| 17-JUL-2023 | HEALTH PROFES | SSIONAL LITERATURE | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | T TYPE | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 73-year-old female patient received bosutinib (BOSUTINIB), from 09Dec2019 to Dec2020 at 200 mg daily; perindopril (PERINDOPRIL), (Batch/Lot number: unknown). The patient's relevant medical history was not reported. Concomitant medication(s) included: NILOTINIB; FLECAINE; LEVOTHYROX; BISOPROLOL.

The following information was reported: HYPOTENSION (non-serious) with onset Dec2020, outcome "recovered" (Dec2020); FATIGUE (non-serious) with onset 16Apr2021, outcome "recovered" (2021). The action taken for perindopril was dosage reduced.

The reporter considered "hypotension" and "fatigue" not related to bosutinib.

Additional information: Hypotension, grade 1, unrelated to the study drug bosutinib, related to concomitant perindopril. Fatigue, grade1, unrelated to the study drug bosutinib or concomitant medications.

Follow-up (07Sep2022): This is a follow-up report received from the CRO. Updated information includes: for event fatigue updated outcome to not recovered (stop date delated)

Follow-up (17Jul2023): This is a follow-up to a non-interventional study for protocol B1871047 received from investigator site via the CRO. Updated information: outcome of event fatigue.

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

Case Comment: There is insufficient evidence to demonstrate that the adverse events hypotension and fatigue were related to bosutinib. Based on the available information and in agreement with the reporter this case is considered as not related to suspect drug. The follow-up information received does not alter the previous company clinical evaluation.

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| | | | | INFOR | | | | | | I | | .= 0.7.1 | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | ^{2a. AGE} 74 Years | 3. SEX Female | 3a. WEIGHT 86.00 kg | Day 10 | Month JAN | T | Year 1022 | 8-12 | AF | HECK A PPROPI OVERSE | RIAT | | NC | | | | |
| | CTION(S) (including relevant RRED TERM] (Related sympheter) The trunk and face [E | t tests/lab data) otoms if any separated by comma Ory skin] | s) | | | | | | | 5 | | ATIENT | | | | | | | |
| | : OBSERVATIONA FE CONDITIONS (| L STUDY- EVALUATION OF USE | FICACY | ND SAFE | TY OF | BOSU | JLIF | | | → PR HC | ROLON(DSPITA | GED LISA | INPA ATION | | | | | | |
| | | port (Post Authorization P) for protocol B187104 | Study) rec | eived from | contac | table | | | | OF DI: | VOLVEI R SIGNI SABILIT CAPAC | IFICA TY O | ANT | TENT | Г | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | | FE HREATE | ENIN | IG | | | | | |
| | | II. SUSPEC | T DRU | IG(S) IN | FORMAT | ION | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosutinib (BO | (include generic name) SUTINIB) Unknown | | | | | | | | | | | EACTIO E AFTEI i? | | ГОРРІ | NG | | | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | 16. ROUTE(S) #1) Unkno | OF ADMINISTR WN | RATION | | | | | YE | es 🗌 | NO | O 🛮 NA | | | | | |
| 17. INDICATION(S) FOR #1) Unknown | USE | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 09-DEC-2019 | · | | | 19. THERAPY DURATION #1) Unknown YES NO | | | | | | | | | | | NA | | | | |
| | | III. CONCOMIT | ANT D | RUG(S) | AND HI | STOF | RY | | | | | | | | | | | | |
| | JG(S) AND DATES OF ADM RIL (PERINDOPRIL | MINISTRATION (exclude those use .) ; Ongoing | ed to treat re | eaction) | | | | | | | | | | | | | | | |
| | NILOTINIB); Ong FLECAINIDE ACE | | | | | | | | | | | | | | | | | | |
| #4) ELIQUIS (AF | PIXABAN) ; Ongoi | ng | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT I | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo | onth of period | d, etc.) | | | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | | | |
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| | | IV. MANUF | ACTU | RER INF | ORMAT | ION | | | | | | | | | | | | | |
| Pfizer Inc | SS OF MANUFACTURER | | | 26. REM | ARKS | | | | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Boulev New York, NY 100 Phone: 212 733 40 | 01 UNITED STATES | 3 | | | | | | | | | | | | | | | | | |
| 1 110110. 212 700 40 | 0.40 | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC 2022002 | | | | ME AND ADDRE | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPOR | T SOURCE | | NAME | AND ADDF | RESS V | VITHHI | ELD. | | | | | | | | | | | |
| 07-SEP-2023 | M HEALTH PROFES | ш | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | T TYPE | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 74-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB), from 09Dec2019 to Dec2020 at 200 mg daily. The patient's relevant medical history was not reported. Concomitant medication(s) included: PERINDOPRIL (ongoing); NILOTINIB (ongoing); FLECAINE (ongoing); ELIQUIS (ongoing). The following information was reported: DRY SKIN (non-serious) with onset 10Jan2022, outcome "recovered" (12Apr2022), described as "Skin xerosis on the trunk and face".

The reporter considered "skin xerosis on the trunk and face" not related to bosutinib.

Additional information: Skin xerosis on the trunk and face, grade 1, non-serious, unrelated to the study drug or concomitant medications. The event dry skin was rated grade 1. The event dry skin outcome was not recovered. Action taken not applicable. Event dry skin was reported as non-serious. The investigator considered that the event dry skin was unrelated to Bostunib or to any concomitnant drug. Event description was provided as AE6A CUTANEOUS XEROSIS ACCOMPANIED BY ECZEMATIFORM LESIONS AND SCRATCHING LESIONS. Dry skin was reported as non clinically significative in the medical file.

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 includes: Outcome for event CUTANEOUS XEROSIS ON TRUNK AND FACE updated to recovered on 12Apr2022; new event added: dry skin (start on 28Jan2022, outcome not recovered, non serious).

Follow-up (07Sep2023): This is a non-interventional study follow-up report received from the clinical team. Updated information included: event dry skin (start on 28Jan2022) deleted.

Case Comment: Based on the available information, the Company considers the reported event 'skin xerosis on the trunk and face' is unrelated to suspect drug bosutinib but more likely an inter-current medical condition.

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| SUSPEC | T ADVERSE F | REACTION REPO | ORT | | | | | | | | | | | | | | | | |
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| | | I DEA | OTION IN | | 4 ATION | | | T | <u> </u> | Ш | | ш | | | | <u> </u> | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. KEA 2. DATE OF BIRTH | 2a. AGE | | 3a. WEIGHT | 4-6 R | EACTIO | ON ONS | SET | 8-1 | 2 CH | IECK A | LL | | | | | | |
| (first, last) PRIVACY | FRANCE | Day Month Year PRIVACY | 48 Years F | emale | 59.50 kg | Day 17 | Mont FEI | | Year 2022 | | | PROPI | | | N | | | | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR hepatic cytolysis [H | ED TERM] (Related symp | tests/lab data) toms if any separated by comm | aas) | | | | | | | 1 | | TIENT | D OR | ₹ | | | | | |
| Case Description: 0 | | _ STUDY - EVALUATION | ON OF EFF | TICACY | AND SAFET | Y OF | BOS | ULIF | : | | → PR HC | ROLONO DSPITA | GED LISA | INPAT TION | | | | | |
| This is a non-intervene reporter(s) (Physicial | eived from c | ontac | table | | | | OF DI: | VOLVEI R SIGNI SABILIT CAPAC | IFICA TY OI | ANT | ENT | | | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | | E IREATE | NIN | G | | | | | |
| | | II. SUSPEC | CT DRUG | (S) IN | FORMATI | ON | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (ir #1) Bosulif (BOSUT | - | tablet | | (Contir | nued on Addit | ional lı | nforma | ation I | Page | | DID RE ABATE DRUG | AFTER | | OPPIN | G | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | ROUTE(S) () Unknov | OF ADMINISTRA WN | TION | | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | SE | | | 47 | | | | | | 21. | | ACTIO PEAR A RODU(| FTE | TER | | | | | |
| 18. THERAPY DATES(from #1) MAR-2020 / 18- | • | | | THERAPY (| | | | | | | YE | s 🛛 | NO | | NA | | | | |
| | | III. CONCOMI | TANT DR | UG(S) | AND HIS | STOF | RY | | | | | | | | | | | | |
| 22. CONCOMITANT DRUG | S(S) AND DATES OF ADM | IINISTRATION (exclude those u | sed to treat react | tion) | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIS From/To Dates 15-MAR-2021 to O Unknown to Ongoi | ingoing | allergies, pregnancy with last m Type of History / Notes Relevant Med Hi Relevant Med Hi | story C | escription Colitis (Co | olitis) nyeloid leuk | emia (| (Chro | nic m | nyelo | oid le | ukae | mia) | | | | | | | |
| | | IV. MANUF | FACTURE | R INF | ORMATIO | NC | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Boulevan New York, NY 1000 Phone: 212 733 404 | rd East 1 UNITED STATES | | 26. REMARKS | | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2022003 | | | | IE AND ADDRES AND ADDRE | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 28-SEP-2023 | 24d. REPORT STUDY HEALTH PROFES | | NAME | AND ADDRE | ESS W | /ITHH | IELD. | • | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | | - | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 48-year-old female patient received bosutinib (BOSULIF), first regimen from Mar2020 to 18Feb2022 at 500 mg daily and second regimen since 28Feb2022 at 400 mg 1x/day. The patient's relevant medical history included: "EDEMATO CONGESTIVE COLITIS", start date: 15Mar2021 (ongoing); "Chronic myeloid leukemia" (ongoing). The patient's concomitant medications were not reported. The following information was reported: HEPATIC CYTOLYSIS (non-serious) with onset 17Feb2022, outcome "recovered" (28Feb2022). Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage reduced.

The reporter considered "hepatic cytolysis" related to bosutinib.

Reporter Comment: withdrawal of bosutinib from 18Feb2022 to 28Feb2022; resumption at 400 mg daily after phone advice from the patient's hematologist. Consultation by phone since the increased of AST and ALT. Waiting for additional information for possible other cause.

Additional information: Readministration of bosutinib on 28Feb2022 following ALAT/ASAT stabilization. Event Hepatic cytolysis was rated grade 3. Biology of 21Feb2022 (grade 3). Rechallenge was negative.

Follow-up(17May2022): New information received from investiational site via CRO. Updated information: hepatic cytolysis outcome updated to recovered on 28Feb2022, and clinical course provided.

Follow-up (12Jul2023): This is a follow-up to a non-interventional study for protocol B1871047 received from investigational site via CRO. Updated information includes: Lab data (additional AST and ALT values, previously reported values of AST and ALT were corrected).

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

Follow-up (26Jul2023): new information received from the investigator via the CRO. Updated information included patient's weight, clinical details.

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

Follow-up (28Jul2023): This is a non-interventional study follow-up report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. Updated information: medical history added (Chronic myeloid leukemia).

Follow-up (28Sep2023): 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 start date and daily dose of the first bosutinib dosage regimen and action taken updated from "Temporarily withdrawn" to "Dose reduced".

Case Comment: Based on a plausible temporal relationship, causality for the onset of grade 2 hepatic cytolysis secondary to Bosutinib cannot be ruled out. The underlying malignancy may be contributory. The follow-up information received does not alter the previous company clinical evaluation.

| # | Date | Test / Assessment / Notes | Results | Normal High / Low |
|---|-------------|----------------------------|------------------------------|-------------------|
| 1 | 17-FEB-2022 | Alanine aminotransferase | 275 | |
| 2 | 21-FEB-2022 | Alanine aminotransferase | 318 | |
| 3 | 28-FEB-2022 | Alanine aminotransferase | 123 | |
| 4 | 17-FEB-2022 | Aspartate aminotransferase | 131 | |
| 5 | 21-FEB-2022 | Aspartate aminotransferase | 114 | |
| 6 | 28-FEB-2022 | Aspartate aminotransferase | 48 | |
| 7 | 18-FEB-2022 | Ultrasound abdomen | non-complicated chelestiasis | |

| ADDITIONAL INFORMATION | | | | | | | | | | | |
|--|---|---------------------------|--|--|--|--|--|--|--|--|--|
| 14-19. SUSPECT DRUG(S) continued | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION | | | | | | | | |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #2 | 400 mg, 1x/day; Unknown | Unknown | 28-FEB-2022 / Unknown; Unknown | | | | | | | | |

| | | | | | | | | | | | CIC | M | S F | OF | RM | | |
|---|--|--|---------------------|---------------------------|-------------------------|---------------|-----------|-------------|-------------|----|-----|-------------|---|------------|-------------|----|---|
| | | | | | | | | | | | | | | | | | |
| SUSPECT A | ADVERSE F | REACTION REF | PORT | | | | | | | | | | | | | | |
| | | | | | | Т | | | T | П | П | _ | _ | <u> </u> | | | Г |
| | | | | | | | \square | | | | | | | | | | |
| | | I. RE | EACTION | INFOR | MATION | | 7 | | | | | | | | | | |
| (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH Day Month Ye | 2a. AGE | 3. SEX | | | ACTIO | | SET Year | _ | | | CK ALL ROPRIA | TE TO |) | | |
| PRIVACY 1 | FRANCE | PRIVACY | 76 Years | Male | 97.00 Da | ay | Unl | | Teal | | | ADV | ERSE R | EAC | ΓΙΟN | | |
| 7 + 13 DESCRIBE REACTION, Event Verbatim [PREFERRED CHRONIC ANTRAL G Rectal polyp [Rectal p | FERM] (Related symp SASTRITIS [Ch | toms if any separated by cor | mmas) | | | | | | | | | INVO PRO | ENT DIE DLVED O LONGEI PITALIS | R D INF | | NT | |
| Case Description: OB UNDER REAL-LIFE C | CONDITIONS C | OF USE | | | | | | | • | | ш | OR S | OLVED P SIGNIFIC ABILITY (| CANT OR | ISTEI | NT | |
| The initial case was missing the following minimum criteria: adverse event unspecified. Upon receipt of collow-up information on 01Mar2022, this case now contains all required information to be considered valid. | | | | | | | | | | | | LIFE | | | | | |
| | (Continued on Additional Information Page) | | | | | | | | | | | | EATENIN | NG | | | |
| | | II. SUSPE | ECT DRU | G(S) IN | IFORMATIO | N | | | | _ | | | | | | | |
| 14. SUSPECT DRUG(S) (included #1) Bosulif (BOSUTINI | , | ablet | | • | inued on Addition | $\overline{}$ | nforma | ition F | Page | | ABA | | CTION IFTER S | TOPI | PING | | |
| 15. DAILY DOSE(S) #1) 200 mg, daily | | | | 6. ROUTE(S) #1) Unkno | OF ADMINISTRATION | ON | | | | | | YES | NO | > [2 | NA D | ١. | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | 21 | RE/ | APPE | CTION AR AFTI ODUCTIO | | | | |
| 18. THERAPY DATES(from/to) #1) 24-MAR-2021 / 27 | -FEB-2022 | | | 9. THERAPY #1) 11 mo | DURATION on this 4 days | | | | | | | YES | □ NC | ₽ [2 | 3 NA | ١. | |
| | | III. CONCON | MITANT D | RUG(S |) AND HIST | OR | Υ | | | | | | | | | | |
| 22. CONCOMITANT DRUG(S) A #1) XARELTO (RIVA | | 1 * | se used to treat re | eaction) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTO From/To Dates Unknown | RY. (e.g. diagnostics, | allergies, pregnancy with las Type of History / Note Relevant Med recovered | es . | Description | carcinoma (Bla | adde | r can | cer) | | | | | | | | | |
| | | IV. MANI | UFACTUE | RER INI | FORMATIO | N | | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF MANUFACTURER Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | |
| | 24b. MFR CO 20220034 | | | | ME AND ADDRESS | | | | , | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 21-JUL-2023 | 24d. REPORT STUDY HEALTH PROFES | LITERATUR | RE | NAME | E AND ADDRES | SS W | 'ITHH | ELD. | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | | P: | | | | | | | | | | | | | | |

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 76-year-old male patient received bosutinib (BOSULIF), first regimen from 24Mar2021 to 27Feb2022 at 200 mg daily, second regimen since 28Feb2022 (ongoing) at 200 mg (200 mg, monday, tuesday, wednesday, thursday and friday) and third regimen since 28Feb2022 (ongoing) at 300 mg (300 mg, saturday and sunday). The patient's relevant medical history included: "BLADDER CARCINOMA" (not ongoing), notes: recovered. Concomitant medication(s) included: XARELTO taken for iron deficiency anaemia. The following information was reported: CHRONIC GASTRITIS (non-serious), outcome "recovered", described as "CHRONIC ANTRAL GASTRITIS"; RECTAL POLYP (non-serious), outcome "recovered" (18Feb2022). Relevant laboratory tests and procedures are available in the appropriate section. The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of rectal polyp.

Additional information: event chronic antral gastritis was assessed as non-serious and grade 1, rectal polyp was non-serious and grade 2. Coloscopy performed on 18Feb2022 was within the limits of normal with removal of a rectal polyp. The coloscopy scheduled for 18Feb2022 (anemia Microcytic ferridefy, under xarelto): Fibroscopie Oeso-Gastro-Duodenale (FOGD): Normal, colonoscopy: ablation of a small polyp. Clinical examination: weight 91 kg, ps (performance status 0). In the conclusion of the hystological examination of 18Feb2022: chronic antral gastritis of moderate intensity of mild activity, without intestinal atrophy or metaplasia, asymptomatic patient.

The reporter considered "chronic antral gastritis" and "rectal polyp" not related to bosutinib. No follow-up attempts are possible. No further information is expected.

Follow-up (12Jul2023): This is a follow-up report received from the CRO. Updated information included: suspect drug Bosulif details (Action Taken: Dose Not Changed).

Follow-up (21Jul2023): This is a follow-up report received from the investigator. Updated information included: updated dosage regimens, updated description of lab tests, additional lab data.

Case Comment: Based on the available information and action taken, there was no reasonable possibility that the events "chronic antral gastritis" and "rectal polyp" were related to bosutinib or concomitant drugs. This case will be re-assessed should additional information become available. The follow-up information received does not alter the previous company clinical evaluation.

13. Lab Data

| # Date | Test / Assessment / Notes | s | Results | Normal High / Low |
|--|---|------------------------|--|--|
| 1 18-FEB-2022 | Colonoscopy within the limits of | tol h | normal | |
| | normal. removal of | а гестаі роіур | | |
| 2 | Eastern Cooperative Group performance | 0, | 0 | |
| 3 18-FEB-2022 | Histology chronic antral gastri intestinal metaplasia | | chronic antral gastritis of moderate intensity of tensity of mild activity, withou atient | ut atrophy nor |
| 4 | Oesophagogastrod | uodenoscopy | normal | |
| 5 | Weight | | 91 kg | |
| 14-19. SUSPECT DRUG(S) continue | d | | | |
| 14. SUSPECT DRUG(S) (include generic name) | 15. DAILY D 16. ROUTE(| OSE(S); S) OF ADMIN | 17. INDICATION(S) FOR USE | 18. THERAPY DATES (from/to); 19. THERAPY DURATION |
| #1) Bosulif (BOSUTINIB) Film-co | ated tablet; 200 mg, | Monday, | Unknown | 28-FEB-2022 / |

| 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 | Tuesday, Wednesday, | | Ongoing; |
| | Thursday and Friday; | | Unknown |
| | Unknown | | |
| #1) Bosulif (BOSUTINIB) Film-coated tablet; Regimen #3 | 300 mg, Saturday and Sunday; Unknown | Unknown | 28-FEB-2022 / Ongoing; Unknown |

| | | | | | | | | | | | | | CI | ON | 1S | FO | RM |
|---|---------------------------|---|------------|---|---------------------|----------|-----------|-----------------------------|--------------------------|---|-----|-------------|-----------------|--------|--------|--------|--------|
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| SUSPEC | T ADVERSE I | REACTION REPO | ORT | | | | | | | | | | | | | | |
| | | - | | - | | | П | | Т | Τ | Г | 一 | \top | \top | \top | \top | \top |
| | | | | | | | \square | | | | | | \perp | | | | |
| | | I. REA | CTION | INFOR | MATION | | 7 | | | | | | | | | | |
| 1. PATIENT INITIALS (first, last) | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year | 2a. AGE 72 | 3. SEX | 3a. WEIGHT Unk | 4-6 R | REACTION | ON ONS | SET Yea | ┥. | , | APP | ROPRI | IATE | | | |
| PRIVACY | FRAINCE | PRIVACY | Years | Male | Ulik | 22 | MA | | 202 | | , | ADV | /ERSE | REA | CTIO | N | |
| 7 + 13 DESCRIBE REACT Event Verbatim [PREFERF Dyspnea [Dyspnoe | RED TERM] (Related sym | it tests/lab data) ptoms if any separated by comm | as) | | | | | | | | | INVO | OLVED | OR | | | |
| Case Description: UNDER REAL-LIF | | | ON OF EF | EFFICACY AND SAFETY OF BOSULIF PROLONGED INPAHOSPITALISATION INVOLVED PERSIS | | | | | | | | | | | ION | | |
| This is a non-interreporter(s) (Physic | contac | table | | | | | OR S | SIGNIF ABILITY APACIT | TICAN Y OR | NT | L | | | | | | |
| (Continued on Additional Information Page) | | | | | | | | | | | | LIFE THR | E REATEN | NING | | | |
| | | II. SUSPEC | חשט די | | | | | | | , <u>, , , , , , , , , , , , , , , , , , </u> | | | | - | | | |
| 14. SUSPECT DRUG(S) (i #1) Bosulif (BOSU | | | 71 51.0 | <u> </u> | TOTUNE. | 1011 | | | | 20 | | ATE A | ACTION AFTER | | PPIN | G | |
| 15. DAILY DOSE(S) #1) | | | | s. ROUTE(S) 1) Unkno | OF ADMINISTRA WN | ATION | | | | | | YES | s 🔲 1 | NO | ⊠₁ | NA | |
| 17. INDICATION(S) FOR L #1) Unknown | JSE | | | | | 21 | REA | APPE | ACTION EAR AF ODUC | TER | | | | | | | |
| 18. THERAPY DATES(from #1) Unknown | n/to) | | |). THERAPY 1) Unkno | | | | YES | 1 🔲 | NO | ⊠ ▷ | NA | | | | | |
| | | III. CONCOMI | TANT DI | RUG(S |) AND HIS | STOF | RY_ | | | | | _ | | | | | |
| 22. CONCOMITANT DRUG | G(S) AND DATES OF ADM | MINISTRATION (exclude those us | | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | |
| From/To Dates | ISTORY. (e.g. diagnostics | , allergies, pregnancy with last many Type of History / Notes | | etc.) Description | | | | | | | | | | | | | |
| Unknown | | | | | | | | | | | | | | | | | |
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| | | IV. MANUF | FACTUR | FR INF | | ∩N | | | | | | | | | | | |
| 24a. NAME AND ADDRES | S OF MANUFACTURER | 17.170.033 | AOTOL | 26. REM | | <u> </u> | | | | | | | | | | | |
| Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | 1 UNITED STATE | | | | | | | | | | | | | | | | |
| | 245 MED CO | CATEDOL NO | | OED NA | *** ***D **DDBE | 22 OF F | | | | | | _ | | | | | |
| | 24b. MFR CC 2022003 | | | | ME AND ADDRES | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPOR | | NAME | AND ADDR | ESS V | VITH | HELD | - | | | | | | | | | |
| 04-MAR-2022 | STUDY STUDY HEALTH | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 72-year-old male patient received bosutinib (BOSULIF). The patient's relevant medical history and concomitant medications were not reported.

The following information was reported: DYSPNOEA (non-serious) with onset 22May2021, outcome "recovered" (21Jul2021), described as "Dyspnea". The action taken for bosutinib was dosage not changed.

According to the investigator event was related to study drug and unrelated to concomitant treatment.

Additional information: the event dyspnea was grade 2.

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

Case Comment: Based on available information and known AE profile of bosutinib, the reasonable possibility of an association between Dyspnea and suspect product cannot be ruled out.

| | | | | | | | | | CI | OM | SI | FOI | RM | | | | | | | | | | | |
|---|--|--|--|--|--------------------|----------|---|----------|--------------|---|------|-----------------|--------|------------------------|---|---|--|--|--|--|--|--|--|--|
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| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | | | | | | | |
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| | | | | :::=== | | | | <u>r</u> | Ш | | | | | <u> </u> | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION 2a. AGE | 3. SEX | MATION 3a. WEIGHT | | REACTIC | N ONS | CT | 8-12 | CH | IECK AL | | | | | | | | | | | | |
| PRIVACY | FRANCE | Day Month Year PRIVACY | 74 Years | Male | Unk | Day 14 | Mont JAN | h | Year 2021 | 1 | AP | PROPRI VERSE | IATE T | | 1 | | | | | | | | | |
| | CTION(S) (including relevant RRED TERM] (Related symp ESIONS [Skin lesion | t tests/lab data) ptoms if any separated by comma: DN] | s) | PATIENT DIED INVOLVED OR PROLONGED INPATIENT | | | | | | | | | | | | | | | | | | | | |
| | : OBSERVATIONA FE CONDITIONS (| | ON OF EF | EFFICACY AND SAFETY OF BOSULIF | | | | | | | | | | ON | | | | | | | | | | |
| | | port (Post Authorization P) for protocol B187104 | | Study) rec | eived from | contac | ctable | | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY | | | | | | | | | | | | | | |
| | (Continued on Additional Information Page | | | | | | | | | | | | | Page) LIFE THREATENING | | | | | | | | | | |
| | | II. SUSPEC | T DRU | G(S) IN | FORMA | TION | | | | | | | | | | | | | | | | | | |
| #1) Bosulif (BOSU | II. SUSPECT DRUG(S) INFORMATION 4. SUSPECT DRUG(S) (include generic name) 4.) Bosulif (BOSUTINIB) Film-coated tablet 4. 2) GLIVEC (IMATINIB MESILATE) | | | | | | | | | | | | | PING |) | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/da #2) UNK | ау | | # | 6. ROUTE(S) 41) Unkno 42) Unkno | | RATION | | | | | YE | is 🔲 r | ۷O [| ⊠ № | A | | | | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION | | | | | | | | | | | | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 07-NOV-2019 #2) Unknown | • | | # | 19. THERAPY DURATION #1) 27 days #2) Unknown | | | | | | | | | | | A | | | | | | | | | |
| | | III. CONCOMIT | ANT D | RUG(S | AND H | ISTO | RY | | | | | | | | | | | | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | MINISTRATION (exclude those use | ed to treat re | action) | | | | | | | | | _ | _ | _ | _ | | | | | | | | |
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| -2 OTHER RELEVANT | "STORY (diamention | | " -f - oriod | | | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT I From/To Dates 2011 to 2011 | HISTORY. (e.g. diagnostics, | , allergies, pregnancy with last mo Type of History / Notes Relevant Med His operated | • | Description | al aortic ar | neurysı | m (Aor | tic ar | eury | rsm) | | | | | | | | | | | | | | |
| 2019 to 2019 | | Relevant Med His ENDARTERECTO | | Carotid a | rtery occlu | ision (C | Carotid | l arte | ry oc | clusi | ion) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | | | | | |
| 24a NAME AND ADDRE | SS OF MANUFACTURER | IV. MANUF | ACTUF | RER INF | | ION | | | | | | | | _ | | _ | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulev | ard East 01 UNITED STATES | S | | Auto | | | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC | ONTROL NO. | | | ME AND ADDR | | | | | | | | | | | | | | | | | | | |
| | 2022003 | | NAME AND ADDRESS WITHHELD. NAME AND ADDRESS WITHHELD. | | | | | | | | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPORT | T SOURCE LITERATURE | | INAIVIL | AND ADD | INLOG (| / | ILLD. | | | | | | | | | | | | | | | | |
| 09-MAR-2022 | ₩ HEALTH PROFES | | | | | | | | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | T TYPE FOLLOWUP: | | | | | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 74-year-old male patient received bosutinib (BOSULIF), from 07Nov2019 to 03Dec2019 at 500 mg 1x/day; imatinib mesilate (GLIVEC), (Batch/Lot number: unknown). The patient's relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011, notes: operated; "LEFT INTERNAL CAROTID ARTERY BLOCKED", start date: 2019, stop date: 2019, notes: ENDARTERECTOMY; "ENDARTERECTOMY" (unspecified if ongoing). The patient's concomitant medications were not reported.

The following information was reported: SKIN LESION (non-serious) with onset 14Jan2021, outcome "recovered" (08Apr2021), described as "MINIMAL SKIN LESIONS". The action taken for imatinib mesilate was dosage not changed. Additional information: minimal skin lesions were non-serious, grade 1, unrelated to bosutinb and related to concomitant drug GLIVEC. The site described: during the consultation of 14Jan2021, the patient presented some minimal skin lesions on the arms and legs that were not pruritic without argument for a toxidermia. No additional concomitant treatments or modification of current treatments.

The reporter considered "minimal skin lesions" not related to bosutinib.

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

Case Comment: In concurrence with the reporter, the reported event 'minimal skin lesions' is unrelated to the administration of bosutinib. The event occurred more than 1 year after the last dose of bosutinib. The patient's other medication may provide an explanation for the event.

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|----------------------------------|
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

| | | | | | | | | | | | | С | 10 | MS | FO | RM | | | |
|--|--|---|---|--|----------------|--------------------|-----------|--------------|-------------|-------------------|-----------|-----------------------------|-------|--------|----|---------|--|--|--|
| | | | | | | | | | | | | | | | | | | | |
| SUSPECT A | DVERSE R | EACTION REP | ORT | | | | | | | | | | | | | | | | |
| | | | | | | | П | | Τ | П | T | П | Т | \top | Τ | Τ | | | |
| | | | | | | | 4 | | | | | | | 丄 | | \perp | | | |
| | ·, T | | ACTION | | | 4 | 7 | | | 1., | - | | | | | | | | |
| (first, last) | RANCE | 2. DATE OF BIRTH Day Month Yea PRIVACY | 2a. AGE 75 Years | 3. SEX Male | 3a. WEIGHT Unk | 4-6 R Day 21 | Mon OC | | Year 202 | | AF | HECK AI PPROPE OVERSE | RIATI | | N | | | | |
| 7 + 13 DESCRIBE REACTION(S Event Verbatim [PREFERRED T purpura [Purpura] | S) (including relevant t ERM] (Related sympt | ests/lab data) oms if any separated by con | nmas) | PATIENT DIED INVOLVED OR | | | | | | | | | | | | | | | |
| Case Description: OB: UNDER REAL-LIFE C | | FFICACY | AND SAFET | ΓY OF | BOS | SULIF | | | Н | ROLONO DSPITAL | LISA | TION | | | | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) received from contactable reporter(s) (Physician and Other HCP) for protocol B1871047. | | | | | | | | | EIVI | | | | | | | | | | |
| | nued on Addit | tional I | nform | ation F | Page | , [|] LIF | FE IREATE | NIN | G | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) #1) Bosulif (BOSUTINIB) Film-coated tablet #2) GLIVEC (IMATINIB MESILATE) | | | | | | | | | | AFTER | | OPPIN | IG | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/day #2) UNK | | #1) Unkno | 6. ROUTE(S) OF ADMINISTRATION 1) Unknown 2) Unknown | | | | | | | | YES NO NA | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown #2) Unknown | #1) Unknown | | | | | | | | | | REAPI | EACTIO PEAR A RODUC | FTE | | | | | | |
| 18. THERAPY DATES(from/to) #1) 07-NOV-2019 / 03- #2) Unknown | DEC-2019 | | , | 19. THERAPY DURATION #1) 27 days #2) Unknown | | | | | | | | NA | | | | | | | |
| | | III. CONCON | | |) AND HIS | STOF | RY | | | | | | | | | | | | |
| 22. CONCOMITANT DRUG(S) A | AND DATES OF ADMI | NISTRATION (exclude those | e used to treat re | eaction) | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTOR | 2V (a a diagnostics s | raine prognancy with lac | +th of pario | -1 ata \ | | | | | | | | | | | | | | | |
| From/To Dates 2011 to 2011 | Tr. (e.g. diagnostico, c | Type of History / Note Relevant Med | es | Description | al aortic ane | eurysn | n (Ao | rtic ar | neur | vsm) | | | | | | | | | |
| 2019 to 2019 | | operated Relevant Med ENDARTEREC | , | | artery occlusi | • | • | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | IV. MANU | JFACTUI | | ORMATION | ON | | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard E New York, NY 10001 U Phone: 212 733 4045 | ast | | | 26. REN | 1ARKS | | | | | | | | | | | | | | |
| | 24b. MFR CON | ITROL NO. | | | ME AND ADDRES | | | | | | | | | | | | | | |
| | 20220039 | 1824 | | | AND ADDRI | | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT STUDY | SOURCE LITERATUR | ₹E | INAME | AND ADDRI | ess V | vi i Hh | ⊐ELD. | | | | | | | | | | | |
| 09-MAR-2022 | HEALTH PROFESS | | | _ | | | | | | | | | | | | | | | |
| 27-FEB-2024 | 25a. REPORT TYPE 27-FEB-2024 Initial Followup: | | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), from 07Nov2019 to 03Dec2019 at 500 mg 1x/day; imatinib mesilate (GLIVEC), (Batch/Lot number: unknown). The patient's relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011, notes: operated; "LEFT INTERNAL CAROTID ARTERY BLOCKED", start date: 2019, stop date: 2019, notes: ENDARTERECTOMY; "ENDARTERECTOMY" (unspecified if ongoing). The patient's concomitant medications were not reported.

The following information was reported: PURPURA (non-serious) with onset 21Oct2021, outcome "recovered" (27Jan2022). The action taken for bosutinib was unknown; for imatinib mesilate was dosage not changed.

The reporter considered "purpura" not related to bosutinib.

Additional information: event was non-serious, rated grade 1, unrelated to bosutinib and related to concomitant drug GLIVEC. The site described: the patient presented during the consultation of 21Oct2021 a purpura of the upper limbs.

Case Comment: Based on the available information, the event purpura is not related to bosutinib. The last dose of bosutinib was administered on 03DEC2019.

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|----------------------------------|
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

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|--|---|--|---|---|------------------------------|--------|-----------|--------|-------------|----------|---|-------------|----------------------------|-----------------|------|-----|---|--|
| | | | | | | | | | | | | | | | | | | |
| SUSPEC | T ADVERSE I | REACTION REP | ORT | | | | | | | | | | | | | | - | |
| | | | | | | | П | | | П | | Τ | Τ | П | Т | Т | | |
| | | | | | | | | T | | | | | | | | | _ | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. RE | ACTION 2a. AGE | 3. SEX | MATION 3a. WEIGHT | 4.6.5 | PEACTI | ON ONS | ·гт | 8-12 | ^ CI | יייברו | K ALL | | | | _ | |
| PRIVACY | FRANCE | Day Month Yea | | Male | Unk | Day 06 | Mor SE | ith | Year 202 | 1 | Al | PPRC | OPRIA | TE TO EACTIO | NC | | | |
| 7 + 13 DESCRIBE REACTI Event Verbatim [PREFERR Other Serious Crite HYPOACOUSIA [H | RED TERM] (Related symeria: Medically Sig | nmas) | PATIENT DIED INVOLVED OR PROLONGED INPATIENT HOSPITALISATION | | | | | | | | | | ٢ | | | | | |
| | eceipt of follow-u | nformation received on information on [14N ogether. | • | _ , | | | | _ | ; | | | R SIG | VED P GNIFIC ILITY (| OR | TENT | | | |
| OBSERVATIONAL CONDITIONS OF | | IATION OF EFFICAC | Y AND SAF | | BOSULIF U | | | | |) [| 그 밖 | IFE HREA | ATENIN | NG | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | • | | | | | | |
| 14. SUSPECT DRUG(S) (ir #1) Bosulif (BOSUT | | | | <u> </u> | | | | | | 1 | DID RI ABATI DRUG | E AF | | TOPPIN | NG | | - | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/day | , | | 6. ROUTE(S 1) Unkno | YES NO NA | | | | | | | | | | | | | | |
| 17. INDICATION(S) FOR U #1) Unknown | SE | | | | | | | | | 1 | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 18. THERAPY DATES(from #1) 07-NOV-2019 / | · | | | 19. THERAPY DURATION YES NO NA NA | | | | | | | | NA | | _ | | | | |
| | | III. CONCOM | IITANT D | RUG(S |) AND HIS | STOI | RY | | | | | | | | _ | | _ | |
| 22. CONCOMITANT DRUG | S(S) AND DATES OF ADM | MINISTRATION (exclude those | used to treat rea | action) | | | | | _ | | | | _ | | _ | _ | ٠ | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | _ | |
| 23. OTHER RELEVANT HIS From/To Dates 2011 to 2011 Unknown | STORY. (e.g. diagnosucs | , allergies, pregnancy with last Type of History / Node Relevant Med I Relevant Med I | s History | Description Abdomir | nal aortic and mectomy (A | - | , | | neur | ysm) | 1 | | | | | | | |
| | | IV. MANL | JFACTUR | RER IN | FORM <u>ATI</u> | ON | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF MANUFACTURER Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC 2022003 | | | | ME AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER 14-MAR-2022 | 24d. REPOR STUDY HEALTH | LITERATUR | Έ | NAMI | E AND ADDR | ESS \ | WITHI | HELD. | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | TE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047.

A 75 year-old male patient received bosutinib (BOSULIF), from 07Nov2019 (Batch/Lot number: unknown) to 03Dec2019 at 500 mg 1x/day. Relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011; "OPERATED ABDOMINAL AORTIC ANEURYSM" (unspecified if ongoing); "LEFT INTERNAL CAROTID BLOCKED", start date: 2019, stop date: 2019; "Endarterectomy" (unspecified if ongoing). There were no concomitant medications.

The following information was reported: HYPOACUSIS (medically significant) with onset 06Sep2021, outcome "recovered" (16Sep2021), described as "HYPOACOUSIA". Therapeutic measures were taken as a result of hypoacusis. The patient went to the emergency on 13Sep2021 for hypoacousia for a week. Cerumen plug in the left ear: physiological serum 5 times a day then extraction of the plug by the doctor in 48 or 72 hours.

The investigator considered there was not a reasonable possibility that the event "hypoacousia" was related to bosutinib. No follow-up attempts are possible. No further information is expected.

Case Comment: In concurrence with the investigator, the reported 'hypoacousia' is unrelated to the study drug bosutinib. The event is not consistent with the known drug safety profile and occurred more than 21 months after the last dose of bosutinib was administered.

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|---|
| 2019 to 2019 | Relevant Med History | Carotid artery occlusion (Carotid artery occlusion); |
| Helmone | Dalamari Mari III | File of the state |
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

| | | | | | | | | | | | | | CI | ON | MS | FO | RM |
|---|-------------------------------------|-----------------------------------|--|---|----------------|---------------|--------|----------------|------------|--------------------------|------------------|------|---------------------------|---------------|---------------|----|----|
| | | | | | | | | | | | | | | | | | |
| SUSPECT A | ADVERSE R | REACTION REPO | RT | | | | | | | | | | | | | | |
| 333. 23. 7 | | | | | | | П | | _ | _ | П | _ | $\overline{}$ | $\overline{}$ | $\overline{}$ | _ | т |
| | | | | | | | И | | | | | | | | | | |
| | | I. REA | CTION | INFOR | MATION | | | | | | | | | | | | |
| (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH | 2a. AGE | 3. SEX | 3a. WEIGHT | $\overline{}$ | EACTIO | | | _ | | | ECK AL | | : TO | | |
| PRIVACY F | FRANCE | Day Month Year PRIVACY | 74 Years | Male | | Day 06 | JU | | Yea 202 | | | | /ERSE | | | N | |
| 7 + 13 DESCRIBE REACTION(Event Verbatim [PREFERRED 1] BILATERAL PLEURA | 「ÉRM] (Related symp | toms if any separated by comma | as) | PATIENT DIED INVOLVED OR PROLONGED INIBATIENT | | | | | | | | | | | | | |
| Case Description: OBSERVATIONAL STUDY - EVALUATION OF EFFICACY AND SAFETY OF BOSULIF UNDER REAL-LIFE CONDITIONS OF USE | | | | | | | | | | OLONG SPITAL OLVED | ISAT PER | TON | | | | | |
| This is a non-interventional study report (Post Authorization Safety Study) for protocol B1871047. A 74 year-old male patient received bosutinib (BOSULIF), from | | | | | | | | | | | | | | | | | |
| \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION 14. SUSPECT DRUG(S) (include generic name) 20. DID REACTION | | | | | | | | | | | | | | | | | |
| #1) Bosulif (BOSUTINI #2) SPRYCEL (DASAT | B) Film-coated t | | = := : : : : : : : : : : : : : : : : : | | | <u> </u> | | | ABA | | E AFTER STOPPING | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/day #2) UNK | | # | 8. ROUTE(S) 1) Unkno 2) Unkno | | YES NO NA | | | | | | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown #2) Unknown | | | | | | | | | | 2 | RE/ | APPE | ACTION EAR AF RODUC | TER | | | |
| 18. THERAPY DATES(from/to) #1) 07-NOV-2019 / 03- #2) Unknown | DEC-2019 | | # | 19. THERAPY DURATION | | | | | | | | NA | | | | | |
| | | III. CONCOMI | TANT D | RUG(S | _) AND HIS | TOF | RY | - " | =" | | - " | - | _ | - | _ | = | _ |
| 22. CONCOMITANT DRUG(S) | AND DATES OF ADM | INISTRATION (exclude those us | sed to treat rea | action) | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 4 | | | | 7 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT HISTOI From/To Dates | RY. (e.g. diagnostics, | allergies, pregnancy with last mo | | etc.) Description | | | | | | | | | | | | | |
| 2011 to 2011 | | Relevant Med His | | | al aortic ane | urysm | n (Ao | rtic a | inei | ırysn | n) | | | | | | |
| Unknown | | Relevant Med His | story | Aortic an | eurysm repa | ir (Ao | rtic a | neur | ysn | n rep | air) | | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | _ | | — | | | |
| 24a. NAME AND ADDRESS OF | MANUTE OT LIDED | IV. MANUF | FACTUR | 26. REN | | <u>NC</u> | | | | | | _ | | _ | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | |
| | 24b. MFR COI | NTPOL NO | | 25h NA | ME AND ADDRES | S OF R | FPORT | rep | | | | _ | | _ | | | |
| | 20220039 | | | | : AND ADDRE | | | |). | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT | | | NAME | AND ADDRE | ESS W | /ITHF | HELD |). | | | | | | | | |
| 09-MAR-2022 | STUDY HEALTH PROFES | SIONAL CHER: | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | ATE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

07Nov2019 (Batch/Lot number: unknown) to 03Dec2019 at 500 mg 1x/day; dasatinib monohydrate (SPRYCEL) (Batch/Lot number: unknown). Relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011, notes: OPERTAED; "OPERTAED ABDOMINAL AORTIC ANEURYSM" (unspecified if ongoing); "CLOGGED LEFT INTERNAL CAROTID", start date: 2019, stop date: 2019, notes: ENDARTERECTOMY; "ENDARTERECTOMY" (unspecified if ongoing). The patient's concomitant medications were not reported.

The following information was reported: PLEURAL EFFUSION (hospitalization) with onset 06Jun2020, outcome "recovered" (27Jun2020), described as "BILATERAL PLEURAL EFFUSION". The patient was hospitalized for pleural effusion (start date: 20Jun2020, discharge date: 27Jun2020, hospitalization duration: 7 day(s)). The patient underwent the following laboratory tests and procedures: chest x-ray: satisfactory chest x-ray control, notes: satisfactory chest x-ray control: almost complete disappearance of the right effusion and persistence of a blunting of the left pleural recesses. The action taken for bosutinib was reported as post-therapy. The action taken for dasatinib monohydrate was temporarily withdrawn. Therapeutic measures were taken as a result of pleural effusion.

The investigator considered there was not a reasonable possibility that the event "bilateral pleural effusion" was related to bosutinib.

Additional information: event grade 3. the patient was hospitalized from 20Jun2020 to 27Jun2020 for treatment of bilateral pleural effusion. 2 evacuation punctures. According to the investigator, the event was unrelated to the study drug bosutinib but related to concomitant drug SPRYCEL. The cause of pleural effusion is most likely related to its treatment with SPRYCEL from its CML. suspension of SPRYCEL and patient is put on LASILIX at 40 mg. The patient returns home on 27Jun2020 after satisfactory chest x-ray control: almost complete disappearance of the right effusion and persistence of a blunting of the left pleural recesses.

Case Comment: In concurrence with the investigator, the reported pleural effusion is unrelated to the study drug bosutinib. Of note, the event occurred more than 6 months after the last dose of bosutinib was administered. The patient's other medication may provide an alternative explanation for the event.

13. Lab Data

| # | Date | Test / Assessment / Notes | | Results | Normal High / Low | | | | |
|---|------|---------------------------|-----------------|-----------------|-------------------|--|--|--|--|
| 1 | | Chest X-ray | | satisfactory | chest x-ray | | | | |
| | | | | control | | | | | |
| satisfactory chest x-ray control: almost complete disappearance of the right effusion | | | | | | | | | |
| | | and persistence of a blu | unting of the l | eft pleural rec | esses. | | | | |

| From/To Dates | Type of History / Notes | Description |
|---------------|--|--|
| 2019 to 2019 | Relevant Med History ENDARTERECTOMY | Carotid artery occlusion (Carotid artery occlusion); |
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

| | | | | | | | | | | | | | | CIG | ON: | /IS | FΟ | RM |
|--|---|--|-----------------|---|-------------------|--------|------|--------------|--------|-------------|--|-------------|------------------------------------|-----------------|-----|---------|----|----|
| | | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | | Т | | | | | T | T | Т | Т | \top | Τ | |
| | | | | | | | | 4 | | | | | | | L | \perp | | |
| | · OOUNTDV | | | | MATION | 10 | | 77101 | . 2010 | | 1.,, | . , | 2005 | 217 411 | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE OF BIRTH Day Month Year PRIVACY | 74 Years | 3. SEX Male | 3a. WEIGHT Unk | Day 14 | | Month JAN | | Year 021 | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION | | | | | | | |
| EXERTIONAL DY | CTION(S) (including relevant RRED TERM] (Related symp YSPNEA [Dyspnoea EDEMAS [Periorbit | s) | | | | | | | | 1 | _ _ ; | INVC PRO | ENT DI DLVED LONGE PITALI | OR ED II | | ENT | | |
| | : OBSERVATIONAL FE CONDITIONS (| ON OF EF | FICACY | AND SAFE | TY O | FB | BOSI | JLIF | | | _ (| OR S | OLVED SIGNIFI | ICAN | NT | ≣NT | | |
| 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) | | | | | | | | | | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) #1) Bosulif (BOSU #2) GLIVEC (IMA | JTINIB) Film-coated | tablet | | | | | | | | | 20. | | TE A | CTION FTER : | | PPIN | 3 | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/da #2) UNK | ау | | # | 6. ROUTE(S) OF ADMINISTRATION 1) Unknown 2) Unknown | | | | | | | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | USE | | | | | , | | | | 21. | REA | PPE | CTION AR AF ODUCT | TER | | | | |
| 18. THERAPY DATES(fro #1) 07-NOV-2019 #2) Unknown | · | | # | 9. THERAPY DURATION 11) 27 days YES NO 12 O UNKNOWN | | | | | | | | | IA | | | | | |
| | | III. CONCOMIT | ANT D | RUG(S | AND HI | STO | RY | / | | | | | | | | | | |
| 22. CONCOMITANT DRU | JG(S) AND DATES OF ADM | MINISTRATION (exclude those use | ed to treat rea | action) | | | | | | | | | | | | | | |
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| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 23. OTHER RELEVANT From/To Dates 2011 to 2011 | HISTORY. (e.g. diagnostics, | allergies, pregnancy with last mo Type of History / Notes Relevant Med His operated | | Description | al aortic an | eurys | sm (| Aort | ic an | eur | ysm) | ١ | | | | | | |
| 2019 to 2019 | | Relevant Med His ENDARTERECTO | | Carotid a | rtery occlus | sion (| Car | otid | arter | у ос | cclus | ion) |) | | | | | |
| | | | | | | | | | | | | | | | | | | |
| 240 NAME AND ADDRE | SS OF MANUFACTURER | IV. MANUF. | ACTUR | ER INF | | ION | | | | | | | | | _ | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CO 2022003 | | | | ME AND ADDRE | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | ER 24d. REPORT | T SOURCE | | NAME | AND ADDF | RESS | WI٦ | ГННЕ | ELD. | | | | | | | | | |
| 09-MAR-2022 | HEALTH PROFES | Ш | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | TE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 74-year-old male patient received bosutinib (BOSULIF), from 07Nov2019 to 03Dec2019 at 500 mg 1x/day; imatinib mesilate (GLIVEC), (Batch/Lot number: unknown). The patient's relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011, notes: operated; "LEFT INTERNAL CAROTID ARTERY BLOCKED", start date: 2019, stop date: 2019, notes: ENDARTERECTOMY; "ENDARTERECTOMY" (unspecified if ongoing). The patient's concomitant medications were not reported.

The following information was reported: DYSPNOEA EXERTIONAL (non-serious) with onset 14Jan2021, outcome "recovered" (08Apr2021), described as "EXERTIONAL DYSPNEA"; PERIORBITAL OEDEMA (non-serious) with onset 14Jan2021, outcome "recovered" (08Apr2021), described as "PERIORBITAL OEDEMAS". The action taken for bosutinib was unknown; for imatinib mesilate was dosage not changed.

Additional information: events exertional dyspnea and periorbital oedemas were non-serious, grade 1. The investigator considered that events were unrelated to bosutinib and related to concomitant drug GLIVEC. The site described: the patient presented during the consultation of 14Jan2021 an exertional dyspnea and periorbital oedemas. No additional concomitant treatments or modification of current treatment for these adverse events.

The reporter considered "exertional dyspnea" and "periorbital oedemas" not related to bosutinib.

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

Case Comment: In concurrence with the investigator, the reported exertional dyspnea and periorbital oedemas are unrelated to the administration of bosutinib. The events occurred more than 1 year after the last dose of bosutinib. The patient's other medication may provide an explanation for the events.

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|----------------------------------|
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

| | | | | | | | | | | | | CI | ON | IS | FO | RM | | |
|---|---|--|--|---|-------------------|----------|---------|----------------------------|-------|----------------|------------|---------|-----------|----|----|----|--|--|
| | | | | | | | | | | | | | | | | | | |
| SUSPE | CT ADVERSE F | REACTION REPO | RT | | | | | | | | | | | | | | | |
| | | | | | | | | | П | | T | П | Τ | Τ | Τ | Τ | | |
| | | | | | | | | ľ | Ш | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | I. REAC | CTION 2a. AGE | INFOR 3. SEX | MATION 3a. WEIGHT | _ | REACTIO | N ONS | CT | 8-12 | , CF | IECK AL | | | | | | |
| PRIVACY | FRANCE Day Month Year 75 Unk Day Month Year | | | | | | | | | APPROPRIATE TO | | | | | | | | |
| 7 + 13 DESCRIBE REAC Event Verbatim [PREFER ASTHENIA [Astho | | t tests/lab data) ptoms if any separated by comma | ıs) | | | | | | | | אור אור | TIENT D | OR | | | | | |
| | : OBSERVATIONA FE CONDITIONS (| L STUDY - EVALUATIC OF USE | ON OF EF | FFICACY | AND SAF | ETY O | FBOS | ULIF | | | НС | OLONG | ISATI | ON | | | | |
| 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) | | | | | | | | | | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) #1) Bosulif (BOSUTINIB) Film-coated tablet #2) GLIVEC (IMATINIB MESILATE) 20. DID REACTION ABATE AFTER STOPPING DRUG? | | | | | | | | | | | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/da #2) UNK | ау | | 16. ROUTE(S) OF ADMINISTRATION #1) Unknown #2) Unknown | | | | | | | | □ ^ | 1A | | | | | | |
| 17. INDICATION(S) FOR #1) Unknown #2) Unknown | | | | | | | REAP | ACTION PEAR AF RODUC | TER | | | | | | | | | |
| 18. THERAPY DATES(fro #1) 07-NOV-2019 #2) 31-JUL-2020 | / 03-DEC-2019 | | # | 9. THERAPY ‡1) 27 day ‡2) Unkno | 'S | | | | | | YE | s 🔲 | VO | | ۱A | | | |
| | | III. CONCOMIT | TANT D | RUG(S |) AND H | ISTO | RY | | | | | | | | | | | |
| | 1 1 | MINISTRATION (exclude those use HYDRATE) ; 15-JAN-2 | | | 20 | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| -2 OTHER RELEVANT | ""STORY / diagnostics | " | " -f - oriod | | | | | | | | | | | | | | | |
| From/To Dates 2011 to 2011 | HISTORY. (e.g. diagnosiics, | , allergies, pregnancy with last mo Type of History / Notes Relevant Med His | • | Description | al aortic ar | neurys | m (Aor | tic ar | neury | /sm) | | | | | | | | |
| 2019 to 2019 | | operated Relevant Med His ENDARTERECTO | | Carotid a | rtery occlu | ision (0 | Carotid | arte | ry oc | clusi | ion) | | | | | | | |
| | | | | | | | | | | | | | | | | | | |
| | | IV. MANUF | ACTUF | | | ION | | | | | | | | | | | | |
| 24a. NAME AND ADDRESS OF MANUFACTURER Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard East New York, NY 10001 UNITED STATES Phone: 212 733 4045 | | | | | | | | | | | | | | | | | | |
| | 24b. MFR CC 2022003 | | | | ME AND ADDR | | | | | | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURE | 24d. REPORT | | | NAME | AND ADD | RESS | NITHH | ELD. | | | | | | | | | | |
| 25-APR-2023 | STUDY HEALTH | LITERATURE OTHER: | | | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | ATE OF THIS REPORT 25a. REPORT TYPE | | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 75-year-old male patient received bosutinib (BOSULIF), from 07Nov2019 to 03Dec2019 at 500 mg 1x/day; imatinib mesilate (GLIVEC), since 31Jul2020 (ongoing) (Batch/Lot number: unknown). The patient's relevant medical history included: "ABDOMINAL AORTIC ANEURYSM", start date: 2011, stop date: 2011, notes: operated; "LEFT INTERNAL CAROTID ARTERY BLOCKED", start date: 2019, stop date: 2019, notes: ENDARTERECTOMY; "ENDARTERECTOMY" (unspecified if ongoing). Concomitant medication(s) included: SPRYCEL, start date: 15Jan2020, stop date: 22Jun2020.

The following information was reported: ASTHENIA (non-serious) with onset 06May2020, outcome "not recovered". The action taken for bosutinib was unknown; for imatinib mesilate was dosage not changed.

Asthenia was documented as chronic since 05Jul2021. Asthenia was rated grade 1.

The reporter considered "asthenia" not related to bosutinib and related to concomitant drug GLIVEC.

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

Follow-up (25Apr2023): 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: updated event verbatim (from Chronic asthenia to Asthenia), updated event onset date (from 05Jul2021 to 06May2020), concomitant medication (SPRYCEL), start date and ongoing therapy status for GLIVEC.

Case Comment: In concurrence with the reporter, the reported asthenia is unrelated to the study drug bosutinib. The patient's other medication may provide an explanation for the event.

| From/To Dates | Type of History / Notes | Description |
|---------------|-------------------------|----------------------------------|
| Unknown | Relevant Med History | Endarterectomy (Endarterectomy); |

| | | | | | CIOMS FORM | | | | | | | |
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| SUSPECT ADVERSE REACTION REPORT | | | | | | | | | | | | |
| COOLEGE ADVENCE REACTION REPORT | | | | ļ | | | | | | | | |
| | | | | | | | | | | | | |
| | I. REACTION INFORMATION | | | | | | | | | | | |
| 1. PATIENT INITIALS | 1a. COUNTRY | | 2a. AGE | 3. SEX 3a. WEIGHT 4-6 REACTION ONSET | 8-12 CHECK ALL | | | | | | | |
| PRIVACY | FRANCE | Day Month Year PRIVACY | 79 Years | Female 58.00 Day Month 22 AUG 2018 | APPROPRIATE TO ADVERSE REACTION | | | | | | | |
| 7 + 13 DESCRIBE REACTIO Event Verbatim [PREFERREI Diffuse pain [Pain] | N(S) (including relevant t D TERM] (Related sympt | tests/lab data) toms if any separated by commas) | | PATIENT DIED INVOLVED OR | | | | | | | | |
| Case Description: O UNDER REAL-LIFE | | | FICACY AND SAFETY OF BOSULIF | PROLONGED INPATIENT HOSPITALISATION | | | | | | | | |
| | 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) | | | | | | | | | | | | |
| II. SUSPECT DRUG(S) INFORMATION | | | | | | | | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) #1) Bosutinib (BOSUTINIB) Unknown | | | | 20. DID REACTION ABATE AFTER STOPF DRUG? | | | | | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, 1x/day | | | | ROUTE(S) OF ADMINISTRATION 1) Unknown | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown | E | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| | | | | 9. THERAPY DURATION 1) 7 days | | | | | | | | |
| | | III. CONCOMITA | ANT DE | RUG(S) AND HISTORY | | | | | | | | |
| 22. CONCOMITANT DRUG(S | 3) AND DATES OF ADMI | INISTRATION (exclude those used | d to treat read | ction) | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| 23. OTHER RELEVANT HIST From/To Dates Unknown | rORY. (e.g. diagnostics, a | allergies, pregnancy with last month Type of History / Notes Relevant Med Histo | | etc.) Description None () | | | | | | | | |
| | | | | | | | | | | | | |
| | | IV MANUFA | | ER INFORMATION | | | | | | | | |
| 24a. NAME AND ADDRESS (| OF MANUFACTURER | 1 7. 1717 (1 401 7) | 101011 | 26. REMARKS | | | | | | | | |
| Pfizer Inc Stella Pietrafesa 66 Hudson Boulevard New York, NY 10001 Phone: 212 733 4045 | UNITED STATES | | | | | | | | | | | |
| | 24b. MFR COM | NTROL NO. | | 25b. NAME AND ADDRESS OF REPORTER | | | | | | | | |
| | 20220040 |)0652 | | NAME AND ADDRESS WITHHELD. | | | | | | | | |
| 24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT STUDY | 24d. REPORT SOURCE NAME AND ADDRESS WITHHELD. ▼ASTUDY | | | | | | | | | | |
| 10-MAR-2022 | ₩ HEALTH PROFESS | ш | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPORT | TYPE FOLLOWUP: | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 79-year-old female patient (unknown if pregnant) received bosutinib (BOSUTINIB), from 19Apr2016 to 25Apr2016 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: PAIN (non-serious) with onset 22Aug2018, outcome "recovered" (22Nov2018), described as "Diffuse pain".

Additional information: The event 'diffuse pain' was rated grade 1. The patient complained of diffuse pain during the consultation on 22Aug2018. The patient has then been on therapeutic abstention for 5 months. These pains are not described during the following consultation on 22Nov2018.

The reporter considered "diffuse pain" not related to bosutinib.

Case Comment: Based on the information currently available, there is not a reasonable possibility that the event "Diffuse pain" is related to the suspect drug, but most likely represents patient intercurrent medical condition.

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| SUSPECT ADVERSE REACTION REPORT | | | | | | | | | | | | | | | | | | | |
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| | | 1 | | | | MATION | $\overline{}$ | 4 | | | | ı. | | | | | | | |
| 1. PATIENT INITIALS (first, last) PRIVACY | 1a. COUNTRY FRANCE | 2. DATE O Day Mont PRIV | h Year | 74 Years | 3. SEX Male | за. WEIGHT Unk | Day 19 | , | Mont JUI | | Yea 202 | ır | 8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION | | | | | | |
| 7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [PREFERRED TERM] (Related symptoms if any separated by commas) branch occlusion retinal vein occlusion eye right [Retinal vein occlusion Hypertension [Hypertension] | | | | | | patient died involved or prolonged inpatient Hospitalisation | | | | | | | | | | | | | |
| Case Description: UNDER REAL-LIF | OBSERVATIONA E CONDITIONS | L STUDY - E OF USE | VALUATIO | ON OF E | FFICACY | AND SAF | ETY (| OF I | BOS | ULIF | = | | INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR | | | | | | |
| This is a non-interv reporter(s) (Physic | | | | | Study) red | ceived from | n cont | acta | able | | | | | | APACIT | Υ | | | |
| | | | | | (Cont | inued on Ad | dition | al Inf | forma | ation I | Pag | e) | ☐ ¦ | JIFE ΓHR | EATEN | IING | | | |
| | | II. S | SUSPEC | T DRU | G(S) IN | IFORMA | TIOI | N | | | | 1 | | _ | | | | | |
| 14. SUSPECT DRUG(S) (include generic name) #1) Bosulif (BOSUTINIB) Film-coated tablet | | | | | | | | | 20 | | TE A | CTION AFTER | | PPING | G | | | | |
| 15. DAILY DOSE(S) #1) 500 mg, daily | | | | | 16. ROUTE(S) #1) Unkno |) OF ADMINIST OWN | TRATION | V | | | | YES NO NA | | | | | | | |
| 17. INDICATION(S) FOR USE #1) Unknown | | | | | | | | | | | | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? | | | | | | | |
| 1 | | | | 19. THERAPY #1) 27 day | | | | | | | | YES NO NA | | | | | | | |
| | | III. CO | NCOMIT | TANT C | RUG(S |) AND H | IISTO | OR' | Y | | | | | | | | | | |
| 22. CONCOMITANT DRUG | | MINISTRATION (ex | xclude those us | | _ | | | | | | | | | | | | | | |
| "., === (| | , , 3 | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | |
| 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 Cataract (Cataract) | | | | | | | | | | | | | | | | | | | |
| | | | ▼ | | | | | | | | | | | | | | | | |
| | | IV. | MANUF | -ACTUI | RER IN | FORMAT | TION | 1 | | | | | | | | | | | |
| 24a. NAME AND ADDRESS Pfizer Inc Stella Pietrafesa 66 Hudson Bouleva New York, NY 1000 Phone: 212 733 404 | rd East 1 UNITED STATE | | | | 26. REM | MARKS | | _ | | | _ | | | _ | | | | | |
| | | ONTROL NO. | | | l l | ME AND ADD | | | | | | | | | | | | | |
| 24c. DATE RECEIVED | 2022004 24d. REPOR | | | | NAME AND ADDRESS WITHHELD. NAME AND ADDRESS WITHHELD. | | | | | | | | | | | | | | |
| 25-APR-2023 | STUDY HEALTH PROFE | | LITERATURE OTHER: | | The same with the same of the | | | | | | | | | | | | | | |
| DATE OF THIS REPORT 27-FEB-2024 | 25a. REPOR | | FOLLOWUP: | | | | | | | | | | | | | | | | |

7+13. DESCRIBE REACTION(S) continued

A 74-year-old male patient received bosutinib (BOSULIF), from 07Nov2019 to 03Dec2019 at 500 mg daily. The patient's relevant medical history included: "diabetes type 2" (ongoing); "Cataract" (unspecified if ongoing); "AMD" (ongoing); "Glaucoma" (ongoing). Concomitant medication(s) included: GLIVEC.

The following information was reported: HYPERTENSION (non-serious) with onset 19Jun2020, outcome "recovered" (20Jun2020); RETINAL VEIN OCCLUSION (hospitalization) with onset 15Jul2021, outcome "recovered" (01Feb2022), described as "branch occlusion retinal vein occlusion eye right". The action taken for bosutinib was dosage not changed. Therapeutic measures were taken as a result of retinal vein occlusion.

Clinical course: Vitrectomy done in ambulatory. On 25Apr2023, was reported intravitreal hemorrhage due to occlusion of retinal vein branch occlusion complicated by a macroaneurysm plus non vascular glaucoma glaucoma (history) stage I with iridial rubeosis in the iridocrone angle and proliferative diabetic retinopathy without ocular hypertonia (history of T2D). 1st intervention 09Nov2021 surgery (ambulatory) by vitrectomy plus retinal panphotocoagulation operative follow-up marked by massive recurrence of intravitreal hemorrhage, with no spontaneous favorable evolution. 2nd operation (ambulatory) 01Feb2022 additional dissection of the neovascular veils of retinal panphotocoagulation and placement of silicone oil. Favorable outcome.

The event retinal vein occlusion was rated grade 3 serious due to hospitalization, and hypertension was rated grade 3 non-serious.

The reporter considered "branch occlusion retinal vein occlusion eye right" and "hypertension" not related to bosutinib or to any concomitant drug.

Follow-up (21Mar2022). This follow-up is received from the investigational site via CRO. Updated information included: recovery date of event hypertension was 20Jun2020 (not 20Jun2021).

Follow-up (25Apr2023): This is a follow-up non-interventional study report (Post Authorization Safety Study) received from the investigational site via the CRO for protocol B1871047.

Updated information included: reporter details, RMH, event 'Vitreous haemorrhage' recoded to 'Retinal vein occlusion', outcome, seriousness and clinical course.

Case Comment: Based on the information available, the reported branch occlusion retinal vein occlusion eye right and hypertension are unrelated to the study drug bosutinib. The events occurred more than 6 months after the last dose of bosutinib was administered.

| From/To Dates | Type of History / Notes | Description | |
|--------------------|-------------------------|---|--|
| Unknown to Ongoing | Relevant Med History | Age-related macular degeneration (Age-related macular | |
| | | degeneration); | |
| Unknown to Ongoing | Relevant Med History | Glaucoma (Glaucoma); | |