EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 January 2022
EMA/126509/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bosulif

International non-proprietary name: bosutinib

Procedure No. EMEA/H/C/002373/II/0050/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment	
Description	**Date**
Start of procedure	19 Jul 2021
CHMP Rapporteur Assessment Report	20 Aug 2021
PRAC Rapporteur Assessment Report	18 Aug 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC endorsed relevant sections of the assessment report	02 Sep 2021
CHMP members comments	06 Sep 2021
Updated CHMP Rapporteur Assessment Report	n/a
Request for supplementary information	16 Sep 2021
Submission of MAH's responses	14 Oct 2021
Re-start of procedure	18 Oct 2021
CHMP Rapporteur Assessment Report	6 Dec 2021
PRAC Rapporteur Assessment Report	19 Nov 2021
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC endorsed relevant sections of the assessment report	02 Dec 2021
CHMP members comments	06 Dec 2021
Updated CHMP Rapporteur Assessment Report	15 Dec 2021
2nd Request for supplementary information	16 Dec 2021
Submission of MAH's responses	22 Dec 2021
Re-start of procedure	29 Dec 2021
CHMP Rapporteur Assessment Report	18 Jan 2022
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	n/a
Opinion	27 Jan 2022

Table of contents

1. Background information on the procedure

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 25 June 2021 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	Type IA	I
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

(Type II) C.I.4 - Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect results from studies B1871039 (specific obligation) and B1871040 (post-authorisation safety study); The Package Leaflet is updated accordingly. An updated RMP (version 6.1) has also been submitted.
Update of Annex II to remove the specific obligation and conversion of the conditional marketing authorisation into a marketing authorisation not subject to specific obligations. Section 5.1 of the SmPC and Section 6 of the PL are updated accordingly to remove the reference to the conditional marketing authorisation. In addition, the SmPC was updated to reflect the deletion of the product from the list of medicines subject to additional monitoring.
(Type IA) A.6 - Update of the ATC code in section 5.1 of the SmPC according to the new WHO classification.
In addition, the MAH took the opportunity to update the list of local representatives for Belgium, Luxemburg, Germany and Northern Ireland in the Package Leaflet.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP – latest version 6.1).

2. Overall conclusion and impact on the benefit/risk balance

At time of approval, the second generation tyrosine kinase inhibitor(s) (TKIs) Bosutinib has been considered efficacious in CML patients, but efficacy for the currently approved last-line indication was only shown in a very limited population selected retrospectively from an exploratory study. Thus, this efficacy have been further explored prospectively in a larger population in study B1871039 which was imposed at the time of initial approval as specific obligation in the context of a Conditional Marketing Authorization. With this procedure new confirmatory data from the post approval Study B1871039 (specific obligation) were submitted. This trial was a single arm, open-label, non-randomized, multi-center Phase 4 study to evaluate bosutinib in participants with chronic or advanced chronic phase (CP)/accelerated phase (AP)/blast phase (BP) Ph+ CML who were resistant or intolerant to prior treatment with commercially available tyrosine kinase inhibitor(s) (TKIs) or who were otherwise not candidates for treatment with commercially available TKIs such as imatinib, dasatinib, and nilotinib (ie., presence of a BCR-ABL1 mutation or medical condition making commercially available TKIs unsuitable for a participant).

The new data presented in the final clinical study report of this study (B1871039) and assessed in the ongoing variation EMEA/H/C/002373 /II/0050/G confirm that the second generation TKI Bosutinib is efficacious in CML patients in the approved late/last-line indication as defined above and reasonably

presumed at the time of approval. Therefore, the applicant has fulfilled the last remaining specific obligation for approval and generated sufficient confirmative data on efficacy and safety in the last line indication.

With respect to the newly available safety results from Study B1871039, they are similar to that observed for bosutinib as reported in the SmPC and for the approved 500 mg dose in particular. No new safety signals were detected from this study.

CMA approval for this indication was subject to specific obligations in order to generate sufficient data on efficacy and safety in the last line indication. This data from trial B1871039 (specific obligation)(hereafter referred to as Study 1039) together with data from Study B1871040 (Category 3 study) (hereafter referred to as Study 1040) confirm the positive benefit-risk balance stated at the time of the conditional approval of Bosulif.

Thus, the MAH has now fulfilled the specific obligation in Annex II. Therefore the deletion of the SOB from annex II of the PI and conversion of the conditional marketing authorisation into a marketing authorisation no longer subject to specific obligation can be approved. All the rest of changes in the SmPC and Package leaflet, including the update of the ATC code per the new WHO classification, are also acceptable.

The benefit-risk balance of Bosulif remains positive in both indications:

for the treatment of adult patients with: CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. (Conditional approval on 27 March 2013):

as well as in the indication:

for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) [approved on 23 April 2018.]

In conclusion, the group of variations can be approved.

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB
A.6	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	Type IA	I
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

(Type II) C.I.4 - Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to reflect results from studies B1871039 (specific obligation) and B1871040 (post-authorisation safety study); The Package Leaflet is updated accordingly. An updated RMP (version 6.0) has also been submitted.
Update of Annex II to remove the specific obligation and conversion of the conditional marketing authorisation into a marketing authorisation not subject to specific obligations. Section 5.1 of the SmPC and Section 6 of the PL are updated accordingly to remove the reference to the conditional marketing authorisation. In addition, the SmPC was updated to reflect the deletion of the product from

the list of medicines subject to additional monitoring.
(Type IA) A.6 - Update of the ATC code in section 5.1 of the SmPC according to the new WHO classification.
In addition, the MAH took the opportunity to update the list of local representatives for Belgium, Luxemburg, Germany and Northern Ireland in the Package Leaflet.

is recommended for approval.

As a consequence, pursuant to Article 14-a(8) of Regulation No 726/2004 and following the fulfilment of all remaining Specific Obligations, the CHMP recommends the granting of a marketing authorisation in accordance with Article 14(1) of Regulation No 726/2004.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

The following obligation has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the Opinion:

Description	Due date
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Final Clinical Study Report: 31 May 2022

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Bosulif-H-C-002373-II-0050/G'

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Bosutinib (compound number: SKI 606), a substituted 4-anilinoquinolone-3-carbonitrile, is an oral, potent, and selective tyrosine kinase inhibitor (TKI). The molecular formula is C26 H29 Cl2 N5 O3 ☐ H2O, the weight is 548.46 (monohydrate); 530.45 (anhydrous), and the chemical name is: -[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile monohydrate.

Mechanism of Action

Bosutinib is a tyrosine kinase inhibitor (TKI) that has very potent inhibitory activity against SRC and ABL kinases and to a lower degree activity against other serinethreonine/tyrosine kinases (Boschelli 2001). The use of chemical proteomics technology identified more than 45 novel tyrosine and serine/threonine kinases targeted by bosutinib (Remsing, 2009).

Bosutinib also inhibits Lyn, Hck, PDGFR (minimally), c-Kit (minimally), c-Fms, Tec family receptors, EphA and B receptors, Trk family kinases, Axl family kinases, some members of the ErbB family, the non-receptor tyrosine kinase Csk, serine/threonine kinases of the Ste20 family, AMPK and two calmodulin-dependent protein kinases. Furthermore, bosutinib is not a substrate for ABC transporters. Bosutinib inhibits SRC kinase with an IC50 of 1.2nM and ABL kinase with an IC50 of 1 nM (Boschelli, 2008). SRC, a nonreceptor protein tyrosine kinase, belongs to a broader class of structurally related kinases which function as regulators in various signal transduction pathways triggered by multiple surface receptors. This broader class of SRC family kinases (SFKs) are involved in BCR-ABL signalling and thus the development and progression of chronic myelogenous leukemia (CML) (Boschelli, 2008; Remsing, 2009). Bosutinib inhibits the abnormal BCR-ABL kinase that promotes CML.

Therapeutic indications

On 27 March 2013 Bosulif® (hereafter referred to as bosutinib) received a conditional Marketing Authorization (MA) for the **treatment of adult participants with CP, AP, and BP Ph+ CML previously treated with one or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options**, with the requirement of the conversion to full MA based on the submission of final clinical study report of study **B1871039 (hereafter referred as 1039)** a single-arm open-label, multi-center efficacy and safety study of bosutinib in participants with Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

At the time of bosutinb initial MA application, the last line indication was approved based on data in post-hoc defined subpopulation of patients with an unmet medical need from 3160A4-200-WW (B1871006). The pivotal study B1871006 was an open-label, uncontrolled efficacy and safety phase I/II study of bosutinib in Ph+ leukaemia. It was performed to explore whether bosutinib has some efficacy in second and third line CP-CML-patients as well as in some of those with more advanced CML stages (AP-CML and BP-CML). During approval for the last-line indication efficacy data for a subpopulation of 52 patients, defined post hoc, was claimed as pivotal. Bosutinib also provided clinical benefit to patients in the CU setting, derived from patient narratives provided by the treating physicians, which included patients who had exhausted all available TKI therapies or for whom treatment with other available TKI(s) was deemed unsuitable by their physicians.

The present submission provides a comprehensive evaluation of final efficacy and safety results from 4-year follow-up data Study 1039 (specific obligation) and 10-year data analysis from Study 1040 (Category 3) supporting the use of bosutinib at 500 mg once daily, for the treatment of CP, AP, and BP Ph+ CML previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options and supports updates to the product information efficacy and safety sections based on those studies and the all-leukemia pool analysis.

The Rapporteur agrees that these results continue to show that bosutinib has demonstrated clinically meaningful efficacy and a manageable safety profile in participants with previously treated CML.

TABLE 1. LISTING OF ALL STUDIES INCLUDED IN THIS REGULATORY SUBMISSION

Protocol No. (Country)/Study Start/Status	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group) (No. of Subjects)	Duration of Treatment
Clinical Study Reports Pertinent to Clinical Efficacy and Safety					
B1871039 (Multinational)/ FSFV: 07 Nov 2014 LSLV: 13 Oct 2020 Status: Completed	A Phase 4 Safety and Efficacy Study of Bosutinib (Bosulif®) in Patients with Philadelphia Chromosome Positive Chronic Myeloid Leukemia Previously Treated with One or More Tyrosine Kinase Inhibitors	Bosutinib (Route: Oral; Dose Regimen: 500 mg once daily)	Treated: 163 (Full Analysis Set)	Full Analysis Set: Sex: 88 M/75 F Median Age (min/max): 61 (20/89) years Race: W/B/A/O: 143/4/1/15	The Safety Population is the same as the Full Analysis Set: (n=163) Median: 37.80 months (range: 0.16-50.07)
B1871040 (Multinational)/ FSFV: 28 Aug 2013 LSLV: 05 Jun 2020 Status: Completed	An Open-Label Bosutinib Treatment Extension Study for Subjects with Chronic Myeloid Leukemia who have Previously Participated in Bosutinib Studies B1871006 or B1871008	Bosutinib Route: Oral; Dose Regimen: Same dose administered at the time of completion of the respective parent study	Enrolled: 820 (Full Analysis Set) Treated: 818 (Safety Population) Study B1871040: of the 818 treated in either Studies B1871006 or B1871008, 260 enrolled in Study B1871040. Of the 260, 188 were treated in Study B1871040.	Full Analysis Set: Sex: 449 M/ 371 F Median Age (min/max): 52 (18/92) years Race: W/B/A/O[a]: 535/43/196/46	Safety Population (n=818): (Patients from Study B1871006 + B1871040 [n=570]) Median: 11.13 months (range 0.03-170.49) Safety population: (Patients from Study B871008 + B1871040 [n=248]) Median: 61.69 months (range 0.03-145.86)
Completed Study – Non-Interventional Study					

Protocol No. (Country)/Study Start/Status	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group) (No. of Subjects)	Duration of Treatment
B1871052 (UK, NL) Data collected between 19 Oct 2015 and 19 Jan 2017 Status: Completed	A Retrospective Observational Research Study to Describe the Real-World Use of Bosutinib in the United Kingdom	Bosutinib Route: Oral; Starting Dose Regimen: 100, 200, 300, 400, 500 mg once daily	Treated: 87	Sex: 47 M/40 F Median Age (min/max): 62.7 (24.8/90.1) years	Safety Population (n=87): Median:15.6 months (range:0.3-66.0)

Source: Clinical Study Report for Studies B1871039, B1871040 and B1871052 Abbreviations: A=Asian; B=Black; CSR=clinical study report; F=female; FSFV=first subject, first visit;; M=male; max=maximum; min=minimum;; NA=not applicable; NIS=Non-interventional study; No=number; NL=Netherlands; LSLV=last subject, last visit; O=other; PCD=primary completion date; W=White a. Other=45 other + 1 American/Alaskan Indian native

In February 2018, Bosulif® (hereafter referred to as bosutinib) was finally approved in the EU also for the treatment of adult patients with **newly diagnosed Ph+ CP CML** (1L indication) based on the data from the pivotal Study B1871053 (AV001; hereafter referred to as Study 1053).

The submission for the first line indication included 1-year data from Study 1053. Data from the primary endpoint, MMR at Month 12, demonstrated superiority of bosutinib over imatinib. Recently the applicant has provided also the 60 months follow-up data by November 2020 as committed during the approval and an update of the product information was agreed during variation procedure II48.

CHMP agreed with the MAH view that the available results allow to conclude that bosutinib has also a clinically meaningful efficacy in patients with newly diagnosed CP CML.

Post-marketing Experience

Bosutinib was first approved in the United States on 04 September 2012. Cumulatively, as of 03 March 2021 it was estimated that 36,053 patients worldwide had been exposed to bosutinib commercially since it was first approved.

It was estimated that 3058 participants worldwide had participated in Pfizer-bosutinib development program, 2456 participants of whom had been exposed to bosutinib as a single agent (n=2093), in combination with placebo, or in combination with other study drugs (n=305). In addition, 242 participants worldwide had been exposed to bosutinib on a compassionate use basis and 711 participants worldwide had been exposed to bosutinib via Pfizer-sponsored non-interventional studies.

No new safety signals were identified from the post-marketing data and the annual review of safety data as reflected by the previous renewal and PSUR assessments.

5.1. Clinical Aspects

Methods – analysis of data submitted

This application concerns the joint submission of final results from Study B1871039 (hereafter referred to as Study 1039), which is the Specific Obligation to conduct a single-arm, open-label, multi-center efficacy and safety study of bosutinib in participants with Ph+ CML previously treated with 1 or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, in order to convert the Conditional Authorization of bosutinib to Standard Marketing Authorization.

This application also includes results from the 10-year follow-up extension Study B1871040 (hereafter referred to as Study 1040) including newly diagnosed Ph+ CML participants from study B1871008 (hereafter referred to as Study 1008) and previously treated Ph+ leukemia participants from B1871006 (hereafter referred to as Study 1006), which is an additional pharmacovigilance activity category 3 study listed in the RMP.

Study 1039

Study 1039 was a single arm, open-label, non-randomized, multi-center Phase 4 study to evaluate bosutinib in participants with chronic or advanced CP/AP/BP Ph+ CML who were resistant or intolerant to prior treatment with commercially available TKIs or who were otherwise not candidates for treatment with commercially available TKIs such as imatinib, dasatinib, and nilotinib (ie., presence of a BCR-ABL1 mutation or medical condition making commercially available TKIs unsuitable for a participant).

The study protocol was agreed with CHMP as part of a post approval measure. The initial study was to include 150 participants with at least 75 in 4th or later line, however it was later amended to decrease the number of participants in the 4th or later-line cohort from the initial target of 75 to at least 45 participants (Study 1039 Protocol, Amendment 1). This was agreed by CHMP.

The difficulty in enrolling participants in 4th or later line was discussed with the Rapporteur, Co-Rapporteurs and EMA PL on 06 March 2017 (in the context of a pre-submission meeting to discuss suitability of Study AV001/1053 for extension of the indication to 1st line CML treatment).

The Rapporteur acknowledged the recruitment difficulties and indicated that it would be acceptable to stop the enrollment with 45 participants in 4th line cohort and the Co-Rapporteur recommended that the MAH conducts an in-depth analysis of recruitment feasibility and suggested to seek central scientific advice before terminating recruitment in the 4th line cohort.

Protocol assistance justifying closing recruitment in the 4th line cohort was sought and in July 2017, CHMP agreed with the MAH's proposal (EMEA/H/SA/3608/1/2017/PA/II). Therefore, the recruitment was closed on 11 September 2017 with a total of 163 participants of which 51 participants were treated in the 4th line setting. The entry of the last subject into the study was on 18 September 2017.

The initially proposed strategy to close early Study 1039 in November 2019 with approximately 3 years of follow-up was revised and the study was closed in October 2020 when at least 90% (n=148) of the 163 participants in the overall study population had already permanently discontinued the study (not due to study closure by the Sponsor) or had a minimum follow-up of 4 years and therefore had completed the required follow-up. The Rapporteur considered the proposal to close the study in October 2020, with a longer follow-up, acceptable.

Study 1039 was a single-arm, open-label, non-randomized, multicenter Phase 4 study evaluating bosutinib in participants with CP/AP/BP Ph+ CML who were resistant or intolerant to prior treatment with commercially available TKIs, or were otherwise not candidates for treatment with commercially available TKIs such as imatinib, dasatinib or nilotinib (ie, presence of a BCR-ABL1 mutation or medical condition making commercially available TKIs unsuitable).

Participants were to receive bosutinib for at least 4 years from the time of first dose until disease progression, unacceptable toxicity, participant withdrawal of consent, death, or sponsor discontinuation of study. Participants who discontinued bosutinib prior to completing at least 4 years of therapy were to be followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Key efficacy endpoints were:

<u>Primary Endpoints</u>**:**

- Cumulative confirmed MCyR defined as CCyR or PCyR by 1 year (52 weeks) in 2nd and 3rd line CP participants
- Cumulative confirmed MCyR by 1 year (52 weeks) in 4th and later line CP participants
- Cumulative confirmed OHR defined as CHR or RCP by 1 year (52 weeks) in AP andBP participants.

Secondary Endpoints**:**

- Cumulative MCyR in CP, AP, and BP participants
- Cumulative MMR, MR4, MR4.5 in CP, AP, and BP participants
- Duration of CCyR
- Duration of MMR

Study 1040

Study 1040 was a treatment extension study to allow the opportunity of long-term treatment with bosutinib for Ph+ leukemia participants who received bosutinib in Studies 1006 and 1008 and who were considered to derive clinical benefit from continued treatment with bosutinib.

Participants received the same bosutinib dose administered at the time of completion of the parent study. The PK analysis set included all participants treated with bosutinib and who had 1 reported bosutinib concentration.

To fulfill the MAH commitment from variation II/01 for analysis of the PK of bosutinib administered once daily, a total of 1 predose PK sample per subject was collected from all participants (except from those enrolled at sites in China) following at least 2 weeks of uninterrupted dosing with bosutinib at the same dose level.

Following at least 2 weeks of uninterrupted dosing with bosutinib at the same dose level, the geometric mean steady-state Ctrough of bosutinib ranged from 62.0 to 99.4 ng/mL for doses ranging from 200 mg to 600 mg. The geometric mean bosutinib Ctrough values observed in this study were similar to previous studies for doses ranging from 300 mg to 600 mg.

Study 1040 was a roll-over treatment extension study to allow the opportunity of long-term treatment with bosutinib for Ph+ leukemia participants who received bosutinib in Studies 1006 and 1008 and who were considered to derive clinical benefit from continued treatment with bosutinib. Participants enrolled included those who, at the time of this protocol approval, were still receiving bosutinib in either one of the parent studies and were benefiting from bosutinib treatment as judged by the investigator, as well as those participants who had already discontinued bosutinib as part of the parent studies and were in long-term follow-up for survival or had completed the parent study. The former group continued to receive bosutinib as part of the extension study; the latter group only entered into the long-term survival follow-up part of the extension study.

Each participant remained in the extension study, either on bosutinib treatment or in long-term survival follow-up, until the last participant reached 10 years of follow-up, as calculated from the date of his/her first dose of bosutinib administered in the parent study.

Data from the two parent studies were combined with the data from this study for the analysis. The 820 participants in Study 1040 analysis included 570 participants who were previously treated in Study 1006 and 250 participants who were previously enrolled in Study 1008.

Key efficacy endpoints were:

- Cumulative MCyR, CCyR, MMR and MR4 for Study 1006 participants only
- Duration of MCyR/CCyR for Study 1006 participants only
- Duration of MMR/MR4 for Study 1006 participants only
- Time to MCyR, CCyR, MMR, and MR4 for Study 1006 participants only
- PFS for Study 1006 participants only
- Transformation to AP/BP for Study 1006 participants only
- BCR-ABL1 mutations present at treatment discontinuation
- OS

5.1.1. Clinical Efficacy aspects

Results

Key efficacy results were:

Study 1039

- In Study 1039, the primary endpoint of cumulative confirmed MCyR by 1 year (52 weeks) was 76.5% in the CP2L/CP3L cohort and was 62.2% in the CP4L cohort. In both cohorts, majority of participants achieved a deeper response relative to baseline while on treatment with bosutinib, 69.4% and 57.8%, respectively. In the 4 participants with AP CML, the primary endpoint of cumulative confirmed OHR rate by 1 year (52 weeks) was 75.0%.
- In the Total CP cohort, the cumulative MCyR and CCyR rates at any time were 83.9% and 81.1%. Among participants without the respective baseline response, 59.4% and 63.5% achieved MCyR and CCyR, respectively.
- In the Total CP cohort, 71.8% of participants had at least MMR, with most participants having a deep molecular response as well, 59.7% and 48.3% had MR4 and MR4.5, respectively. Among participants without the respective baseline response, 59.5%, 52.7% and 42.7% achieved MMR, MR4, and MR4.5, respectively.
- The benefit of bosutinib was consistently observed across lines of treatment, including in participants treated in 4th line. The benefit of bosutinib was also observed in participants who were resistant or intolerant to prior treatment.
- In responders, the K-M probability of maintaining MCyR, CCyR, MMR and MR4 at Year 3 was 95.6%, 96.5%, 87.2%, and 80.7%, respectively.
- There were no on-treatment progressions to AP or BP among Ph+ CP participants.
- The OS rate in the Total CP cohort was high with a K-M probability of survival of 88.3% at Year 4.

Study 1040

1. The cumulative MCyR, CCyR, MMR and MR4 rates were 59.9%, 49.6%, 42.1% and 37.1%, respectively, in the CP2L cohort and were 42.0%, 32.1%, 17.8% and 15.0%, respectively, in the CP3L cohort. The corresponding rates were 37.0%, 28.8%, 11.9% and 10.3%, respectively, in the ADV cohort and 40.3%, 30.6%, 16.7% and 13.0% respectively, in the AP cohort.
2. Among responders in the CP2L cohort, the K-M probability of maintaining MCyR, CCyR, MMR, and MR4 at Year 10 was 65.3%, 63.4 %, 63.4%, and 60.8%, respectively. Similarly, in responders in the CP3L cohort, the K-M probability of maintaining MCyR, CCyR and MMR at Year 10 was 55.3%, 40.8%, and 70.0%, respectively. The K-M probability of maintaining MCyR, CCyR, and MMR at Year 10 in responders in the ADV cohort was 30.6%, 29.6%, and 66.0%, respectively, and 40.8%, 40.0%, and 66.7%, respectively, in the AP cohort.
3. The rate of on-treatment transformation to AP or BP was 5.3% and 4.2% in participants in the CP2L and CP3L cohorts, respectively. In participants with AP, 3.8% transformed to BP. Most transformations occurred during the first 3 years of treatment.
4. A favorable long-term survival was observed with bosutinib with a K-M probability of survival at Year 10 of 71.5%, 60.4%, and 34.2% in CP2L, CP3L, and ADV participants, respectively. In participants in the AP cohort, the OS rate at Year 10 was 50.7%.

5.1.2. Discussion of efficacy results

It is agreed with the applicant, that the efficacy results of Study 1039 further confirm the initial results of Study 1006 and the benefit of bosutinib in participants with previously treated CML. The 10-year follow-up of participants from Study 1006 demonstrated a favorable long-term efficacy with bosutinib.

5.1.3. Clinical Safety aspects

Key safety results:

Key safety results from **Study 1039** showed:

- In the Total CP cohort, the median duration of treatment for the overall population was 40.87 months and the median dose intensity was 306.35 mg/day. Across all time points, the most frequent daily dose was 500 mg from study start to Year 2 and 400 mg from Year 2 and onwards.
- The safety profile in this study was generally consistent with the known safety profile of bosutinib. There were no new safety signals identified.
- Most AEs associated with bosutinib treatment were manageable with dose reductions, dose interruptions and/or supportive medication.
- GI and liver-related AEs were frequent, however, no relevant differences in the frequency of these AEs was seen compared to other bosutinib studies in pretreated participants. The majority of participants were successfully rechallenged and were able to remain on treatment.
- While the incidence of certain AESIs such as cardiac, vascular, effusion and renal AESIs was higher than previously reported in other studies, the heavily pretreated nature of the

participants and the fact that approximately half (47.4%) were intolerant to all prior TKIs might have contributed to this higher incidence. In addition, participants in this study had a higher incidence of cardiac, vascular, effusion and renal medical history events than in other bosutinib studies. However, an analysis of these AESIs did not identify any new safety signals and overall, the majority of participants with AESIs were able to remain on treatment.

- In the Total CP cohort, there were 17 (10.9%) participants who died on study. The OS rate at Year 4 was 88.3%, results were similar across lines of therapy. The median duration of follow-up was 47.81 months (Table 12). Of the 17 participants in the Total CP cohort who died on study, 2 (11.8%) participants died due to CML and 15 (88.2%) participants died either due to an unknown reason or due to other reasons. No AP participants died on study and 2 Ph- participants died on study, within 28 days of last dose due to unrelated AEs

Key long-term safety results from **Study 1040** showed:

- The median duration of treatment was 61.69 months in the CP1L cohort and 11.13 in the Total 2+ L cohort. The corresponding median dose intensity was 462.57 mg/day and 442.02 mg/day respectively. In the Total 2+ L cohort, for every year, the majority (≥55%) of the participants were receiving high doses (≥500 mg/day) of bosutinib at the beginning of each year.
- The safety profile of bosutinib in this study was consistent with the known safety profile of bosutinib and the information contained in the current product label. There were no new safety signals identified with long-term follow-up (≥10 years).
- Overall, bosutinib was well-tolerated with toxicities that were manageable by dose interruption, dose reduction, and/or standard medical therapy and were mostly reversible.
- An analysis of the AESIs did not identify any new safety signals with longer follow- up. While GI and liver-related AEs were frequent, the majority of participants were successfully rechallenged and were able to remain on long-term treatment. Compared to the AESI incidence in the parent studies, there was a slight increase in the overall incidence of cardiac, vascular, effusion, and renal AESIs with longer time on treatment. However, the type of events was overall consistent with the parent study results and no new safety signals were identified.
- Results from all-leukemia pool showed that the safety results were generally consistent with the known safety profile of bosutinib.

5.1.4. Discussion of Safety results

Assessor's comment

The Rapporteur agrees with the applicant that according the now available data Bosutinib has a well characterized safety profile that is distinct from other TKIs. This view is confirmed by the long-term data now available, showing the absence of new safety signal. Insofar, it could be agreed that the AEs associated with bosutinib treatment were manageable with dose reductions/dose interruptions and/or supportive medication.

Nevertheless, a summary table regarding efficacy as well as safety, which allows to compare directly the data at the time of the conditional marketing authorization and those now available from the specific obligation trial as well as from the current analyses presented was missing. The applicant was

requested to provide this table to allow a comprehensible overview of differences occurred. (Issue resolved by Response to request for supplementary information.)

6. Risk management plan

The MAH submitted an updated RMP version with this application. The main proposed RMP changes were the following:

RMP Part/Module	Major Change(s)
PART I. PRODUCT OVERVIEW	No updates.
PART II. SAFETY SPECIFICATION	
PART II. Module SI. Epidemiology of the Indications and Target Populations	Epidemiology data updated to the new data lock point (01 January 2021).
PART II. Module SII. Non-Clinical Part of the Safety Specification	No updates.
PART II. Module SIII. Clinical Trail Exposure	Clinical trial exposure updated to the new data lock point (01 January 2021).
PART II. Module SIV. Populations Not Studies in Clinical Trials	Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme Table updated.
PART II. Module SV Post-Authorisation Experience	Post-marketing exposure updated to the new data lock point (01 January 2021).
PART II. Module SVI. Additional EU Requirements for the Safety Specification	No updates.
PART II. Module SVII. Identified and Potential Risks	Characterisation of risks updated with CT data (DLP 01 January 2021). MAH added justification for risk removal.
PART II. Module SVIII Summary of the Safety Concerns	Updated proposing removal of the important identified risks, important potential risk and missing information except for use in paediatric patients.
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Removed B1871039, B1871040, B1871048 as these studies are now complete. In addition, removed Investigation of the Real-World Use of CYP3A4 Inhibitors, CYP3A4 Inducers, and PPIs with Bosutinib as the investigation is complete.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	Removed B1871039 as this study is now complete.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	No updates.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Updated additional pharmacovigilance activities.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Updated the annexes of the RMP.

Safety Specification

The MAH proposed to remove the following safety concerns:

As a result of the completion of CT B1871039, CT B1871040, and the analysis of the all leukaemia pooled studies (B1871053, B1871008, B1871006, B1871007, B1871039, B1871048) and any agreed additional pharmacovigilance activities such as NIS B1871052 and B1871048, no new important

identified or potential risks have been observed for bosutinib since the last EU RMP (version 5.0, HA approved 03 September 2020).

Therefore, the MAH is proposing to remove the following important identified risks Hepatotoxicity, Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting), SJS/TEN, QT prolongation, Renal Dysfunction, Increased Toxicity Due to Interactions with CYP3A4 Inhibitors, Lack of Efficacy Due to Interactions with CYP3A4 Inducers, Lack of Efficacy Due to Interactions with PPIs) and the important potential risk of Cardiac Toxicity (Excluding QT Prolongation). The risks are well characterised with exposure data from 1372 patients in all-leukaemia pool and an estimated worldwide bosutinib exposure to 35,317 patients since approval. In addition, there are no outstanding additional pharmacovigilance or risk minimisation activities and there is no reasonable expectation that any pharmacovigilance activity can further characterise the risks or further characterisation of the risks is not expected to result in additional risk minimisation activities beyond what is already described in the SmPC. The risks are well known to healthcare professionals as well as a common risk in the patient population and are appropriately communicated in the SmPC. The risks will continue to be characterised via routine pharmacovigilance.

Assessor's comment

The MAH proposes to remove several risks from the initial list of safety concerns and does not identify or add any new important risks. Briefly, the important identified risks Hepatotoxicity, Gastrointestinal Toxicities (GI) (Diarrhoea, Nausea, Vomiting), Stevens-Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis event (TEN), QT prolongation, Renal Dysfunction, Increased Toxicity Due to Interactions with CYP3A4 Inhibitors, Lack of Efficacy Due to Interactions with CYP3A4 Inducers, Lack of Efficacy due to Interactions with Proton Pump Inhibitors (PPIs)), and the important potential risk of Cardiac Toxicity (Excluding QT Prolongation) should be removed from the RMP since they have been evaluated in two recently finalized CT s. Furthermore, data from bosutinib-related, pooled leukemia studies were also assessed for the updated risk evaluation.

The aforementioned risk are listed in the Summary of Product Characteristics (SmPC) and there are no efforts for further in-depth characterization via additional pharmacovigilance activities, currently.

Concerning hepatotoxicity, 38,8% of the patients included in the leukemia studies had at least one hepatic AESI that was detectable by augmented Alanine Aminotransferase, Aspartate Aminotransferase, or blood alkaline phosphatase, respectively. Interestingly, the incidence of liver-related AESI s was higher in newly diagnosed patients compared to pretreated patients. In general, hepatotoxicity was manageable with dose reductions/interruptions and standard medical therapy and few led to permanent treatment discontinuation. Since the median time to first event was 29.0 days, the risk of bosutinib-induced hepatotoxicity can be reduced with liver function tests prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated. Therefore, the hepatotoxicity as an important identified risk for bosutinib can be removed from the RMP and will continuously monitored via routine pharmacovigilance.

Gastrointestinal toxicities (Diarrhea, Nausea, Vomiting) were reported in 85.8% of the patients in all leukemia studies. The most frequent GI AESIs were diarrhea (80.4%), nausea (41.5%), and vomiting (33.7%). The majority of gastrointestinal events were Grade 1 or 2 in severity and manageable with dose reductions/interruptions and/or standard medical therapy and few led to permanent treatment discontinuation. Product labelling recommends patients with recent or ongoing clinically significant gastrointestinal disorder should use bosutinib with caution and only after a careful benefit-risk assessment as respective patients were excluded from the clinical studies. The gastrointestinal-related

risks are extensively characterized and minimized through provision of relevant information on the PL. Thus, gastrointestinal toxicities can be removed from the RMP.

In all leukemia, bosutinib-related studies, 1.1% of patients had at least 1 SJS/TEN AESI although the frequency was higher in another CT (CT B1871048). Overall, 0.3% of patients permanently discontinued treatment due to SJS/TEN AESIs. The important risks associated to SJS/TEN are sufficiently minimized by provision of relevant information in the product label. Thus, SJS/TEN can be removed as an important identified risk and is continuously observed via routine pharmacovigilance.

In all leukemia, bosutinib-related studies, 1.3% of patients had at least 1 QT prolongation AESI. Overall, 0.1% of patients permanently discontinued treatment due to QT prolongation AESIs and there were no deaths due to QT prolongation. The important risks associated to QT prolongation are minimized through provision of relevant information in the product label. The proarrhythmic potential is described as a potential AE for bosutinib and patients who develop a QT prolongation should permanently discontinue bosutinib. Monitoring for an effect on the QT is advisable and a baseline electrocardiogram (ECG) is recommended prior to initiating therapy with bosutinib and as clinically indicated. Therefore, QT prolongation as an important identified risk can be removed from the RMP. The occurrence of QT prolongation events will be monitored via routine pharmacovigilance.

Renal impairment is a frequent AESI associated with bosutinib. In the pooled leukemia studies, 14,8% of the patients had at least 1 renal dysfunction AESI. This important and identified risk is characterized and a renal function assessment prior to treatment initiation and during treatment is recommended in the SmPC. Especially patients who have a pre-existing renal compromise or who are using medicinal products with the potential nephrotoxic side effects should have an assessment of renal function prior to bosutinib treatment. The relevant information are provided in the product label and can be deleted from RMP. The risk of renal dysfunction is further monitored by routine pharmacovigilance.

The concomitant use of bosutinib with strong or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur. In the pooled leukemia, bosutinib-related studies, patients who received bosutinib and a CYP3A4 inhibitor suffered from diarrhea (85.1%), nausea (49.8%), rash (42.8%), vomiting (40.6%), thrombocytopenia (35.9%), anemia (31.9%), pyrexia (31.3%), and abdominal pain (31.1%). The risks associated to increased toxicity due to interaction with CYP3A4 inhibitors are described in the SMPC. Therefore, this important and identified risk can be removed and the risk is continuously monitored via routine pharmacovigilance.

The risks associated to lack of efficacy of bosutinib due to interactions with CYP3A4 inducers are described in the SmPC and the concomitant use of bosutinib with strong or moderate CYP3A4 inducers should be avoided (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin among many others). The MAH does not provide any new data concerning the simultaneous application of bosutinib and CYP3A4 inducers. However, since the relevant information are provided in the SmPC the risk can be removed and should be further evaluated by routine pharmacovigilance.

Concerning the simultaneous use of PPIs and bosutinib, the MAH found a 1.1% of patients with a report of lack of efficacy. Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated whenever possible. The information are accessible in the SmPC and the risk can be removed and followed up by routine pharmacovigilance.

Cardiac toxicity (excluding QT prolongation) is an important potential risk and 14.9% of patients included in the MAH´s bosutinib-related studies had at least 1 cardiac toxicity AESI. 20 patients died due to cardiac toxicity AESIs but, generally, cardiac toxicity AESIs were manageable with dose reductions or interruptions and few led to permanent treatment discontinuation. Since cardiac disorders are listed in the SmPC and are well-known, this important potential risk can be removed and will be followed by routine pharmacovigilance.

In summary, the proposed changes of the MAH are acceptable owing to the reason that the above listed identified and potential risks are known, included in the SmPC, and there are no additional pharmacovigilance activities required for further characterization.

Section SVII.3 should only describe details of current Important Identified Risks, Important Potential Risks, and Missing Information. The MAH is requested to update this section in line with the updated summary of safety concerns.

Summary of the safety concerns

Table 46. Summary of Safety Concerns

Important Identified Risks	~~Hepatotoxicity~~ ~~Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)~~ ~~SJS/ TEN~~ ~~QT Prolongation~~ ~~Renal Dysfunction~~ ~~Increased Toxicity Due to Interactions with CYP3A4 Inhibitors~~ ~~Lack of Efficacy Due to Interactions with CYP3A4 Inducers~~ ~~Lack of Efficacy Due to Interactions with PPIs~~
Important Potential Risk	~~Cardiac Toxicity (Excluding QT Prolongation)~~
Missing Information	Use in Paediatric[a] Patients ~~Safety in Patients with Cardiac Impairment~~ ~~Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders~~ ~~Long-Term Safety (>365 Days~~

a. age: ≤17 years

Considering the data in the safety specification, the safety concerns listed above are appropriate.

Assessor's comment

The MAH is requested to delete the removed safety concerns (strikethrough) from the Summary of safety concerns.

Pharmacovigilance plan

Table 47. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Phase 1/2 to assess the PK and to investigate safety and tolerability profile of bosutinib in the paediatric population (CT ITCC-054/AAML1921) Ongoing	The Phase 1 main objective is to determine the Recommended Phase 2 Dose of Bosutinib for $RP2D_{R/I}$ and $RP2D_{ND}$ paediatric patients with Ph+ CML. The Phase 2 main objectives are: To assess • The pooled safety and tolerability profile of bosutinib • The overall survival and safety parameters for up to 2 years • The bosutinib PK in paediatric patients with ND and R/I Ph+ chronic CML for up to 2 years after the LPFV • To describe the clinical efficacy of bosutinib in paediatric patients for up to 2 years after LPFV	Use in Paediatric Patients	CT being conducted by an external cooperative group as part of a Clinical Research Collaboration with the data to be transferred to the MAH. Final clinical study report	31 March 2024

Assessor's comment

The completed studies CT B1871039 (category 2 specific obligation study) and CT B1871040 (category 3 study) have been removed from the pharmacovigilance plan, which is endorsed.

Plans for post-authorisation efficacy studies

The fullfilled SOB clinical trial B1871039 was removed from the RMP.

Risk minimisation measures

No updates for Part V were proposed.

Assessor's comment

After the removal of safety concerns, Part V requires revision. Risk minimisation measures concerning risks that are not included in the summary of safety concerns should be deleted.

Summary of the risk management plan

The summary of the risk management plan needs to be updated inline with the revised summary of safety concerns and risk minimisation measures.

Annexes

The annexes have been updated appropriately.

6.1. Overall conclusion on the RMP

The changes to the RMP and the changes to the conditions and obligations of the MA are acceptable.

7. Changes to the Product Information

As a result of this group of variations, section(s) 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to reflect the new results from the studies B1871039 (SOB) and B1871040 (category 3). Section 5.1 was also updated with the new ATC code as per the WHO classification. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Changes are also made to the PI to bring it in line with the current QRD template version 10.2.

In addition, the list of local representatives for Belgium, Luxemburg, Germany and Northern Ireland in the PL is being revised.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

7.1.1. Additional monitoring

Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Bisulif (bosutinib) is removed from the additional monitoring list as the condition to the marketing authorisation/specific obligation(s) have been fulfilled.

Therefore, the statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information, preceded by an inverted equilateral black triangle, is removed from the summary of product characteristics and the package leaflet.

8. Benefit risk discussion

Favourable effects

In the indication for the treatment of adult patients with: CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. (Conditional approval on 27 March 2013):

Bosutinib is a second generation TKI that binds the kinase domain of Bcr-Abl, which is characteristic for Ph+ chronic myeloid leukemia (CML), in an intermediate conformation thereby inhibiting Abl kinase activity in vitro with an IC50 of 1 nM. In cell lines transfected with both wild type and imatinib-resistant mutant BCR-ABL it suppresses proliferation. In imatinib-sensitive CML cell lines, the in-vitro inhibitory activity of bosutinib is up to 100-fold that of imatinib, with IC50 values ranging from 1 to 20 nM. In imatinib-resistant cell lines (with or without mutations) bosutinib inhibited proliferation up to 114-fold that of imatinib. Bosutinib has been shown to inhibit phosphorylation of various signalling proteins and downstream substrates of Bcr-Abl, most notably the transcription factor Stat5 and the docking protein CrkL.

As Bosutinib failed in the pivotal Study 3000-WW to achieve the primary objective Complete Cytogenetic Response (CCyR) at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib, approval for the initially intended first-line CP-CML indication was not considered. For a second-line indication a comparative study for bosutinib against the EU-approved second line TKIs (dasatinib and nilotinib) was considered necessary for approval, which was not available. Therefore, only a last line indication based on data in post-hoc defined subpopulation of patients with an unmet medical need from study 200-WW was approved at the end.

The pivotal study 3160A4-200-WW was an open-label, uncontrolled efficacy and safety phase I/II study of bosutinib in Philadelphia chromosome-positive (Ph+) leukaemia. It was performed to explore whether bosutinib has some efficacy in second and third line CP-CML-patients as well as in some of those with more advanced CML stages (AP-CML and BP-CML). During approval for the last-line indication efficacy data for a subpopulation of 52 patients, defined post hoc, was claimed as pivotal.

Of the 52 patients identified, 36 patients were in the CP CML subpopulation (21 who had previously received 2 prior TKIs and 15 who had received 1 prior TKI). Of the 21 CP CML patients treated with bosutinib following failure of imatinib and 1 additional second-generation TKI identified, 9 of these patients had Major Cytogenetic Response (MCyR) or better including 2 patients with complete molecular response (CMR), 1 patient with major molecular response (MMR), 4 patients with CCyR, and 2 patients with partial cytogenetic response (PCyR) and had a treatment duration exceeding 24 weeks. In addition, 7 other patients had a complete hematological response (CHR) on bosutinib treatment. Among the 9 patients with a response of MCyR or better, duration of MCyR ranged from 8 to 204 weeks with a treatment duration ranging from 35 to 215+ weeks. There were 15 patients who received imatinib and no other second-generation TKI who met these criteria. Of these 15 patients with "unmet medical need" who had received prior imatinib only, 9 patients had a response on bosutinib treatment of MCyR or better, including 3 patients with CMR, 1 patient with MMR, 4 patients with CCyR, and 1 patients with PCyR with a duration of MCyR ranging from 12 to 155 weeks and a treatment duration ranging from 24 to 197+ weeks.

There was also a subpopulation of 16 advanced phase patients (5 AP CML and 11 BP CML patients) that failed treatment with either imatinib alone or imatinib in addition to one or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a

history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) were not considered appropriate treatment options. Of these, 4 of the 5 AP patients had notable treatment duration with a range from 46 to 114 weeks with responses including CMR (1 patient), CCyR (2 patients) and major haematologic response (MaHR) (1 patient) with 1 patient still on treatment. Among the 11 BP CML patients, 3 patients remained on treatment for more than 24 weeks with notable responses (2 patients with a CCyR and 1 patient with a MaHR) and a treatment duration ranging from 46 to 118 weeks with one patient still on treatment.

From the last updated analyses of the non- comparative observational open study 3160A4-200-WW (B1871006) with and chronic phase second and third-line Ph+ CML patients, the Kaplan-Meier (KM) probability of maintaining CHR at 5 and 4 years was 66% and 63% and that for maintaining MCyR reached at 5 and 4 years was 71% and 69% for CP2L and CP3L. This seems to confirm the view that bosutinib remains an clear option for patients not eligible for other second generation TKIs.

Based on the last analysis from the initial first line CML Study 3000-WW (B1871008; snapshot of 14 May 2014; ~≥48 months after last patients first visit, median (range) treatment duration ~ about 50 months) cumulative rates of CCyR were 79% and 81% for BOS and IM respectively, while the KM probability of maintaining CCyR at 4 years was 93% and 89%. Cumulative rates of MMR were 70% and 69% for BOS and IM respectively. The cumulative incidence of on-treatment transformation to AP/BP CML* at 4 years was 2.0% and 4.4% for BOS and IM, respectively; 37% and 27% of patients discontinued treatment prior to 4 years without an event. Differences between the two treatment groups are small and not significant. The slightly inferior outcome of bosutinib in comparison to imatinib might be explained by the higher level of toxicity comparable to that observed with other second generation TKIs (nilotinib and dasatinib). This issue obviously had a consistent confounding effect also on the new results, but is still in line with that what was already discussed during the initial MAA.

Bosutinib also provided clinical benefit to patients in the compassionate use (CU) setting, which included patients who had exhausted all available TKI therapies or for whom treatment with other available TKI(s) was deemed unsuitable by their physicians. This CU information, derived from patient narratives provided by the treating physicians, further underscores the value of bosutinib.

Now confirmative data from the post approval SOC trial Study 1039 were submitted. This trial was a single arm, open-label, non-randomized, multi-center Phase 4 study to evaluate bosutinib in participants with chronic or advanced CP/AP/BP Ph+ CML who were resistant or intolerant to prior treatment with commercially available TKIs or who were otherwise not candidates for treatment with commercially available TKIs such as imatinib, dasatinib, and nilotinib (ie., presence of a BCR-ABL1 mutation or medical condition making commercially available TKIs unsuitable for a participant).

The study protocol was agreed with CHMP as part of a post approval measure. The initial study was to include 150 participants with at least 75 in 4th or later line, however it was later amended to decrease the number of participants in the 4th or later-line cohort from the initial target of 75 to at least 45 participants.

By 52 weeks, 76.5% participants in the combined CP2L/CP3L cohort had cumulative confirmed MCyR, 69.4% of participants had achieved a deeper response relative to baseline, and 7.1% maintained their baseline response for at least 52 weeks.

By 52 weeks, 62.2% of participants in the CP4L cohort had cumulative confirmed MCyR, 57.8% achieved a deeper response relative to baseline, and 4.4% maintained their baseline response for at least 52 weeks.

Among participants without the respective response at baseline, 59.4% and 63.5% achieved MCyR and CCyR, respectively. Participants in earlier treatment lines achieved higher response rates than more heavily pretreated participants.

Among resistant vs intolerant participants without the respective response at baseline, 56.5% (95% CI: 34.5, 76.8) vs 66.7% (95% CI: 29.9, 92.5) and 58.8% (95% CI: 40.7, 75.4) vs 72.2% (95% CI: 46.5, 90.3) achieved MCyR and CCyR, respectively.

In the Total CP cohort, 71.8%, 59.7% and 48.3% of participants, attained or maintained MMR, MR4 and MR4.5, respectively. Participants in earlier treatment lines achieved higher response rates as well as deeper responses than more pretreated participants. The median time to CCyR among responders was 2.99 months (range: 0.30-17.63).

In the Total CP cohort, there were 17 (10.9%) participants who died on study. The OS rate at Year 4 was 88.3%, results were similar across lines of therapy. The median duration of follow-up was 47.81 months (Table 12). Of the 17 participants in the Total CP cohort who died on study, 2 (11.8%) participants died due to CML and 15 (88.2%) participants died either due to an unknown reason or due to other reasons. No AP participants died on study and 2 Ph- participants died on study, within 28 days of last dose due to unrelated AEs. OS at Year 4 was 88.0% (95% CI: 78.1, 93.6) in resistant participants and 88.6% (95% CI: 78.5, 94.1) in intolerant patents.

Indication for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) [approved on 23. April 2018.]

In the new pivotal trial AV001 for the first line indication treatment with bosutinib 400 mg once daily was statistically significant superior in reaching the primary endpoint of MMR at 12 months (48 weeks) in comparison to the comparator 400 mg imatinib [B: 47.2% vs I: 36.9%, 1-sided p-value=0.0100, mITT). Sensitivity analyses demonstrated that the improvement in MMR at 12 months in favor of bosutinib was maintained also in the ITT population.

Superiority with respect to in MMR rate in the bosutinib arm over the imatinib arm was also consistent at 18 months (B: 56.9% vs I:47.7%, 1-sided p-value=0.0208 in the mITT population; 56.7% vs 46.6%, 1-sided p-value=0.0099 in the ITT population) in the pivotal trial AV001. Pre-specified subgroup analyses by baseline characteristics of age, race, and gender in Study AV001 showed that the benefit of bosutinib treatment on the primary endpoint was consistent with the benefit of bosutinib treatment in the overall population.

Consistency of efficacy was confirmed by the outcome of the key secondary endpoint of CCyR by 12 months (48 weeks) which indicated a statistically significant superiority for bosutinib compared with imatinib (B: 77.2% vs I: 66.4%, 1-sided p value=0.0037).

Uncertainties and limitations about favourable effects

- *Uncertainty in the knowledge about the beneficial effects*

In the indication for the treatment of adult patients with: CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. (Conditional approval on 27 March 2013):

The new data presented in the final clinical study report of this study (B1871039) and assessed in the ongoing variation EMEA/H/C/002373 /II/0050/G confirm that the second generation TKI bosutinib is efficacious in CML patients in the approved late/last-line indication as defined above and reasonably presumed at the time of approval. Therefore, the applicant has fulfilled the last remaining specific

obligation for approval and generated sufficient confirmative data on efficacy and safety in the last line indication.

First line Indication: for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) [approved on 23 April 2018.]

None.

Unfavourable effects

The most common TEAEs of bosutinib included gastrointestinal events, predominantly diarrhoea; myelosuppression, mainly thrombocytopenia; and transaminase elevations, particularly ALT. Hepatotoxicity, gastrointestinal effects, renal impairment and cardiac arrhythmias are the most important toxicities associated with bosutinib.

From the data in the pivotal Study 200-WW the CHMP was of the opinion that the safety profile of bosutinib was manageable. And it was generally similar across all CML reference populations (CP, AP, and BP). However, taking into account safety results from Study 3000-WW (planned as pivotal for the first line indication), it was concluded that toxicity is clearly more pronounced than with imatinib.

Gastrointestinal toxicity of bosutinib was significant and diarrhoea was identified consistently as dose-dependent and dose-limiting for bosutinib in all clinical studies. However, it seems manageable with passage dose-interruption and when appropriate information is provided.

As with other TKI therapies for CML, myelosuppression events, including those of higher severity (Grade 3 or 4) were prevalent; however, they have been shown to be manageable with treatment modifications and supportive therapies.

Hepatic toxicity with bosutinib seemed primarily to involve isolated transaminase elevations, which occurred most frequently within the first 6 months of treatment. The subjects remained asymptomatic despite the laboratory abnormalities and the majority of subjects did not require treatment discontinuation, even though almost 30% of patients in bosutinib arm reported hepatic-related AEs that led to treatment interruption. There were no cases of permanent hepatic injury and no liver-related deaths in CML patients treated with bosutinib. However, Hy's law cases associated with the use of bosutinib are documented.

Pharmacokinetic studies have shown 2-fold increases of bosutinib exposure and elimination half-life in patients with hepatic impairment. Thus, bosutinib is contraindicated in patients with hepatic impairment.

Renal dysfunction was in addition added as a important identified risk for bosutinib following an extensive review of renal function data (eGFR over time) during the last observation period. These investigations were triggered by findings in a study in patients with pre-existing renal impairment due to a hereditary renal disease (ADPKD). In CML patients also a decline over time in eGFR can be observed during treatment with bosutinib; however, a similar decline is also seen in imatinib treated patients.

Additionally, a high rate of QTc-time prolongation related to drug exposure is a known risk. During the last 1-year PSUR reporting interval no serious AEs pertaining to this risk had been reported; however, there were 7 cases (all MC) reported in total from post-marketing sources which is in line with previous knowledge about this known risk.

Based on pharmacovigilance monitoring activities, there was no new safety information specific to bosutinib that contributed importantly to the risks of bosutinib.

The important risks associated with the use of bosutinib are adequately minimized through provision of relevant product information in the RSI to support safe use of the product. Risks have been evaluated in the context of the enumerated benefits of the product.

With respect to the now available safety results from Study 1039 are similar to that observed for bosutinib in general and for the approved 500 mg dose in particular. No new safety signals were detected from this study

In the Total CP cohort of trial 1039, the median duration of treatment for the overall population was 40.87 months and the median dose intensity was 306.35 mg/day. Across all time points, the most frequent daily dose was 500 mg from study start to Year 2 and 400 mg from Year 2 and onwards.

The safety profile in this study was generally consistent with the known safety profile of bosutinib. There were no new safety signals identified.

Most AEs associated with bosutinib treatment were proven to be manageable with dose reductions, dose interruptions and/or supportive medication. As known from the available data before, GI and liver-related AEs were confirmed to be frequent, however, no relevant differences in the frequency of these AEs was seen compared to other bosutinib studies in pretreated participants. The majority of participants were successfully re-challenged and were able to remain on treatment.

While the incidence of certain AESIs such as cardiac, vascular, effusion and renal AESIs was higher than previously reported in other studies, the heavily pretreated nature of the participants and the fact that approximately half (47.4%) were intolerant to all prior TKIs might have contributed to this higher incidence.

In addition, participants in this study had a higher incidence of cardiac, vascular, effusion and renal medical history events than in other bosutinib studies. However, an analysis of these AESIs did not identify any new safety signals and overall, the majority of participants with AESIs were able to remain on treatment.

Key long-term safety results from Study 1040 showed with a median duration of treatment was 61.69 months in the CP1L cohort and 11.13 in the Total 2+ L cohort. The corresponding median dose intensity was 462.57 mg/day and 442.02 mg/day respectively. In the Total 2+ L cohort, for every year, the majority (≥55%) of the participants were receiving high doses (≥500 mg/day) of bosutinib at the beginning of each year.

Also the safety profile of bosutinib during long term treatment in this study was consistent with the known safety profile of bosutinib and the information contained in the current product label. There were no new safety signals identified with long-term follow-up (≥10 years).

Overall, bosutinib adds a significant, but overall tolerable toxicities that were manageable by dose interruption, dose reduction, and/or standard medical therapy and were mostly reversible as already initially presumed. An analysis of the AESIs did not identify any new safety signals with longer follow-up.

Compared to the AESI incidence in the parent studies, there was a again slight increase in the overall incidence of cardiac, vascular, effusion, and renal AESIs with longer time on treatment. However, the type of events was overall consistent with the parent study results and no new safety signals were identified.

Uncertainties and limitations about unfavourable effects

Although gastrointestinal and particularly hepatic toxicity might be manageable with adequate control, as recommended in the approved product information, these risks need to be closely observed. The

limited additional data regarding the identified important risks confirmed that these risks are still adequately covered in the product information. As agreed previously, the overall impact of concomitant medication taken to control the toxicities needs to be considered in particular for patients with additional cardiovascular or renal risk factors as demonstrated in study B1871039 (specific obligation for approval) and B1871040 .

A proarrhythmic potential of bosutinib could not be fully excluded, although the thorough QT study was negative and data available from the PSURs seemed not to indicate a change in risk. However, as during the clinical development program in other studies clinically relevant QTc prolongations have been observed and patients with cardiac risk factors had been excluded from the clinical studies, bosutinib should furthermore be only administered with caution to patients who have a history of or predisposition for QTc prolongation. Monitoring for an effect on the QTc interval is recommended in the SmPC.

No other new safety signal in the approved population was derived from the final study report of trial B18711039 and 1040 as well as from the postmarketing analysis in the target population as discussed in the previous renewals; in particular no further case fulfilling so-called "Hy's law" was observed. Bosutinib is currently not intended for the use in the pediatric population.

Missing information for bosutinib consist of use of bosutinib in paediatric patients (age: <17 years), safety in elderly patients (age: >65 years), safety in patients with renal impairment, safety in patients with cardiac impairment, safety in patients with recent or ongoing clinically significant gastrointestinal (GI) disorders, and use of bosutinib in pregnant/lactating women; the preceding patient populations are in need of further characterisation regarding the use of bosutinib.

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

In the indication for the treatment of adult patients with: CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. (Conditional approval on 27 March 2013):

A sizeable proportion of patients fail to achieve responses with imatinib, dasatinib or nilotinib or develop intolerance due to intolerable toxicity with the available TKIs. This is a growing problem in the clinical management of CML patients. Bosutinib has been considered to be a possible treatment option for these patients, as it had shown that CP and advanced CML patients, who are resistant and/or intolerant to imatinib, dasatinib and nilotinib, had a clinically relevant benefit from treatment with this drug.

Bosutinib is associated with pronounced toxicity, particularly hepatotoxicity and gastrointestinal toxicity, however, the safety profile in the subpopulation with a high medical need and no other alternative at the time being was considered acceptable.

In Study 200-WW bosutinib was associated with a clinically significant benefit in the subpopulations of CP, AP, and BP CML patients, who were previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib were not considered appropriate. This effect was consistent also during the latest reporting period, which seemed to indicate a consistent long term benefit for this population.

At the time of approval, bosutinib was the only available TKI treatment option in this subpopulation and the toxicity profile was deemed acceptable. Thus, a positive benefit-risk balance in this subpopulation was concluded allowing conditional approval.

All relevant known safety issues are adequately included in the product information.

CMA approval for this indication was subject to specific obligations in order to generate sufficient data on efficacy and safety in the last line indication. This data from trial 1039 together with data from Study 1040 as provided confirm the positive benefit-risk balance stated at the time of the conditional approval of Bosulif.

Thus, the requested deletion of the SOB from annex II of the PI and request for conversion of the Conditional Marketing Authorisation to a Marketing Authorisation not subject to specific obligation can be approved.

First line - Indication for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) [approved on 23. April 2018.]

Based on significantly improved MMR and CCyR at 12 months, together with evidence of faster and deeper molecular responses observed with CCyR and MMR, bosutinib in the pivotal Study AV001 has demonstrated clinically relevant superior efficacy in comparison to the standard of care imatinib in the treatment of newly diagnosed patients with Ph+ CP CML.

The well-known safety risks associated with bosutinib treatment (most important: hepatotoxicity, gastrointestinal toxicity and myelotoxicity) were confirmed by the consistently higher TEAE, SAE, grade 3/4 event rates in the bosutinib arm. However, the only slightly higher permanent discontinuation rate for bosutinib indicated that these risks can be seen as tolerable and manageable in clinical practice due to the broad experience with these types of agents.

Therefore, in view of the robust efficacy benefit over standard treatment (imatinib) in terms of MMR at 12 months and the observed manageable toxicity, the benefit-risk balance in the proposed indication is considered positive.

Balance of benefits and risks

The benefit-risk balance of Bosulif remains positive in both indications:

for the treatment of adult patients with: CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. (Conditional approval on 27 March 2013):

as well as in the indication:

for the treatment of adult patients with newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) [approved on 23 April 2018.]

9. Request for supplementary information

9.1. Other concerns

Clinical aspects

1. Regarding the proposed changes in the Product information: The MAH is requested to submit a new PI on the basis of the final approved version of var II/48 and only highlight the changes that are submitted in var II/50/G.

2. Regarding the proposed conversion of the Conditional Authorization of bosutinib to Standard Marketing Authorization after fulfilment of the specific obligation by submission of the final results from trial B1871039 (additional pharmacovigilance activity category 3 study listed in the RMP): The MAH is requested to submit a summary table regarding efficacy as well as safety, which allows to compare directly the data at the time of the conditional marketing authorization and those now available from the specific obligation trial as well as from the current analyses presented. The table should allow a comprehensible overview of differences occurred.

RMP aspects

3. Part SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information needs to be updated. All Important Identified Risks, Important Potential Risks, and Missing Information which have been proposed for removal from the List of Safety concerns should be deleted.
4. SVIII: All removed safety concerns (strikethrough) should be deleted.
5. Part V: This complete part requires revision in line with the revised summary of safety concerns.
6. The Summary of the risk management plan needs to be updated in line with the revised summary of safety concerns and risk minimisation measures.

10. Assessment of the responses to the request for supplementary information

10.1. Other concerns

Clinical aspects

Question 1. Regarding the proposed changes in the Product information: The MAH is requested to submit a new PI on the basis of the final approved version of var II/48 and only highlight the changes that are submitted in var II/50/G.

Summary of the MAH's response

The PI annotated and clean versions have been updated as requested: the approved PI version within var II/48 is used as base text and the PI annotated version highlights the changes resulting from var II/50/G.

Assessment of the MAH's response

The requested annotated version of the product information, providing a comprehensible overview about all changes in the product information, is attached in Annex I document. The proposed changes are acceptable.

Issue partly resolved.

SmPC Section 5.1

1. As per SmPC guideline "*It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population*.". Therefore, please justify the new results on additional endpoints (i.e. MMR/MR4, Time to and Duration of CCyR, etc.) from the 10 -years analysis in Section 5.1. Otherwise, please remove these new results from Section 5.1.

2. Table 10: Single arm trials in oncology are not suitable to ascertain a treatment effect on OS or PFS due to the lack of a comparator. Therefore, please remove the new results on PFS/OS from table 10.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2. Regarding the proposed conversion of the Conditional Authorization of bosutinib to Standard Marketing Authorization after fulfilment of the specific obligation by submission of the final results from trial B1871039 (additional pharmacovigilance activity category 3 study listed in the RMP): The MAH is requested to submit a summary table regarding efficacy as well as safety, which allows to compare directly the data at the time of the conditional marketing authorization and those now available from the specific obligation trial as well as from the current analyses presented. The table should allow a comprehensible overview of differences occurred.X

Summary of the MAH's response:

The initial conditional marketing authorization in pretreated patients was based on two year follow-up data from Study 3160A4-200-WW (B1871006).

A comparison of efficacy and safety results between Study B1871006 (at the time of the initial approval [2 years follow-up] and at 4 years [for comparison with 1039]) and Study B1871039 (final analysis with 4 years of follow-up) has been performed. The 2 trials evaluated the same endpoints that are relevant for the current evaluation of efficacy outcomes in chronic myelogenous leukaemia (CML).

To assess the validity of the cross-trial comparison, the main differences in the baseline demographic characteristics and the endpoint analysis of the 2 trials are summarized.

A comparison table of all baseline characteristics for Study 1039 and Study 1006 is provided in Table 1. There were 4 chronic phase fourth line (CP4L) patients in Study 1006 (pooled with the CP third line [CP3L] patients for analysis).

Table 1. Baseline Demographic Characteristics – Studies 1039 and 1006

Table 1. Baseline Demographic Characteristics – Studies 1039 and 1006

	Study 1039			Study 1006	
	CP2L (N=46)	CP3L (N=61)	CP4L (N=49)	CP2L (N=284)	CP3L[b] (N=119)
Median age, years (range)	54.5 (20- 89)	65.0 (28-85)	61.0 (21-85)	53.0 (18-91)	56.0 (20-79)
Sex, n (%)					
Female	23 (50.0)	24 (39.3)	28 (57.1)	135 (47.5)	66 (55.5)
Male	23 (50.0)	37 (60.7)	21 (42.9)	149 (52.5)	53 (44.5)
Race, n (%)					
Asian	0 (0.0)	1 (1.6)	0 (0.0)	62 (21.8)	15 (12.6)
Black	2 (4.3)	1 (1.6)	1 (2.0)	16 (5.6)	6 (5.0)
Other	5 (10.9)	4 (6.6)	4 (8.2)	20 (7.0)	11 (9.2)
White	39 (84.8)	55 (90.2)	44 (89.8)	186 (65.5)	87 (73.1)
ECOG PS[a], n (%)					
0	34 (73.9)	40 (65.6)	32 (65.3)	217 (76.4)	85 (71.4)
1	12 (26.1)	20 (32.8)	13 (26.5)	65 (22.9)	33 (27.7)
2	0 (0.0)	1 (1.6)	4 (8.2)	1 (0.4)	0 (0.0)
Number of prior therapies, n (%)					
1	44 (95.7)	0 (0.0)	0 (0.0)	184 (64.8)	0 (0.0)
2	2 (4.3)	58 (95.1)	0 (0.0)	100 (35. 2)	52 (43.7)
3	0 (0.0)	3 (4.9)	43 (87.8)	0 (0.0)	65 (54.6)
4	0 (0.0)	0 (0.0)	6 (12.2)	0 (0.0)	2 (1.7)
Prior interferon therapy, n (%)					
No	44 (95.7)	58 (95.1)	43 (87.8)	184 (64.8)	54 (45.4)
Yes	2 (4.3)	3 (4.9)	6 (12.2)	100 (35.2)	65 (54.6)
Prior TKI treatment, n (%)					
Imatinib	35 (76.1)	57 (93.4)	49 (100.0)	284 (100.0)	119 (100.0)
Dasatinib	5 (10.9)	41 (67.2)	49 (100.0)	0 (0.0)	92 (77.3)
Nilotinib	6 (13.0)	24 (39.3)	49 (100.0)	0 (0.0)	31 (26.1)
Median duration of disease, y					
Resistance to any prior treatment, n (%)	16 (34.8)	35 (57.4)	31 (63.3)	195 (68.7)	99 (83.2
Intolerance to all prior treatment, n (%)	30 (65.2)	26 (42.6)	18 (36.7)	89 (31.3)	20 (16.8

Source: Study B1871039 CSR Table 11, Table 12, Table 31, Table 14.1.2.2.1; Study B1871006 CSR Table 17, Table 18, Table 20, Table 47, Table 48
CP=chronic phase; CP2L=chronic phase second line; CP3L=chronic phase third line; CP4L=chronic phase fourth line; ECOG=Eastern Cooperative Oncology Group; N,n=number of patients; PS=performance status; TKI=tyrosine kinase inhibitor; y=years.
a ECOG PS not collected for 2 patients (1 CP2L and 1 CP3L) in Study 1006

The 2 trials evaluated similar endpoints, however the following differences in study statistical methods must be noted:

(1) Complete cytogenetic response (CCyR) evaluation: In Study 1006, cytogenetic response was evaluated by chromosome banding analysis (CBA) of marrow metaphases or by fluorescent in situ hybridisation (FISH). FISH was used for evaluating all cytogenetic responses. Patients evaluable for cytogenetic response were those with a valid baseline cytogenetic assessment. In Study 1039, CCyR was evaluated by CBA of marrow metaphases (⩾20 to 99 metaphases). FISH was only used to assess CCyR. CCyR was imputed from MMR on a specific date if there was no valid cytogenetic assessment and patients with at least major molecular response (MMR) were counted as confirmed CCyR. Patients evaluable for cytogenetic response were patients with a valid baseline cytogenetic assessment, patients with CCyR by FISH, and patients with at least MMR at baseline.

(2) Molecular response evaluation: In Study 1006, molecular response was evaluated at a central laboratory but not on the International Scale. Molecular response was not evaluated in patients enrolled in China, India, Russia and South Africa (87 for CP2L and 12 for CP3L).

In Study 1039, molecular response was analyzed by an independent central laboratory and responses are based on the International Scale.

(3) In Study 1006, one year corresponds to 48 weeks, in Study 1039 one year corresponds to 52 weeks.

(4) In Study 1006, eligible patients rolled over into an extension study approximately 5 years after last patient dosed for CP2L and 4 years for CP3L. In Study 1039, patients remained on study for a maximum of 4 years.

Although the 2 trials evaluated the same endpoints, the difference in patients' baseline characteristics in the 2 studies precludes a direct comparison between the overall patient populations, therefore the

comparison is done by treatment line and by resistance/intolerance status. Two and four year efficacy results from Studies 1039 and 1006 for CP2L and CP3L are shown in Table 2, and Table 5, respectively. Table 3, Table 4, Table 6 and Table 7 summarize the efficacy results in the CP2L and CP3L cohorts in patients resistant (resistant to ⩾1 prior tyrosine kinase inhibitor [TKI]) to prior treatment and intolerant (intolerant to all TKIs) to prior treatment, respectively.

For response endpoints, only 4 year data is shown for Study 1039 as all patients initially had CCyR and all but 1 patient initially had MMR by Year 2.

In Study 1039, the median (range) treatment duration in the CP2L, CP3L and CP4L cohorts was 47.6 (0.9-50.1), 41.9 (0.4-48.9) and 20.0 (0.2-48.9) months, respectively. In Study 1006 the median (range) treatment duration in the CP2L and CP3L cohorts was 25.6 (0.2-96.3) and 8.6 (0.2-93.2) months, respectively.

Efficacy Comparison in CP2L and CP3L Patients and by Resistant vs Intolerant Status

Table 2. Efficacy Results in Patients in CP2L Treated with Bosutinib– 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039		Study 1006			
	4 Year		2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP2L**	**n/N***	**CP2L**	**n/N***	**CP2L**
Patient still on-treatment, % Year 2 Year 4	33/46 (71.7) 28/46 (60.9)		153/284 (53.8) 123/284 (43.3)			
Discontinued treatment due to disease progression/lack of efficacy, % Year 2 Year 4	1/46 (2.2) 1/46 (2.2)		50/284 (17.6) 65/284 (22.9)			
Cumulative MCyR, % (95% CI)	38/43	88.4 (74.9, 96.1)	151/262	57.6 (51.4, 63.7)	155/262	59.2 (52.9, 65.2)
Achieved MCyR[a], % (95% CI)	8/10	80.0 (44.4, 97.5)	108/204	52.9 (45.9, 60.0)	111/204	54.4 (47.3, 61.4)
Cumulative CCyR[a], % (95% CI)	37/43	86.0 (72.1, 94.7)	119/262	45.4 (39.3, 51.7)	127/262	48.5 (42.3, 54.7)
Achieved CCyR[a] , % (95% CI)	13/16	81.3 (54.4, 96.0)	105/246	42.7 (36.4, 49.1)	113/246	45.9 (39.6, 52.4)
Cumulative MMR[b,c] , % (95% CI)	38/46	82.6 (68.6, 92.2)	60/197	30.5 (24.1, 37.4)	75/197	38.1 (31.3, 45.2)
Achieved MMR[b,c] , % (95% CI)	19/25	76.0 (54.9, 90.6)	54/189	28.6 (22.2, 35.6)	69/189	36.5 (29.6, 43.8)
Cumulative incidence of on-treatment transformation to AP or BP CML, % (95% CI)	0/46	0.0 (0.0, NE)	13/284	4.6 (2.7, 7.8)	15/284	4.9 (3.0, 8.2)
Number of Deaths Overall survival at 1 year, % (95% CI) Overall survival at 2 years, % (95% CI) Overall survival at 3 years, % (95% CI) Overall survival at 4 years, % (95% CI)	5/46 (10.9) 100.0 (100.0, 100.0) 97.8 (85.6, 99.7) 95.7 (83.7, 98.9) 88.9 (75.4, 95.2)		55/284 (19.4) 97.1 (95.1, 99.1) 91.2 (87.8, 94.6) 87.0 (82.9, 91.1) 85.3 (80.9, 89.8)			

Source: Study B1871039 CSR Table 14, Table 15, Table 16, Table 17, Table 22, Table 14.1.1.4.2, Table 14.2.22.1; Study B1871006 Table 53; Study B1871040 CSR Table 14.2.7.1, 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2019 Annex 7 Table 14.1.1.4.1; 2021 RSI Table 14.2.10.4; 2021 RSI Table 14.2.25.1.5

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Overall survival analysis based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval; CP2L=chronic phase second line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE-non estimatible

a. In Study 1039, once MMR has been achieved, CCyR is imputed on the date where MMR is achieved.
b. Molecular response (MR) was not evaluated on the International Scale (IS) in Study 1006.
c. In Study 1006, MR was not evaluated for patients enrolled in China, India, the Russian Federation, and South Africa.

Table 3. Efficacy Results in Patients in CP2L Resistant to Prior Treatment – 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039		Study 1006			
	4 Year		2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP2L**	**n/N***	**CP2L**	**n/N***	**CP2L**
Patient still on-treatment, % Year 2 Year 4	11/16 (68.6) 10/16 (62.5)		107/195 (54.9) 86/195 (44.1)			
Discontinued treatment due to disease progression/lack of efficacy, % Year 2 Year 4	1/16 (6.2) 1/16 (6.2)		43/195 (22.1) 54/195 (27.7)			
Cumulative MCyR, % (95% CI)	13/15	86.7 (59.5,98.3)	102/182	56.0 (48.5, 63.4)	106/182	58.2 (50.7, 65.5)
Achieved MCyR	6/7	85.7 (42.1, 99.6)	77/148	52.0 (43.7, 60.3)	80/148	54.1 (45.7, 62.3)
Cumulative CCyR, % (95% CI)	12/15	80.0 (51.9, 95.7)	78/182	42.9 (35.6, 50.4)	85/182	46.7 (39.3, 54.2)
Achieved CCyR	8/10	80.0 (44.4, 97.5)	74/178	41.6 (34.2, 49.2)	81/178	45.5 (38.0, 53.1)
Cumulative MMR, % (95% CI)	11/16	68.8 (41.3, 89.0)	40/127	31.5 (23.5, 40.3)	51/127	40.2 (31.6, 49.2)
Achieved MMR	9/14	64.3 (35.1, 87.2)	40/126	31.7 (23.7, 40.6)	51/126	40.5 (31.8, 49.6)
Cumulative incidence of transformation to AP or BP CML, % (95% CI)	0/16	0.0 (0.0, NE)	11/195	5.6 (3.0, 9.5)	13/195	6.2 (3.4, 10.1)
Number of Deaths Overall survival at 1 year, % (95% CI) Overall survival at 2 years, % (95% CI) Overall survival at 3 years, % (95% CI) Overall survival at 4 years, % (95% CI)	2/16 (12.5) 100.0 (100.0, 100.0) 100.0 (100.0, 100.0) 93.8 (63.2, 99.1) 87.5 (58.6, 96.7)		41/195 (21.0) 96.3 (93.7, 99.0) 88.3 (83.7, 92.9) 84.1 (78.8, 89.4) 81.6 (75.8, 87.5)			

Source: Study B1871039 CSR Table 14.1.1.4.1.3, Table 14.2.3.1.6, Table 14.2.4.1.6, Table 14.2.8.1.6, Table 14.2.7.1, Table 14.2.22.1; Study B1871006 CSR Table 53, Table 14.2.7; Study B1871040 CSR Table 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2021 RSI Table 14.2.7.4; 2021 RSI Table 14.2.25.1.5, 2021 RSI Table 14.4.1.4.4

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Other analyses based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval; CP2L=chronic phase second line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE=non estimable

Table 4. Efficacy Results in Patients in CP2L Intolerant to Prior Treatment – 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039		Study 1006			
	4 Year		2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP2L**	**n/N***	**CP2L**	**n/N***	**CP2L**
Patient still on-treatment, % Year 2 Year 4	22/30 (73.3) 18/30 (60.0)		46/89 (51.7) 37/89 (41.6)			
Discontinued treatment due to disease progression/lack of efficacy, % Year 2 Year 4	0/30 (0.0) 0/30 (0.0)		7/89 (7.9) 11/89 (12.4)			
Cumulative MCyR, % (95% CI)	25/28	89.3 (71.8, 97.7)	49/80	61.3 (49.7, 71.9)	49/80	61.3 (49.7, 71.9)
Achieved MCyR	2/3	66.7 (9.4, 99.2)	31/56	55.4 (41.5, 68.7)	31/56	55.4 (41.5, 68.7)
Cumulative CCyR, % (95% CI)	25/28	89.3 (71.8, 97.7)	41/80	51.3 (39.8, 62.6)	42/80	52.5 (41.0, 63.8)
Achieved CCyR	5/6	83.3 (35.9, 99.6)	31/68	45.6 (33.5, 58.1)	32/68	47.1 (34.8, 59.6)
Cumulative MMR, % (95% CI)	27/30	90.0 (73.5, 97.9)	20/70	28.6 (18.4, 40.6)	24/70	34.3 (23.4, 46.6)
Achieved MMR	10/11	90.9 (58.7, 99.8)	14/63	22.2 (12.7, 34.5)	18/63	28.6 (17.9, 41.3)
Cumulative incidence of transformation to AP or BP CML[a], % (95% CI)	0/29	0.0 (0.0, NE)	2/89	2.2 (0.4, 7.1)	2/89	2.2 (0.4, 7.1)
Number of Deaths Overall Survival rate at 1 year,% (95% CI) Overall Survival rate at 2 years, % (95% CI) Overall Survival rate at 3 years, % (95% CI) Overall Survival rate at 4 years, % (95% CI)	3/30 (10.0) 100.0 (100.0, 100.0) 96.7 (78.6, 99.5) 96.7 (78.6, 99.5) 89.8 (71.5, 96.6)		14/89 (15.7) 98.9 (96.6, 100.0) 97.7 (94.5, 100.0) 93.3 (87.6, 99.0) 93.3 (87.6, 99.0)			

Source: Study B1871039 CSR Table 14.1.1.4.1.3, Table 14.2.3.1.6, Table 14.2.4.1.6, Table 14.2.8.1.6, Table 14.2.7.1, Table 14.2.22.1; Table 14.4.1.4.4; Study B1871006 CSR Table 53, Table 14.2.7; Study B1871040 CSR Table 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2021 RSI Table 14.2.7.4; 2021 RSI Table 14.2.10.4; 2021 RSI Table 14.2.25.1.5

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Other analyses based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval; CP2L=chronic phase second line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE=non estimable

Table 5. Efficacy Results in Patients in CP3L and CP4L (Study 1039 Only) Treated with Bosutinib – 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039				Study 1006			
	4 Year				2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP3L**	**n/N***	**CP4L**	**n/N***	**CP3L**	**n/N***	**CP3L**
Patient still on-treatment, % Year 2 Year 4		39/61 (63.9) 28/61 (45.9)		24/49 (49.0) 19/49 (38.8)		41/119 (34.5) 29/119 (24.4)		
Discontinued treatment due to disease progression/lack of efficacy, % Year 2 Year 4		2/61 (3.3) 2/61 (3.3)		5/49 (10.2) 6/49 (12.2)		40/119 (33.6) 46/119 (38.7)		
Cumulative MCyR, % (95% CI)	47/55	85.5 (73.3, 93.5)	35/45	77.8 (62.9, 88.8)	44/112	39.3 (30.2, 49.0)	44/112	39.3 (30.2, 49.0)
Achieved MCyR, % (95% CI)	6/10	60.0 (26.2, 87.8)	5/12	41.7 (15.2, 72.3)	25/88	28.4 (19.3, 39.0)	25/88	28.4 (19.3, 39.0)
Cumulative CCyR, % (95% CI)	46/55	83.6 (71.2, 92.2)	33/45	73.3 (58.1, 85.4)	32/112	28.6 (20.4, 37.9)	35/112	31.3 (22.8, 40.7)
Achieved CCyR, % (95% CI)	12/19	63.2 (38.4, 83.7)	8/17	47.1 (23.0, 72.2)	25/104	24.0 (16.2, 33.4)	28/104	26.9 (18.7, 36.5)
Cumulative MMR[a,b] % (95% CI)	42/55	76.4 (63.0, 86.8)	27/48	56.3 (41.2, 70.5)	18/107	16.8 (10.3, 25.3)	19/107	17.8 (11.0, 26.3)
Achieved MMR [a,b] , % (95% CI)	18/28	64.3 (44.1, 81.4)	10/26	38.5 (20.2, 59.4)	14/102	13.7 (7.7, 22.0)	15/102	14.7 (8.5, 23.1)
Cumulative incidence of on-treatment transformation to AP or BP CML, % (95% CI)	0/61	0.0 (0.0, NE)	0/49	0.0 (0.0, NE)	5/119	4.2 (1.8, 9.9)	5/119	4.2 (1.8, 9.9)
Number of Deaths		7/61 (11.5)		5/49 (10.2)		30/119 (25.2)		
Overall survival at 1 year, % (95% CI)		96.7 (87.3, 99.2)		97.9 (85.8, 99.7)		91.4 (86.2, 96.5)		
Overall survival at 2 years, % (95% CI)		95.0 (85.2, 98.3)		95.7 (83.9, 98.9)		84.0 (77.3, 90.8)		
Overall survival at 3 years, % (95% CI)		89.8 (78.7, 95.3)		93.5 (81.1, 97.8)		79.3 (71.5, 87.2)		
Overall survival at 4 years, % (95% CI)		87.7 (75.7, 93.9)		88.5 (74.5, 95.1)		77.7 (69.4, 86.0)		

Source: Study B1871039 CSR Table 14, Table 15, Table 16, Table 17, Table 22, Table 14.1.1.4.2, Table 14.2.22.1; Study B1871006 Table 54, Table 14.2.7.2; Study B1871040 CSR Table 14.2.7.1, 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2019 Annex 7 Table 14.1.1.4.1.1; 2021 RSI Table 14.2.10.4; 2021 RSI Table 14.2.25.1.5

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Other analyses based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval; CP3L=chronic phase third line; CP4L=chronic phase fourth line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE=non estimable

a. Molecular response (MR) was not evaluated on the International Scale (IS) in Study 1006.

b. In Study 1006, MR was not evaluated for patients enrolled in China, India, the Russian Federation, and South Africa.

Table 6. Efficacy Results in Patients in CP3L and CP4L (Study 1039 Only) Resistant to Prior Treatment – 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039				Study 1006			
	4 Year				2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP3L**	**n/N***	**CP4L**	**n/N***	**CP3L**	**n/N***	**CP3L**
Patient still on-treatment, % Year 2 Year 4		24/35 (68.6) 20/35 (57.1)		15/31 (48.4) 13/31 (41.9)		35/98 (35.7) 24/98 (24.5)		
Discontinued treatment due to disease progression/lack of efficacy, % Year 2 Year 4		2/35 (5.7) 2/35 (5.7)		4/31 (12.9) 5/31 (16.1)		38/98 (38.8) 44/98 (44.9)		
Cumulative MCyR, % (95% CI)	28/33	84.8 (68.1, 94.9)	19/27	70.4 (49.8, 86.2)	37/94	39.4 (29.4, 50.0)	37/94	39.4 (29.4, 50.0)
Achieved MCyR	4/7	57.1 (18.4, 90.1)	3/9	33.3 (7.5, 70.1)	24/78	30.8 (20.8, 42.2)	24/78	30.8 (20.8, 42.2)
Cumulative CCyR, % (95% CI)	27/33	81.8 (64.5, 93.0)	18/27	66.7 (46.0, 83.5)	25/94	26.6 (18.0, 36.7)	28/94	29.8 (20.8, 40.1)
Achieved CCyR	8/13	61.5 (31.6, 86.1)	4/11	36.4 (10.9, 69.2)	20/89	22.5 (14.3, 32.6)	23/89	25.8 (17.1, 36.2)
Cumulative MMR, % (95% CI)	20/29	69.0 (49.2, 84.7)	15/30	50.0 (31.3, 68.7)	13/87	14.9 (8.2, 24.2)	14/87	16.1 (9.1, 25.5)
Achieved MMR	9/17	52.9 (27.8, 77.0)	4/17	23.5 (6.8, 49.9)	10/84	11.9 (5.9, 20.8)	11/84	13.1 (6.7, 22.2)
Cumulative incidence of transformation to AP or BP CML, % (95% CI)	0/35	0.0 (0.0, NE)	0/31	0.0 (0.0, NE)	5/98	5.1 (1.9, 10.7)	5/98	5.1 (1.9, 10.7)
Number of Deaths		4/35 (11.4)		3/31 (9.7)		26/98 (26.5)		
Overall Survival at 1 year, % (95% CI)		97.1 (81.4, 99.6)		96.6 (77.9, 99.5)		90.5 (84.6, 96.4)		
Overall Survival at 2 years, % (95% CI)		94.2 (78.7, 98.5)		93.0 (74.7, 98.2)		82.7 (74.9, 90.4)		
Overall Survival at 3 years, % (95% CI)		91.3 (75.3, 97.1)		89.4 (70.6, 96.5)		77.0 (67.9, 86.0)		
Overall Survival at 4 years, % (95% CI)		87.7 (70.4, 95.2)		89.4 (70.6, 96.5)		77.0 (67.9, 86.0)		

Source: Study B1871039 CSR Table 14.1.1.4.1.3, Table 14.2.3.1.6; Table 14.2.4.1.6, Table 14.2.7.1, Table 14.2.7.5, Table 14.2.8.1.6, Table 14.2.22.1; Study B1871006 CSR Table 54, Table 14.2.7.2; Study B1871040 CSR Table 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2021 RSI 14.2.2.1.4.1; 2021 RSI Table 14.2.7.5, 2021 RSI Table 14.2.10.4; 2021 RSI Table 14.2.25.1.5

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Other analyses based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval;CP3L=chronic phase third line; CP4L=chronic phase fourth line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE=non estimable

Table 7. Efficacy Results in Patients in CP3L and CP4L (Study 1039 Only) Intolerant to Prior Treatment – 2 and 4 Year Data Comparison in Studies 1039 and 1006

	Study 1039				Study 1006			
	4 Year				2 Year		4 Year	
Efficacy Parameter	**n/N***	**CP3L**	**n/N***	**CP4L**	**n/N***	**CP3L**	**n/N***	**CP3L**
Patient still on treatment,%								
Year 2		15/26 (57.7)		9/18 (50.0)		6/21 (28.6)		
Year 4		8/26 (30.8)		6/18 (33.3)		5/21 (23.8)		
Discontinued treatment due to disease progression/lack of efficacy, %								
Year 2		0/26 (0.0)		1/18 (5.6)		2/21 (9.5)		
Year 4		0/26 (0.0)		1/18 (5.6)		2/21 (9.5)		
Cumulative MCyR, % (95% CI)	19/22	86.4 (65.1, 97.1)	16/18	88.9 (65.3, 98.6)	7/18	38.9 (17.3, 64.3)	7/18	38.9 (17.3, 64.3)
Achieved MCyR	2/3	66.7 (9.4, 99.2)	2/3	66.7 (9.4, 99.2)	1/10	10.0 (0.3, 44.5)	1/10	10.0 (0.3, 44.5)
Cumulative CCyR, % (95% CI)	19/22	86.4 (65.1, 97.1)	15/18	83.3 (58.6, 96.4)	7/18	38.9 (17.3, 64.3)	7/18	38.9 (17.3, 64.3)
Achieved CCyR	4/6	66.7 (22.3, 95.7)	4/6	66.7 (22.3, 95.7)	5/15	33.3 (11.8, 61.6)	5/15	33.3 (11.8, 61.6)
Cumulative MMR, % (95% CI)	22/26	84.6 (65.1, 95.6)	12/18	66.7 (41.0, 86.7)	5/20	25.0 (8.7, 49.1)	5/20	25.0 (8.7, 49.1)
Achieved MMR	9/11	81.8 (48.2, 97.7)	6/9	66.7 (29.9, 92.5)	4/18	22.2 (6.4, 47.6)	4/18	22.2 (6.4, 47.6)
Cumulative incidence of transformation to AP or BP CML, % (95% CI)	0/26	0.0 (0.0, NE)	0/18	0.0 (0.0, NE)	0/21	0.0 (0.0, NE)	0/21	0.0 (0.0, NE)
Number of Deaths		3/26 (11.5)		2/18 (11.1)		4/21 (19.0)		
Overall Survival at 1 year, % (95% CI)		96.0 (74.8, 99.4)		100.0 (100.0, 100.0)		95.2 (86.1, 100.0)		
Overall Survival at 2 years, % (95% CI)		96.0 (74.8, 99.4)		100.0 (100.0, 100.0)		90.2 (77.3, 100.0)		
Overall Survival at 3 years, % (95% CI)		87.7 (66.4, 95.8)		100.0 (100.0, 100.0)		90.2 (77.3, 100.0)		
Overall Survival at 4 years, % (95% CI)		87.7 (66.4, 95.8)		87.1 (57.3, 96.6)		81.2 (60.8, 100.0)		

Source: Study B1871039 CSR Table 14.1.1.4.1.3, Table 14.2.3.1.6, Table 14.2.4.1.6, Table 14.2.8.1.6, Table 14.2.7.1, Table 14.2.22.1; Study B1871006 CSR Table 54, Table 14.2.7.2; Study B1871040 CSR Table 14.2.13.11, Table 14.2.13.12, Table 14.2.13.13, Table 14.2.13.14; 2021 RSI Table 14.2.10.4; 2021 RSI Table 14.2.2.1.4.1.1, 2021 RSI Table 14.2.7.5; 2021 RSI Table 14 2.25.1.5

*Number of patients over total evaluable patients with a valid baseline assessment for each specific response analysis. Other analyses based on all treated patients and overall events displayed.

AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; CI=confidence interval; CP3L=chronic phase third line; CP4L=chronic phase fourth line; MCyR=major cytogenetic response; MMR=major molecular response; N,n=number of patients; NE=non estimable

Safety Comparison by Treatment Line

Safety results from Study 1039 and Study 1006 for CP2L and CP3L patients are shown in Table 8 and Table 9, respectively.

Table 8. Safety Comparison in CP2L Patients – Studies 1039 and 1006 - 2 and 4 Year Data

	Study 1039 (n=46)		Study 1006 (n=284)	
	2 Year	**4 Year**	**2 Year**	**4 Year**
All Grade TEAEs, n (%)	46 (100.0)	46 (100.0)	283 (99.6)	283 (99.6)
Grade 3 or 4 TEAEs, n (%)	33 (71.7)	36 (78.3)	197 (69.4)	213 (75.0)
SAEs, n (%)	16 (34.8)	21 (45.7)	90 (31.7)	100 (35.2)
TEAEs leading to temporary stop, n (%)	33 (71.7)	35 (76.1)	191 (67.3)	203 (71.5)
TEAEs leading to dose reduction, n (%)	35 (76.1)	35 (76.1)	132 (46.5)	134 (47.2)
TEAEs leading to death, n (%)	1 (2.2)	2 (4.3)	5 (1.8)	7 (2.5)
Median dose intensity (range), mg/day	316.7 (98.4-560.6)	319.9 (98.4-560.6)	434.8 (87.4-599.1)	451.0 (87.4-599.6)
Discontinuations from treatment, n (%)	13 (28.3)	18 (39.1)	131 (46.1)	161 (56.7)
Adverse events	10 (21.7)	12 (26.1)	57 (20.1)	63 (22.2)
Lack of efficacy/progression	1 (2.2)	1 (2.2)	50 (17.6)	65 (22.9)
Other	2 (4.3)	5 (10.9)	24 (8.5)	33 (11.6)

Source: B1871039 CSR Table 14.1.1.4.2; 2019 Annex 6 Table 14.3.1.5.7.1, 2019 Annex 6, Table 14.3.1.5.7.2, 2019 Annex 6, Table 14.3.1.5.7.4, 2019 Annex 6, Table 14.3.1.5.7.5, 2019 Annex 6, Table 14.3.1.5.7.6, 2019 Annex 6 Table 14.3.1.5.7.7, 2019 Annex 7, Table 14.1.1.4.1; SCS T2V2 2021 Table 14.3.1.1.7; 2021 RSI Table 14.4.4.1.1.53; 2021 RSI Table 14.4.4.1.1.54

CP2L=chronic phase second line; n=number of subjects; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Table 9. Safety Comparison in CP3L Patients – Studies 1039 and 1006 - 2 and 4 Year Data

	Study 1039 (n=61)		Study 1006 (n=119)	
	2 Year	**4 Year**	**2 Year**	**4 Year**
All Grade TEAEs, n (%)	61 (100.0)	61 (100.0)	119 (100.0)	119 (100.0)
Grade 3 or 4 TEAEs, n (%)	45 (73.8)	49 (80.3)	77 (64.7)	77 (64.7)
SAEs, n (%)	23 (37.7)	30 (49.2)	34 (28.6)	39 (32.8)
TEAEs leading to temporary stop, n (%)	45 (73.8)	45 (73.8)	77 (64.7)	78 (65.5)
TEAEs leading to dose reduction, n (%)	46 (75.4)	49 (80.3)	56 (47.1)	59 (49.6)
TEAEs leading to death, n (%)	1 (1.6)	4 (6.6)	5 (4.2)	5 (4.2)
Median dose intensity (range), mg/day	321.4 (79.7-500.0)	301.4 (79.7-520.4)	442.4 (64.6-563.2)	441.8 (64.6-580.1)
Discontinuations from treatment, n (%)	22 (36.1)	33 (54.1)	78 (65.5)	90 (75.6)
Adverse events	12 (19.7)	16 (26.2)	24 (20.2)	28 (23.5)
Lack of efficacy/progression	2 (3.3)	2 (3.3)	40 (33.6)	46 (38.7)
Other	8 (13.1)	15 (24.6)	14 (11.8)	16 (13.4)

Source: B1871039 CSR Table 14.1.1.4.2; 2019 Annex 6, Table 14.3.1.5.7.1, 2019 Annex 6, Table 14.3.1.5.7.2, 2019 Annex 6, Table 14.3.1.5.7.4, 2019 Annex 6, Table 14.3.1.5.7.5, 2019 Annex 6, Table 14.3.1.5.7.6, 2019 Annex 6, Table 14.3.1.5.7.7, 2019 Annex 7, Table 14.1.1.4.1.1; SCS T2V2 2021 Table 14.3.1.1.7, 2021 RSI Table 14.4.4.1.1.53; 2021 RSI Table 14.4.4.1.1.54

Assessment of the MAH's response

From the requested summary tables it it agreed with the applicant that patients in Study 1039 were older and had a shorter disease duration at the time of bosutinib treatment start than patients in Study 1006. Similarly, it is noted that patients in Study 1039 had a different disease biology with a lower proportion of resistant patients, which were more heavily pretreated and had more heterogeneous prior treatment sequences than patients in Study 1006 (e.g., imatinib was not always first line treatment in Study 1039).

Overall, patients in the CP2L and CP3L cohorts of Study 1039 had higher cytogenetic and molecular response rates by 4 years compared to patients in the corresponding cohorts in Study 1006. Even though in Study 1039 there were more patients with a cytogenetic or molecular response at baseline, the achieved cytogenetic and molecular rates in patients without the respective response at baseline were also higher in Study 1039. In addition, an indirect comparison between the CP4L cohort of Study 1039 with the CP3L cohort of Study 1006 shows that the efficacy in patients treated with bosutinib in 4th line compares favourably against the efficacy shown in 3rd line in Study 1006, allows concluding that bosutinib provides a clinically relevant benefit in heavily pre-treated patients.

Patients with intolerance to prior treatment have, in general, better outcomes than patients with a previous resistance, this was observed in both Study 1039 and Study 1006 where response rates in intolerant patients were higher than in resistant patients. However, higher rates of cytogenetic and molecular responses were observed in both resistant and intolerant patients in Study 1039 compared to Study 1006, showing that the improved efficacy results seen in Study 1039 are not driven by the higher number of intolerant patients. Moreover, the results obtained in Study 1039 are superior in terms of cytogenetic and molecular responses to those seen in Study 1006, recognizing the small subgroups in Study 1039.

The safety profile of bosutinib was acceptable in both studies. Rates of Grade 3 or 4 TEAEs and SAEs were higher in Study 1039, as were the proportion of patients requiring a temporary treatment stop or a dose reduction. As a result, the median dose intensity was lower in Study 1039. However, the lower dose intensity did not appear to have an impact on efficacy since patients in Study 1039 were able to remain on treatment for longer. Overall, there were fewer permanent treatment discontinuations and fewer discontinuations due to lack of efficacy in Study 1039, however, the percentage of patients with discontinuations due to adverse events was slightly higher owing to the higher proportion of intolerant patients in this study.

Study 1039 illustrates current treatment approaches in CML, which reflect a significant change in treatment practice from the time when the initial bosutinib Study 1006 was carried out in 2006 - 2008. Investigators have a greater number of TKIs available leading to an earlier therapy switch in case of resistance or intolerance and to the selection of the appropriate TKI based on patient-, disease- and treatment-related factors. This is reflected in Study 1039 where patients who are overall more heavily pre-treated have nevertheless, a shorter median disease duration as compared to patients in Study 1006. In addition, investigators now have an increased familiarity in the use of bosutinib and therefore, an increased ability to manage AE through temporary dose reductions and interruptions with only a slight increase in permanent treatment discontinuation due to AEs despite the higher proportion of patients being intolerant to all prior TKIs.

Conclusion:

It is agreed that the provided overview of results from Study 1039 confirm the efficacy and a manageable toxicity profile of bosutinib and a positive benefit-risk balance in the later line indication already observed in Study 1006 at the time of the initial marketing authorization.

Issue resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

Question 3

Part SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information needs to be updated. All Important Identified Risks, Important Potential Risks, and Missing Information which have been proposed for removal from the List of Safety concerns should be deleted.

Summary of the MAH's response

The Risk Management Plan version 6.1 is updated accordingly.

Assessment of the MAH's response

The MAH has updated the RMP accordingly.

Conclusion

Issue resolved.

Question 4

SVIII: All removed safety concerns (strikethrough) should be deleted.

Summary of the MAH's response

The Risk Management Plan version 6.1 is updated accordingly.

Assessment of the MAH's response

The MAH has updated the RMP accordingly.

Conclusion

Issue resolved.

Question 5

Part V: This complete part requires revision in line with the revised summary of safety concerns.

Summary of the MAH's response

The Risk Management Plan version 6.1 is updated accordingly.

Assessment of the MAH's response

The MAH has updated the RMP accordingly.

Conclusion

Issue resolved.

Question 6

The Summary of the risk management plan needs to be updated in line with the revised summary of safety concerns and risk minimisation measures.

Summary of the MAH's response

The Risk Management Plan version 6.1 is updated accordingly.

Assessment of the MAH's response

The MAH has updated the RMP accordingly.

Conclusion

Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

11. 2nd Request for supplementary information (including assessment of Response)

11.1. Other concerns

SmPC Section 5.1

Question 1:
As per SmPC guideline "*It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials, and giving the main characteristics of the patient population*.". Therefore, please justify the new results on additional endpoints (i.e. MMR/MR4, Time to and Duration of CCyR, etc.) from the 10 -years analysis in in Section 5.1. Otherwise, please remove these new results from in Section 5.1.

RESPONSE
Pfizer acknowledges the comment regarding the additional endpoints (i.e.MMR/MR4, Time to and Duration of CCyR, etc.) from the 10 -years analysis in the extension study 1040 inserted in the SmPC Table 8, however Pfizer belives the following considerations should be taken into account:
Pfizer has updated sections of SmPC Table 8 in order to only present endpoints that are relevant to the current clinical practice. Current guidelines recommend CML to be monitored and assessed with real quantitative polymerase chain reaction (PCR) and/or cytogenetics (Baccarani et al, 2013; Hochhaus et al, 2020). Given the standardization of molecular monitoring and the ability of assessing deeper responses through PCR, molecular monitoring and targets are routinely used in clinical practice. As such, previously presented cumulative hematological responses (CHR/OHR) and time to and duration of CHR/OHR have been replaced by cytogenetic and molecular endpoints (MMR, MR4, time to and duration of CCyR, time to and duration of MMR/MR4).
Pfizer considers that the molecular and cytogenetic endpoints from Study B1871040 (study in imatinib resistant or intolerant CML in CP, AP, and BP) presented in Table 8 are clinically relevant and informative for clinicians treating CML and should remain in the SmPC. In addition, this is consistent with the information presented in SmPC Table 10 from study B1871039 (study in Ph+ CML previously treated with 1 or more TKIs), where only cytogenetic and molecular endpoints that are clinically relevant to current clinical practice
are presented.

Assessor's comment:
Justification for inclusion of the new results on additional endpoints (i.e. MMR/MR4, Time to and Duration of CCyR, etc.) from the 10 -years analysis in SmPC Section 5.1 due to there outstanding clinical relevant is sufficient to agreed with the MAH's proposal.

Conclusion:
Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance

Question 2:
Table 10: Single arm trials in oncology are not suitable to ascertain a treatment effect on OS or PFS due to the lack of a comparator. Therefore, please remove the new results on PFS/OS from table 10.

Applicant's response

Pfizer agrees to remove PFS and OS from the SmPC Table 10. The PI annotated and clean versions have been updated as requested. We take this opportunity to correct some errors in the section 4.8 of the SmPC. The TEAE table instead of the ADR table was used to update the following paragraph (corrections are in traked mode):

At least 1 adverse reaction of any toxicity grade was reported for 1,34958 (98.399.0%) patients. The most frequent adverse reactions reported for ≥ 20% of patients were diarrhoea (80.24%), nausea (41.25%), abdominal pain (35.6%), thrombocytopenia (34.34%), vomiting (33.67%), rash (32.829.3%), ALT increased (27.728.0%), anaemia (26.827.21%), pyrexia (23.24%), AST increased (22.35%), abdominal pain (21.822%), fatigue (32.020.421%), and headache (20.13%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 9431,058 068 (77.1868.7%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥ 5% of patients were thrombocytopenia (19.7%), ALT increased (14.46%), neutropenia (10.6%), diarrhoea (10.56%), anaemia (10.3%), lipase increased (10.19.69%), and AST increased (6.7%) and rash (5.0%).

Assessor's comment:
Since the MAH has agreed to remove PFS and OS from the SmPC Table 10 and updated the PI as requested this issue is resolved. Moreover, the correction of some errors in section 4.8 of the SmPC is agreed.
Conclusion:
Issue resolved.

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance