BOSULIF (BOSUTINIB) RISK MANAGEMENT PLAN

RMP Version number: 8.0

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Rationale for submitting an updated RMP: Include paediatric indication for paediatric patients aged 6 years and older.

Summary of significant changes in the RMP:

Part I, Part II, Part VI: Updated indication.

Other RMP versions under evaluation: None

Details of the currently approved RMP

Version number: 8.0

Approved with procedure: EMEA/H/C/002373/X/0058/G

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QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s applicant´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ABL	Abelson Proto-Oncogene
ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute Lymphoblastic Leukaemia
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AP	Accelerated Phase
AR	Adverse Reaction
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration Time Curve
AVDOS	Average Daily Dose
ASXL	Sex Comb-Like 1
BC	Blast Crisis
BCR	Breakpoint Cluster Region
BID	Twice Daily
BP	Blast Phase
CCyR	Complete Cytogenetic Response
CHR	Complete Haematologic Response
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CML	Chronic Myelogenous Leukaemia
CNS	Central Nervous System
CP	Chronic Phase
CP1L	Chronic Phase 1st Line
CRF	Clinical Report Form
CSR	Clinical Study Report
CT	Clinical Trial
CyR	Cytogenetic Response
CU	Compassionate Use
DASISION	Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukaemia Patients
DLP	Data Lock Point
ECG	Electrocardiogram
EEA	European Economic Area
EEIG	European Economic Interest Grouping
EFS	Event-Free Survival
EM	Emerging Market
EMA	European Medicines Agency
ENESTnd	Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients
EPAR	European Public Assessment Report

EU	European Union
EUTOS	European Treatment and Outcome Study
GI	Gastrointestinal
HBV	Hepatitis B Virus
HCP	Healthcare Professional
hERG	Human Ether-A-Go-Go Related Gene
HESS	Haematological Disease Monitoring System
HIV	Human Immunodeficiency Virus
HSCT	Haematopoietic Stem Cell Transplantation
IC_{50S}	50% Inhibitory Concentration
IDM	International Developed Market
IGFBP-1	Insulin-Like Growth Factor Binding Protein 1
IGFBP 3	Insulin-Like Growth Factor Binding Protein 3
INN	International Non-proprietary Names
IRIS	International Randomized Study of Interferon and STI571
IV	Intravenous
KG	Kilogram
LPFV	Last Patient First Visit
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MaHR	Major Haematologic Response
MCyR	Major Cytogenetic Response
MD	Medical Doctor
MG	Milligram
MIDAS	Multinational Integrated Data Analysis System
MMR	Major Molecular Response
ND	Newly Diagnosed
NIS	Non-Interventional Study
OS	Overall Survival
PACE	Ponatinib Ph+ ALL and CML Evaluation
P-gp	Permeability Glycoprotein
PH	Philadelphia
Ph-	Philadelphia Chromosome-Negative
Ph+	Philadelphia Chromosome-Positive
PK	Pharmacokinetic
PL	Package Leaflet
PSUR	Periodic Safety Update Report
QD	Once Daily
QPPV	Qualified Person Responsible for Pharmacovigilance
REDECAN	Spanish Network of Cancer Registries
R/I	Resistant/Intolerant
RMP	Risk Management Plan
RP2D	Recommended Phase 2 Dose
SEER	Surveillance, Epidemiology, and End Results
S-D	Sprague Dawley

SmPC	Summary of Product Characteristics
SPP	Specialty Pharmacy
SRC	Sarcoma
TEAE	Treatment-Emergent Adverse Event
TIDEL	Therapeutic Intensification in De Novo Leukaemia
TKI	Tyrosine Kinase Inhibitor
TOPS	Tyrosine Kinase Inhibitor Optimization and Selectivity Study
TRx	Total Prescriptions
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
UVR	Ultraviolet Radiation
WBC	White Blood Cell

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PART I. PRODUCT OVERVIEW

Active substance (INN or common name)	bosutinib (anhydrous form) bosutinib
Pharmacotherapeutic group(s) (ATC Code)	Protein kinase inhibitors (L01XE14)
Marketing Authorisation Holder/Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	Bosulif
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Protein kinase inhibitor
	Summary of mode of action: Summary of mode of action: Dual SRC BCR-ABL TKI
	Important information about its composition: None
Hyperlink to the Product Information:	Module 1.3.1.
Indication(s) in the EEA	Current: • Treatment of adult patients with CP, AP, or BP Ph+ CML previously treated with 1 or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options • Treatment of adult patients with newly-diagnosed CP Ph+ CML
	New indications: • Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML). • Adult and paediatric patients aged 6 years and older with CP 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. • Adult patients with 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.
Dosage in the EEA	Current: Adult • 500 mg by mouth once daily with food (previously treated Ph+ CML) • 400 mg by mouth once daily with food (newly-diagnosed CP Ph+ CML)

	New: Paediatric • 300 mg/m^2 orally once daily with food (newly-diagnosed CP Ph+ CML) • 400 mg/m^2 orally once daily with food (Ph+ CML with R/I to prior therapy)
Pharmaceutical form(s) and strengths	Current: Oral film-coated tablets: 100 mg, 400 mg, and 500 mg
	New for new dosage form: BOSULIF 50 mg hard-capsules BOSULIF 100 mg hard-capsules • The hard capsule is to be swallowed whole. For patients who are unable to swallow a whole hard capsule(s), each hard capsule can be opened, and the contents mixed with applesauce or yogurt. Mixing the hard capsule contents with apple sauce or yogurt cannot be considered a substitute of a proper meal.
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indications

- Treatment of adult patients with CP, AP, or BP Ph+ CML previously treated with 1 or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options
- Treatment of adult patients with newly-diagnosed CP Ph+ CML.

New Indications

- Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- Adult and paediatric patients aged 6 years and older with CP 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.
- Adult patients with 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.

Incidence:

Europe

Data from 44 European cancer registries, which include national registries covering the entire populations of Iceland, Norway, Sweden, Ireland, England, N. Ireland, Scotland, Wales, Austria, Malta, Slovenia, and Slovakia, estimated overall incidence from a total of 21,796 myeloid malignancies (which included 2468 incident cases of CML) in the period 2000 to 2002. The 44 registries, divided into 5 different regions, estimated a crude incidence rate of 1.10 cases per 100,000 (1.23 males, 0.98 females).[1] Incidence was estimated according to age at diagnosis which ranged from 0 to 99 years.

The age-standardised incidence rates (per 100,000) for each region are listed in Table 1 below:

Table 1. Chronic Myeloid Leukaemia (Europe) Age-Standardised Incidence Rates (per 100,000)

Region	Countries Contributing Registry Data	Incidence
North	Iceland, Norway, Sweden	0.85
United Kingdom and Ireland	Ireland, England, N. Ireland, Scotland, Wales	0.85

Table 1. Chronic Myeloid Leukaemia (Europe) Age-Standardised Incidence Rates (per 100,000)

Region	Countries Contributing Registry Data	Incidence
Centre	Austria, France, Germany, Switzerland, Netherlands	0.92
South	Italy, Malta, Slovenia, Spain	1.16
East	Czech Republic, Poland, Slovakia	0.88

Incidence rates expressed per 100,000 population

In paediatric patients, incidence data in Europe was sparse and limited to select country-specific estimates, as described below. In the UK, the estimated CML incidence from 2016 to 2018 was 0.1-0.3 cases per 100,000 children and adolescents (10-19 years).[2] In children age 0-9 years, the incidence rate was <0.1 per 100,000 children.[2] Between 2010 and 2013, a study conducted using the HESS registry in Lithuania, including CML patients aged 0 to 17 years, reported an incidence rate of 0.14 new cases of CML per 100,000 people.[3] A population-based study conducted between 1983 and 2018, involving individuals aged 0 to 14 years, and utilizing data from 15 Spanish population-based cancer registries associated with the REDECAN, showed an age-standardized incidence rate for chronic myeloproliferative diseases as 1.1 per million child-years for ages 0 to 14 years.[4]

US

Recent estimates of incidence come from the US SEER Program of the National Cancer Institute Cancer Statistics.[5] The overall age-adjusted incidence rate for the 2016 to 2020 period is 1.9 per 100,000 individuals per year, with males having nearly twice the overall rate as females (2.5/100,000 versus 1.5/100,000). In paediatric patients, the overall age-adjusted incidence rate of CML in population aged <15 years was 0.1 per 100,000 children from 2016 to 2020.

The age-specific incidence rates in the US from 2016 to 2020 are shown in Table 2.[5]

Table 2. Chronic Myeloid Leukaemia Age-Specific Incidence Rates (US) per 100,000 (2016 to 2020)

Age	Overall (All Races)	Male	Female
<1	0.3	-	-
1-4	0.1	0.1	-
5-9	0.1	0.1	0.1
10-14	0.1	0.2	0.1
15-19	0.3	0.4	0.2
20-24	0.5	0.6	0.4
25-29	0.6	0.8	0.5
30-34	1.0	1.1	0.8
35-39	1.2	1.5	1.0
40-44	1.5	1.7	1.2
45-49	1.8	2.0	1.6
50-54	2.2	2.5	1.8
55-59	2.7	3.1	2.4
60-64	3.6	4.5	2.7
65-69	4.8	6.0	3.7

Table 2. Chronic Myeloid Leukaemia Age-Specific Incidence Rates (US) per 100,000 (2016 to 2020)

Age	Overall (All Races)	Male	Female
70-74	6.6	8.8	4.8
75-79	9.0	12.5	6.3
80-84	11.2	15.8	8.0
85+	10.7	15.9	7.9

- Indicates less than 16 cases for time interval and no statistic computed.

Prevalence:

Europe

Orphanet Report Series, a consortium of European partners that provides, among other services, a public database of drugs with an orphan designation along with prevalence numbers cited from various data sources (www.orpha.net),[6] cites CML as having a prevalence of 6 per 100,000 persons. With the population of the EU at approximately 448 million[7] a rough estimate of the number of CML cases in the EU would be about 26,880 persons as of January 2021.

In paediatric patients, prevalence data in Europe was sparse and limited to select country-specific estimates, as described below.

A population-based study using French national health insurance data found the crude CML prevalence from 2006 to 2014 was less than 1.6 per 100,000 [95% CI: 1.2-2.0] among children under age 20 with BCR/ABL positive CML and/or previously treated by TKI.[8]

In the UK, there are an estimated 5 cases of CML per year among children and approximately 28 cases each year among teenagers and young adults.[9] Data were not available for subgroup of children with resistant or intolerant CML.

US

According to SEER data, the number of people alive with CML in the US on 01 January 2020 was 66,366 which translates to <0.1% of the US population. Among these CML cases, 37,520 were males and 28,846 were females.[5]

In paediatric patients, the estimated number of children <20 years old alive with CML on 01 January 2020 was 916 cases.[5]

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

In adults, incidence rates in the US increase substantially from below age 65 to ages 65 (Table 2). The incidence rate was highest among adults ages 80-84 years (11.2 per 100,000 population) and lowest among patients <30 years.[5]

In paediatric patients, age-based prevalence data in Europe were sparse. Based on an international cohort study across multiple countries in Europe, 22 of the 479 enrolled patients (4.6%) were diagnosed at an age younger than 3 years old. The median age at diagnosis was 22 months, with a range spanning from 10 to 34 months.[10] In the UK, the age-specific incidence rate was 0.1 per 100,000 population among children of age 10-14 years and 0.3 per 100,000 population among 15 to 19 years children.[2]

Among US paediatric population, the incidence of paediatric CML varied with age (SEER registry data; 2016-2020). A higher incidence was observed in adolescents (age: 15-19 years; incidence: 0.3 per 100,000 population) and infants (age: <1 year; incidence: 0.3 per 100,000 population) compared to children (age: 1-14 years; incidence: 0.1 per 100,000 population) (Table 2).[5,11]

Sex

In the US, the overall age-adjusted incidence rate (2016-2020) is 1.9 per 100,000, with males having nearly twice the overall rate as females (2.5/100,000 versus 1.5/100,000).[5] Similarly, the 5-year age-adjusted CML incidence rate in North America NAACCR; 2016-2020) was 2.4 per 100,000 persons in males compared to 1.5 per 100,000 persons in females.[12]

In Europe, gender-based prevalence data were sparse and limited to country-specific estimates. According to Cancer Research UK, the CML incidence was lower in females than in males. CML accounted for approximately 370 new cancer cases every year (2016-2018) in females and 460 new cases in males.[2]

Gender-based data were similar in paediatric patients. Data from an international cohort study across multiple countries in Europe reported that the ratio male/female in the CML population was 1.75 among patients younger than 18 years.[13] In the US, the SEER registry data (2016-2020) also revealed that males exhibited a higher incidence of CML (0.2 per 100,000 population) in the age group below 20 years compared to females (0.1 per 100,000 population).[5]

Race/Ethnicity

In the US, age-adjusted incidence rates from 2016 to 2020 were highest among the Non-Hispanic White population. Incidence rates per 100,000 population by race/ethnicity were as follows: 2.1 among the Non-Hispanic White population, 1.8 among the Non-Hispanic Black population, 1.8 among Non-Hispanic American Indian/Alaska Native population, 1.6 among the Hispanic population, and 1.2 among the Non-Hispanic Asian/Pacific Islander population.[5]

In paediatric patients, incidence rates per 100,000 children age <20 years old in the US by race/ethnicity were as follows: 0.2 among the Hispanic population, 0.2 among the Non-Hispanic Asian/Pacific Islander population, 0.2 among the Non-Hispanic Black population, and 0.1 among the Non-Hispanic White Population.[5]

Risk Factors

The risk factors for CML include:
- Age: the risk is increasing with age
- Gender: male > female; ratio 1.4:1
- High dose radiation or benzene exposure

The main existing treatment options:

Treatment options for patients with CML depend on the phase of their disease, their age, their co-morbidities, the availability of a matching stem cell donor, and response and tolerability to prior drug treatment for CML.

For adult patients in CP, the standard treatment is a TKI. Imatinib mesylate was the first approved drug in front-line therapy (December 2002) based on the results of the IRIS trial. One thousand one hundred six (1106) patients were randomised to receive imatinib 400 mg QD versus interferon-alpha plus low dose cytarabine. The primary endpoint of this trial was EFS. Events were defined as first occurrence of any of the following while on treatment: death from any cause, progression to AP or BP, loss of CHR, or loss of MCyR; EFS was measured from the initiation of therapy with imatinib (after crossover) until occurrence of any of the events hereof described. The estimated EFS at 48 months after initiation of imatinib following crossover was 86%. After a median follow-up of 19 months, the estimated rate of a MCyR was 87.1% in the imatinib arm and 34.7% in the interferon-alpha plus cytarabine arm. The estimated rates of CCyR were 76.2% and 14.5%, respectively. At 18 months, the estimated rate of freedom from progression to AP or BP was 96.7% in the imatinib arm and 91.5% in the combination-therapy arm.[14] Long-term follow-up data (median follow-up of 60 months) have demonstrated that continuous treatment with imatinib induces a high rate of durable responses and a decreasing rate of relapse in patients with CP CML.[15,16] The most frequently reported AEs included GI disturbances, oedema, rash, musculoskeletal complaints, and, in a small group of patients, hypophosphataemia associated in mineral bone changes. Grade 3 and Grade 4 neutropenia and thrombocytopaenia were reported. Congestive heart failure and cardiotoxicity have been reported; however, the incidence rate has been considered similar to the general population.

Since most patients have shown variable levels of residual molecular disease at the standard dosage of 400 mg, several studies have addressed the question of high dose therapy with imatinib. The TIDEL trial[17,18] demonstrated superior response rates for higher doses of imatinib (600 mg) while the TOPS trial[19] reported that high dose imatinib (800 mg) was associated with more rapid responses and MMR and CCyR identical for both doses. The German CML IV trial[20,21] confirmed a faster response with imatinib 800 mg compared to 400 mg in low and intermediate risk patients but not in high risk patients. However, imatinib 800 mg has not been shown to have lower rates of disease progression than standard dose imatinib and it is associated with higher rates of dose interruption, reductions, or permanent discontinuation due to Grade 3/4 AEs.

In the EU, the imatinib paediatric indications for Ph+ CML include newly-diagnosed patients in CP for whom bone marrow transplantation is not considered as the first line of treatment

and after failure of interferon-alpha therapy in CP, or in accelerated phase or blast crisis. The safety profile of imatinib in paediatric patients is consistent with the safety profile in adults. Growth retardation has been reported in children and pre-adolescents receiving imatinib.

In addition to imatinib, second generation TKIs are now approved and available for front-line treatment of CML: bosutinib, dasatinib, and nilotinib.

Bosutinib is a small molecule, selective inhibitor of SRC and ABL non-receptor tyrosine kinases. The initial approval of bosutinib was based on the data from CT 3160A4-200-WW (B1871006), a non-randomised, single-arm CT which included approximately 570 participants with Ph+ CML in CP, AP, or BP who had failed treatment with 1 or more TKI(s) including imatinib. For the reference population of CP Ph+ CML (participants previously treated with imatinib and either 1 or both of the second generation TKIs [dasatinib and/or nilotinib]), bosutinib demonstrated substantial and durable efficacy as evidenced by MCyR and CCyR being attained or maintained by 38.9% and 30.6% of participants, respectively. These MCyRs were maintained in over two-thirds of responding participants after 2 years. Only 5 of the 117 CP Ph+ CML participants with a valid post-baseline haematologic assessment of CP Ph+ CML in the reference population experienced disease transformation to AP or BP Ph+ CML while on bosutinib treatment. The 2-year Kaplan-Meier estimates of Progression-Free Survival and OS were 73.2% and 82.9%, respectively. Furthermore, bosutinib efficacy was comparable in participants who had 1 or more Ph+ CML mutations at baseline and participants without a mutation, and, notably, CyRs were seen in participants with mutations that would be expected to impart clinical resistance to dasatinib and/or nilotinib.

Subsequently, based on the results of CT AV001 (a Phase 3, multicentre, randomised, open-label study of bosutinib versus imatinib in adult patients with newly-diagnosed CP CML) that demonstrated bosutinib at 400 mg daily was an effective and safe treatment option for patients with newly-diagnosed CP CML, bosutinib was approved for the treatment of adult patients with newly-diagnosed CP Ph+ CML. CT AV001 met its primary and secondary Month 12 efficacy objectives and demonstrated that the proportion of participants with MMR at 12 months (48 weeks) and CCyR by 12 months in the modified intention to treat population were statistically significantly higher in the bosutinib arm compared to the imatinib arm (MMR at 12 months [48 weeks]: bosutinib arm 47.2%, imatinib arm 36.9%; CCyR by 12 months: bosutinib arm 77.2%, imatinib arm 66.4%). CT AV001 also demonstrated clinically and statistically significant improvement of bosutinib over imatinib with earlier as well as deeper molecular responses. Although relatively similar, numerically fewer transformation events (from CP CML to AP/BP CML) and fewer mutations at the end of treatment were observed.

The safety profile of bosutinib includes diarrhoea, liver enzyme elevation, and thrombocytopaenia. The most commonly reported TEAEs of any toxicity grade (incidence ≥20%) were diarrhoea (70.1%), nausea, and thrombocytopaenia (35.1% each), ALT increased (30.6%), and AST increased (22.8%). The most commonly reported Grade 3 or 4 TEAEs (≥5%) were ALT increased (19%), thrombocytopaenia (13.8), AST increased (9.7%), lipase increased (9.7%), diarrhoea (7.8%), and neutropenia (6.7%).

Dasatinib is a potent, orally available small molecule, dual inhibitor of ABL and Src family of kinases that binds to both the active and inactive conformation of the ABL kinase domain. Dasatinib was shown in vitro to be effective against all imatinib-resistant mutations with the exception of the T315I. The DASISION trial[22,23,24] compared the efficacy and safety of dasatinib (100 mg QD) to imatinib (400 mg QD) in first-line treatment of CML. The responses were higher and faster achieved with dasatinib; the confirmed CCyR at 12 months were 77% for dasatinib compared to 66% for imatinib and MMR was 46% versus 28%, respectively. Cumulative response rates by 24 months in dasatinib and imatinib arms were: CCyR in 86% versus 82%, MMR in 64% versus 46%, and BCR-ABL reduction to <0.0032% (4.5-log reduction) in 17% versus 8%. Median time to CCyR calculated by competing risks analysis was 3.2 months with dasatinib and 6.0 months with imatinib; however, OS was identical in both groups. The safety profile was also shown to be similar.

The safety profile of dasatinib includes cytopenias manageable with dose modifications. Dasatinib is associated with a significant but reversible inhibition of platelet aggregation and, therefore, increased risk of bleeding. Pleural effusion is an AE that was reported in 29% of patients with CP CML, 50% of patients with AP CML, and 33% of patients with BP CML and led to the dose interruption in 83% of patients and dose reductions in 71% of patients. Patients having a prior cardiac history and patients with arterial hypertension are at increased risk of developing a pleural effusion. This was also shown for patients receiving a twice daily schedule of treatment (70 mg). Reversible pulmonary arterial hypertension was reported as a rare condition associated to dasatinib. Lymphocytosis from the clonal expansion of the natural killer t cells lymphocytes has been reported and seems to be associated to increase incidences of pleural effusions, however; additional data are needed to confirm these data.

In the EU, the dasatinib paediatric indications for Ph+ CML CP include newly-diagnosed patients or resistant or intolerant to prior therapy including imatinib. The safety profile of dasatinib in paediatric patients was comparable to the safety profile in adults. Growth retardation has been observed in clinical trials with paediatric patients.

Another second generation of TKI, nilotinib, is a highly selective inhibitor of BCR-ABL tyrosine kinase and has been shown to be more potent than imatinib in imatinib-resistant cell lines as well as in imatinib-sensitive cell lines. Nilotinib is indicated for the treatment of adult patients with newly-diagnosed Ph+ CML in the CP.

The ENESTnd trial[25,26,27] of first-line therapy in CP CML compared the efficacy and safety of nilotinib, 300 mg BID or 400 mg BID, to imatinib 400 mg QD. Patients treated with nilotinib had a significant improvement in the time to progression to AP or BP. Superior rates of CCyR and MMR were observed for both doses of nilotinib compared to imatinib and across all Sokal risk groups. The MMR rates at 12 months were 44% for nilotinib 300 mg BID, 43% for nilotinib 400 mg BID, and 22% for imatinib 400 mg QD.

The CCyR rates by 12 months were 80% for the 300 mg dose, 78% for the 400 mg dose and 65% for imatinib 400 mg dose.

The treatment arm of nilotinib 300 mg BID showed the lowest rate of discontinuation related to AEs and was approved by the Food and Drug Administration. The long-term follow-up data confirmed the superiority of nilotinib in inducing molecular responses.

As second line therapy, nilotinib was tested at the dose of 400 mg BID. In imatinib-resistant patients, long-term follow-up results confirmed that responses observed were durable with no change in safety profile.

In patients with AP CML resistant or intolerant to imatinib, rapid and durable responses with a favourable risk/benefit profile have been seen. In patients with BP CML resistant or intolerant to imatinib, the response observed was not durable.

Regarding safety, nilotinib was rarely associated with fluid retention, oedema, or muscle cramps. An increased risk of QT interval prolongation and sudden death of cardiac origin has been reported in patients treated by nilotinib. In addition, nilotinib may be associated with an increased risk of vascular AEs including peripheral arterial occlusive disease.

In the EU, the nilotinib paediatric indications for Ph+ CML CP include newly-diagnosed patients in CP, or patients resistant or intolerant to prior therapy including imatinib in CP. Liver function tests in the children indicate a higher risk of hepatotoxicity. Growth retardation has been documented in paediatric patients treated with nilotinib.

Ponatinib, a potent orally available multi-targeted TKI, has also been developed to treat patients with CML and is shown to be active against many kinase domain mutations including the T315I mutation. The present indication for ponatinib is for the treatment of adult patients with CP, AP, or BP CML that is resistant or intolerant to prior TKIs or those who have the T315I mutation.

The PACE trial[28,29] evaluated the safety and efficacy of ponatinib in patients resistant or intolerant to prior TKI therapy or presenting with the T315I mutation. The primary endpoint was MCyR at any time within 12 months after initiation of therapy for patients in CP CML and MaHR at any time within 6 months after initiation of therapy for patients in AP or BP CML.

Two hundred sixty-seven (267) patients with CP CML were enrolled and the results were as follow: 56% MCyR (51% of patients with resistance to or unacceptable AEs from nilotinib or dasatinib and 70% presenting the T315I mutation).

In the AP CML and BP CML cohorts, 83 patients and 62 patients, respectively, were enrolled and MaHR was 55% and 31%, respectively.

In the CP cohort, the responses induced were durable and higher in patients with T315I mutation. The estimated rate of sustained MCyR of at least 12 months was 91%.

Further analysis showed that young age, less exposure to prior TKIs, and shorter duration of leukaemia were predictive factors for response.

Ponatinib induced haematologic and CyRs in patients with advanced CML and therefore ponatinib was approved in all 3 phases of CML resistant or intolerant to prior TKIs.

The safety profile for ponatinib includes rash, dry skin, abdominal pain, headache, and pancreatitis. Thrombocytopaenia and neutropenia were the most frequent Grade 3/4 toxicities evidenced. Ponatinib is also associated with events of fluid retention (oedema, ascites, pleural effusion, pericardial effusion). Serious venous and arterial thromboembolic events have also been reported including fatal myocardial infarction, stroke, stenosis of arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularisation procedures observed in at least 27% of patients.

In conclusion, imatinib, bosutinib, dasatinib, and nilotinib may all be considered as options for the first-line treatment of CP CML. Bosutinib, dasatinib, nilotinib, and ponatinib are options for patients with CP, AP, or BP CML intolerant or resistant to imatinib, with ponatinib being particularly active in patients with the T315I mutation.

Omacetaxine (homoharringtonine, a cephalotaxus alkaloid) is a protein synthesis inhibitor demonstrating activity against CML lines including the 1 showing T315I mutation.

Omacetaxine was shown to be effective in a study evaluating CP and AP CML patients resistant to a minimum of 2 therapies with a TKI. It was also shown to be effective in patients harbouring the T315I mutation who had failed prior TKI therapy.[30,31,32,33]

The safety profile was considered acceptable, and the most common AEs were thrombocytopaenia, anaemia, diarrhoea, neutropenia, and nausea. Treatment-related Grade 3/4 haematological events included thrombocytopaenia, neutropenia, anaemia, leucopenia, and febrile neutropenia.

Allogeneic HSCT is the only potentially curative treatment for patients with CML. The favourable results encountered with TKIs and the variety of treatment available for refractory patients, in addition to the limitation of donor availability and significant morbidity associated with HSCT, have limited its use as first-line therapy.

Recent advances in using alternative donor sources (cord blood, unrelated donors), non-myeloablative reduced intensity preparative regimens, and more accurate human leucocyte antigen typing of unrelated donors makes it an appropriate treatment in first-line treatment for patients with BP CML at initial presentation at diagnosis. Haematopoietic stem cell transplantation may also be considered for patients with T315I mutation or other BCR-ABL mutations conferring resistance to any TKI therapy or for rare patients intolerant to all TKIs.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

CML is a myeloproliferative disorder characterised by a reciprocal t(9;22)(q34;q11) translocation that results in the formation of the Ph chromosome containing the BCR-ABL1 (hereafter referred to as BCR-ABL) oncogene.[34] The BCR-ABL oncogene encodes the BCR-ABL kinase that activates several downstream signalling pathways, which mediate

myeloproliferation, resistance to apoptosis, and genetic instability. The BCR-ABL gene is observed in all cases of CML, and detection of the gene together with identification of the Ph chromosome by karyotyping is used to confirm the diagnosis of CML.[35] In most patients with CML, BCR-ABL transcripts are characterised by b2a2 and/or b3a2 junctions.[36]

CML comprises 3 distinct phases, which are differentiated by clinical characteristics and laboratory findings: a CP, an AP, and a BP. CML is usually diagnosed in the CP.[34,35,36] Patients may present with fatigue, anaemia, splenomegaly, abdominal discomfort, or infections, but often are asymptomatic, with diagnosis occurring after evaluation of routine blood work for an unrelated medical reason. Untreated CML commonly progresses within 3 to 5 years to blast crisis, also termed BP, usually preceded by an AP. Disease progression is characterised by a progressive loss of white blood cell differentiation and is defined by a blast cell count of 15-29% (peripheral blood) in AP and ≥30% (blood and/or marrow) in BP.[37] BP CML, which resembles acute leukaemia, generally leads to patient death due to infection, thrombosis, or anaemia.

CML accounts for 20% of adult leukaemias.[38]

Paediatric population

CML is a clonal disorder due to balanced translocation t(9;22) (q34;q11) that results in the fusion gene.[39] Children and adolescents tend to have a more aggressive clinical presentation than adults. Notably, there are some differences in the clinical presentation of CML at diagnosis in children and adults, which suggests different underlying biology. The median baseline WBC in adult patients with CML ranges from 80×10^9/L to 150×10^9/L, but is higher in children with CML. WBC was reported to be approximately 250×10^9/L in an international registry study of 200 children with CML (median age: 11.6 years; range: 8 months to 18 years).[40]

CML is categorised as CP, AP, and BP. CP is the most commonly diagnosed phase in CML.[13,41] According to International Chronic Myeloid Leukaemia Paediatric Study in Europe, 92% of patients presented with CP while the remaining 5% were in AP and 3% in BP.[13] Among 169 German patients consecutively registered in the CML-PAED-II trial and registry, 18 (11%) with CML-BP were identified. *De novo* CML-BP was diagnosed in 6% of patients and 5% with secondary CML-BP.[41]

The prognosis of CML relies on three scoring systems: Sokal, EURO, and EUTOS. These systems take into account clinical and hematologic factors, including spleen size, platelet count, and the percentage of blast cells, eosinophils, and basophils in the peripheral blood.[42] Sokal score, Euro and EUTOS scores that predict outcomes in adult patients with CML do not predict response and outcome in paediatric CML. The application of established prognostic CML scores in children has generated inconsistent results.[43]

Some genetic distinctions exist between paediatric and adult CML, including a higher frequency of mutations that contribute to cancer incidences. For example, paediatric patients exhibit the ASXL1 mutation more often than adults. In a study involving a patient cohort of 21 children and young adults diagnosed with CML-CP (median age 14 years, ranging from 0

to 27 years), it was discovered that 29% of paediatric and young adult patients exhibited an ASXL1 mutation. This is in contrast to the lower prevalence of 7–13% observed among adults.[44]

Mortality

The median age of death due to CML in the US is 77 years of age.[45] Mortality due to CML is very rare in paediatric patients and young adults, reflecting a mortality rate of <0.1 per 100,000 persons among individuals age less than 30 years.[5]

Important co-morbidities:

Important co-morbidities for CML are the following:

- Liver and renal dysfunction[46,47,48,49,50]
- Diabetes[47,48,51,52,53]
- Hypertension[47,52,53]
- Cardiovascular diseases[47,48,50,53]
- Pulmonary disease[47,48,50,51,53]
- Osteoarticular diseases (eg, osteoarthritis, disc herniation)[47,48,53]
- GI problems (eg, cholelithiasis and oesophageal reflux)[47,50,53]
- Neurological abnormalities[47,48,50,53]

In paediatric patients, comorbidities in children with CML are less common or rarely seen.[54] There were fewer or no cardiovascular comorbidities reported during an interventional trial in paediatric patients with CML.[55]

Module SII. Non-Clinical Part of the Safety Specification

Non-clinical in vitro and in vivo safety studies have been conducted with bosutinib to support clinical studies. These non-clinical studies were primarily conducted in rat and dog based on the similarity of metabolic profiles to human and suitable PK profiles. The majority of in vivo studies were conducted with oral dosing, the intended route of administration in humans. Study types included safety pharmacology, repeat-dose toxicity (up to 9 months duration), reproductive and developmental toxicity, genetic toxicity, carcinogenicity, and phototoxicity studies.

Based on the non-clinical studies conducted with bosutinib, the primary toxicities observed relative to humans were in the GI tract and with human ether-a-go-go channel interactions. Additional findings identified following bosutinib administration included an effect on fertility and embryo foetal development. Other findings of uncertain risk to humans included lymphoid atrophy and central nervous system effects.

Table 3 below describes the non-clinical safety findings that have potential relevance to human use.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Gastrointestinal toxicity: GI effects were primarily observed in rats as clinical signs of decreased body weight and food consumption. Higher doses that were more severely toxic included clinical signs of dehydration, faecal alterations, red pigment around nose and mouth, yellow discoloration of perineal pelage, high carriage, thin and hunched appearance. Similar findings were reported in dogs.	Bosutinib has been shown to cause gastrointestinal adverse events in humans. Gastrointestinal effect of diarrhoea and vomiting are included in Section 4.4 *Warnings and Precautions* in the SmPC. No additional risk minimization measures need to be added in the summary of safety concerns.
Immunotoxicity: Lymphoid atrophy in thymus, lymph nodes and spleen was observed in rats treated with bosutinib. These effects were mild and reversible. Although the possibility of the direct toxic effect of bosutinib in the lymphoid organs cannot be ruled out, the morphologic changes in lymphoid tissues are consistent with findings secondary to overt toxicity (increased endogenous corticosterone). There was no evidence of compromised immune function in either rats or dogs.	There has been no evidence of compromised immune function in humans.
Genotoxicity: Bosutinib was not genotoxic in in vitro or in vivo assays.	Bosutinib is not expected to have any genotoxic effects.
Carcinogenicity: Bosutinib was not carcinogenic in a 2-year rat carcinogenicity study (09_0837). In the 6-month transgenic rasH2 mouse carcinogenicity study, daily oral gavage administration of 6, 20, or 60 mg/kg/day PF-05208763 to transgenic hemizygous rasH2 mice for up to 26 weeks had no effect on survival and produced no carcinogenic effects.	Bosutinib is not expected to be carcinogenic when used in humans.
Renal toxicity: In toxicity studies of bosutinib of durations up to 6 months in rats and 9 months in dogs, there were no drug-related histological effects on the kidney and no	The relevance of the non-clinical renal findings to humans is not clear. No effects on plasma creatinine were noted in animals, but

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
changes in kidney function as measured by plasma creatinine or blood urea nitrogen. The unbound exposure margins in these studies relative to the human exposure following the 500 mg dose were 1.5, and 1.2 in male and female dogs, and 2.0, and 6.0 in male and female rats, respectively. In a 2-year carcinogenicity study in rats, renal tubular atrophy was observed at an increased incidence, but not severity, relative to vehicle-treated rats at unbound exposure margins of 1.4 in males and 2.8 in females, relative to the human exposure at the 500 mg dose.	this parameter was not measured in the 2-year carcinogenicity study.
Reproductive and development toxicity: In rat fertility studies, bosutinib reduced male fertility, increased embryonic resorptions and reduced the number of viable embryos in females. The administration of bosutinib in the reproductive and developmental toxicity studies resulted in a reduction in the number of viable foetuses in both rats and rabbits as well as decreases in foetal body weight and foetal abnormalities. No adverse reproductive effects were seen at exposures in female rats at 0.2-fold or in female rabbits at 0.7-fold the exposures reported in humans treated with the approved dose of 500 mg/day. Study 17GR319 investigated the effects of bosutinib on rate pre- and post-natal development. The highest dose at which no adverse developmental effects occurred was 10 mg/kg/day, which results in exposure equal to 1.3x the human exposure resulting from the clinical dose of 400 mg (based on unbound AUC in the respective species) (Module 4.2.3.5.2 RPT-17GR319).	Bosutinib has the potential to impair reproductive function, affect fertility, and cause developmental abnormalities in humans. Section 4.6 *Fertility pregnancy and lactation* of the SmPC describes the risks and precautions to be taken for women of childbearing potential.
Lactation: Bosutinib and/or its metabolites were excreted in the milk of lactating rats. Radioactivity was present in the plasma of suckling offspring 24 to 48 hours after lactating rats received a single oral dose of radioactive bosutinib.	It is not known whether bosutinib is excreted in human milk. A potential risk to the breast-feeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with bosutinib. Section 4.6 *Fertility pregnancy and lactation* of the SmPC describes the risks and precautions to be taken.
Effects in juveniles: Studies with bosutinib in 4-week old rats indicated significant decreases in IGFBP-3 but non-significant effects on body weight gain[56] or bone length.[57] In a rat juvenile toxicity study in 7-day old rats, no effects on body weight gain, GH, IGFBP-1, or bone length were observed at the highest tolerated dose level. Study 13GR351 evaluated the potential effects of bosutinib on neonatal growth and development in juvenile rats. Potential effects on bone metabolism were evaluated via measurement of femur length, hormones analysis (growth hormone, insulin-like growth factor-1), clinical pathology evaluation (ALP, calcium, phosphorus), macroscopic examination (bone with marrow, thyroid with parathyroid), organ weight (thyroid with parathyroids), and histopathological examination (femur, stifle joint). The oral	Based on the results from rat juvenile toxicity studies, growth effects are not expected in humans.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
administration of bosutinib at 3 mg/kg had no effect on any bone metabolism parameters evaluated, with systemic exposure (mean total C_{max} and AUC) approximately 8x and 7.4x, respectively, the human exposure at the proposed dose of 400 mg. Mortality and moribundity precluded evaluation of potential effects on bone metabolism at higher doses.	
Studies with oxydechlorinated bosutinib (M2) metabolite: The prominent circulating metabolites in humans had much lower activity in cellular assays than bosutinib. Dosing of rats with the M2 had no treatment-related clinical signs, effects on body weight, food consumption, ophthalmoscopic parameters, clinical pathology, organ weights, or macroscopic or microscopic findings (see 2.6.6, Toxicology Written Summary, Section 8.4.1).	Metabolites of bosutinib are unlikely to be associated with adverse effects.
Phototoxicity: Bosutinib was evaluated for its phototoxic potential in rats. High concentrations of bosutinib in the skin and uveal tract of pigmented rats were not associated with phototoxicity following challenge with UVR exposure.	Bosutinib has a low potential to cause phototoxic effects in humans.
General Safety Pharmacology: • The safety pharmacology of bosutinib was characterised for the CNS and respiratory systems in female rats, and for the cardiovascular system. • In vitro hERG potassium ion channel assays were conducted (see 2.4, Non-Clinical Overview, Section 2.3).	
CNS Effects: CNS effects were limited to greater incidences of impaired gait and decreased pupil size in groups of rats receiving high doses of bosutinib, a dose which resulted in a greater than 8-fold the exposure of participants treated with the approved dose of 500 mg/day (see 2.4, Non-Clinical Overview, Section 2.3).	Bosutinib has a low potential to cause CNS effects in humans.
Respiratory Effects: Bosutinib was administered to rats in order to evaluate the potential effects on the respiratory system. No adverse effects on the respiratory system were observed (see 2.4, Non-Clinical Overview, Section 2.3).	Bosutinib is unlikely to cause adverse respiratory events in humans.
hERG assays: Bosutinib inhibited the hERG potassium ion current in a concentration-dependent manner with calculated IC_{50}s of 0.3 µM (159 ng/mL) and 0.7 µM (371 ng/mL). The lower of the 2 values (0.3 µM) is 12.6-fold above the unbound C_{max} in humans (23.8 nM, 12.6 ng/mL) following administration of the 500 mg dose (see 2.4, Non-Clinical Overview, Section 2.3).	Based on the hERG assay, there is a low potential for bosutinib to cause QTc interval prolongation.
Cardiovascular Safety (including potential for QT interval prolongation): A cardiovascular safety study of oral doses of bosutinib (Module 4.2.1.3 RPT-51769) in dogs did not produce changes in blood pressure. No abnormal atrial or ventricular arrhythmias were detected in this study and there was no bosutinib-related prolongation	There is a low potential for bosutinib to cause cardiovascular effects in patients.

Table 3. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
of the PR, QRS, or QTc interval of the ECG. An increase in heart rate was observed at about 22 hours post-dose.	
A study comparing the cardiovascular effects of bosutinib to imatinib was assessed by echocardiography (Module 4.2.1.3 Report SP3810) in S-D rats. Increases in heart weight and structural changes consistent with hypertrophy were observed in imatinib-treated, but not bosutinib-treated rats. This exposure was approximately 1.5-fold the human area AUC following administration of the 500 mg dose. Rats were treated with bosutinib for 6 months in a cardiovascular study incorporating echocardiography (Module 4.2.1.3 RPT-SP6211) at doses resulting in up to approximately 4-times the clinical exposure following the 500 mg dose. There were no functional changes as measured by echocardiography resulting from bosutinib treatment in the study.[58]	Bosutinib has a low potential of cardiac hypertrophy and any functional changes as measured by echocardiography.
Mechanisms for drug interactions: In vitro, bosutinib has been shown to be an inhibitor of P-gp.	The potential for bosutinib to inhibit P-gp and to increase the intestinal absorption of drugs that are substrates of P-gp was not confirmed in a Phase 1 clinical study in healthy participants, as bosutinib did not affect the systemic exposure of dabigatran.

Module SIII. Clinical Trial Exposure

SIII.1. Brief Overview of Development

Bosutinib is approved for the treatment of adult patients with CP, AP, or BP Ph+ CML previously treated with 1 or more TKI(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, and for the treatment of adult patients with newly-diagnosed CP Ph+ CML. New indications include:

- Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- Adult and paediatric patients aged 6 years and older with CP 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.
- Adult patients with 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.

Cumulatively, it was estimated that 3102 participants worldwide had participated in the Pfizer bosutinib clinical development programme, 2500 of whom had been exposed to bosutinib either as a single agent, in combination with placebo, or in combination with other study drugs, as detailed below.

- 2195 participants had been exposed to bosutinib as a single agent (including 58 participants who had been exposed to bosutinib in combination with placebo).

- 305 participants had been exposed to bosutinib in combination with other study drugs (ie, aprepitant, capecitabine, dabigatran, exemestane, ketoconazole, lansoprazole, letrozole, moxifloxacin, or rifampin).

The remaining 602 participants were exposed to placebo (70), comparator drug in combination with placebo (12), or comparator drug (520).

This RMP is based on the pooled CT results of the safety and tolerability of bosutinib for the treatment of adult participants with Ph+ CML newly-diagnosed CP, second line CP, third line CP, fourth line CP, AP, and BP in the 6 leukaemia trials: CTs AV001 (B1871053), 3160A4-3000-WW (B1871008), 3160A4-200-WW (B1871006), 3160A4-2203-JA (B1871007), B1871039 and B1871048 (Table 4).

In addition, this RMP includes data from the paediatric CT ITCC-054/AAML1921 (n = 56) which is being conducted by an external cooperative group as part of a Clinical Research Collaboration.

Table 4. Bosutinib Clinical Trials Conducted in Participants with Leukaemias

Clinical Trial Number / Status	Title
B1871053; Completed	A Phase 3, multicentre, randomised, open-label study of bosutinib versus imatinib in adult patients with newly-diagnosed CP CML.
B1871008; Completed	A Phase 3, randomised, open-label study of bosutinib versus imatinib in participants with newly-diagnosed CP Ph+ CML.
B1871040; Completed	An open-label bosutinib treatment extension study for participants with CML who have previously participated in bosutinib clinical trials B1871006 or B1871008. Data for participants enrolled in this CT are included under the participants respective parent CT.
B1871006; Completed	A Phase 1/2 study of SKI-606 in Ph+ leukaemias.
B1871007; Completed	A Phase 1/2 study of SKI-606 administered as a single agent in Japanese participants with Ph+ leukaemias.
B1871039; Competed	A Phase 4 safety and efficacy study of bosutinib in participants with Ph+ CML previously treated with 1 or more TKI(s).
B1871048[a]; Primary endpoint completed, study ongoing to collect additional efficacy and safety	A Phase 2, open-label, single arm study of bosutinib monotherapy in Japanese adult participants with newly-diagnosed CP CML.
ITCC-054/AAML1921	A Phase 1/2 study to assess the PK and to investigate the safety, efficacy and tolerability profile of bosutinib in the paediatric population.

a. Last Participant Last Visit was achieved on 04 March 2021; however, the Clinical Study Report is not finalized.

In this RMP, adult participants with CML are separated into 2 pools:

- CML newly-diagnosed CP (CTs B1871053, B1871008 including newly-diagnosed participants from CT B1871040 and B1871048).

- CML regardless of line of therapy (CTs B1871053, B1871008 and B1871006 including B1871040, B1871007, B1871039 and B1871048).

A total of 1348 participants with CML received treatment with bosutinib in the 6 pooled CTs, including 576 participants with newly-diagnosed CP CML and 772 with CP, AP or BP CML previously treated with other TKIs.

Furthermore, bosutinib was administered to participants with Ph+ acute lymphoblastic leukaemia as part of study B1871006 and with solid tumours or breast cancer in 6 additional CTs.

- 24 previously treated participants with Ph+ ALL who received bosutinib as a single agent in B1871006.
- 249 participants with advanced solid tumours who received bosutinib as a single agent: CTs 3160A1-100-US, 3160A1-102-JA, and 3160A2-201-WW.
- 90 participants with solid tumours (mainly breast cancer) who received bosutinib in combination with another anticancer agent: CTs 3160A6-2206-WW, 3160A6-2207-WW, and 3160A6-2208-WW.

Total exposure by pool for the 12 aforementioned CTs in adult participants is presented in Table 5.

Table 5. Total Clinical Trial Exposure in Adult Participants - All Explored Cancer Indications

Cancer Population	Persons	Person Time (years)
Newly diagnosed CML Chronic Phase	576	2393
CML regardless of line of therapy	1348	4652
Ph+ ALL	24	17
Total Leukaemia	1372	4669
Solid tumours, single agent bosutinib	249	53
Solid tumours (mainly breast cancer); bosutinib in combination with another anticancer agent	90	23
Total	1711	4745

The Person Time on treatment for each individual participant is defined as (last dose – first dose + 1)/365.25. The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are round to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

SIII.2. Clinical Trial Exposure

In the following tables, exposure for each indication in participants with CML (newly-diagnosed CP, second line CP, third line CP, fourth line CP, AP, and BP) and for the pool of 6 leukaemia CTs in adult participants, and paediatric participants in CT ITCC-054/AAML1921 are presented by duration of exposure, starting dose, age and gender, and ethnic or racial origin. All exposure data refer to bosutinib.

The data cut-off and snapshot dates for the 6 pooled CTs in adult participants and ITCC-054/AAML1921 in paediatric participants are presented in Table 6.

Table 6. Data Cut-Off and Snapshot Dates for the 6 Pooled Leukaemia Clinical Trials in Adult Participants and ITCC-054/AAML1921 in Paediatric Participants

Clinical Trial	Last Participant First Dose	Cut-Off Date	Approximate Years from Last Participant Enrolment to Data Cut-Off Date	Median Duration of Treatment (months)
B1871053	11 September 2015	12 June 2020	5	55.09
B1871008	30 July 2009	02 September 2020	11	61.69
B1871006	20 April 2010	02 September 2020	10	11.13
B1871007	20 September 2012	07 August 2015	3	30.26
B1871039	18 September 2017	23 November 2020	3	37.80
B1871048	10 April 2018	06 April 2021	36 months	35.93
ITCC-054/AAML1921	24 February 2023	27 February 2023	12 days	13.47

Table 7. Duration of Exposure by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	439	-
≥2 years	401	-
≥3 years	361	-
≥4 years	314	-
≥5 years	133	-
≥6 years	100	-
≥7 years	91	-
≥8 years	85	-
≥9 years	76	-
≥10 years	68	-
≥11 years	35	-
≥12 years	1	12
Total (≥1 dose)	576	2393
Indication: CML Chronic Phase Second Line		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	250	-
≥2 years	205	-
≥3 years	184	-
≥4 years	152	-
≥5 years	127	-
≥6 years	103	-
≥7 years	71	-

Table 7. Duration of Exposure by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

≥8 years	57	-
≥9 years	55	-
≥10 years	48	-
≥11 years	39	-
≥12 years	21	-
≥13 years	5	-
≥14 years	2	28
Total (≥1 dose)	374	1489
Indication: CML Chronic Phase Third Line		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	99	-
≥2 years	83	-
≥3 years	63	-
≥4 years	36	-
≥5 years	20	-
≥6 years	14	-
≥7 years	12	-
≥8 years	11	-
≥9 years	9	-
≥10 years	9	-
≥11 years	3	-
≥12 years	1	-
≥13 years	1	14
Total (≥1 dose)	186	446
Indication: CML Chronic Phase Fourth Line		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	29	-
≥2 years	26	-
≥3 years	23	-
≥4 years	6	-
≥5 years	1	6
Total (≥1 dose)	53	113
Indication: CML Accelerated Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	37	-
≥2 years	23	-
≥3 years	17	-
≥4 years	15	-
≥5 years	10	-
≥6 years	9	-
≥7 years	7	-
≥8 years	6	-
≥9 years	5	-
≥10 years	5	-
≥11 years	3	-

Table 7. Duration of Exposure by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

≥12 years	2	26
Total (≥1 dose)	90	174
Indication: CML Blast Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	5	-
≥2 years	3	-
≥3 years	2	-
≥4 years	2	-
≥5 years	1	6
Total (≥1 dose)	66	35

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 8. Total Duration of Exposure by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	439	-
≥2 years	401	-
≥3 years	361	-
≥4 years	314	-
≥5 years	133	-
≥6 years	100	-
≥7 years	91	-
≥8 years	85	-
≥9 years	76	-
≥10 years	68	-
≥11 years	35	-
≥12 years	1	12
Total (≥1 dose)	576	2393
Indication: CML Regardless of Line of Therapy		
Duration of Exposure	**Persons**	**Person Time (years)**
≥1 year	860	-
≥2 years	742	-
≥3 years	650	-
≥4 years	525	-
≥5 years	292	-
≥6 years	226	-
≥7 years	181	-
≥8 years	159	-
≥9 years	145	-
≥10 years	130	-

Table 8. Total Duration of Exposure by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

≥11 years	80	-
≥12 years	25	-
≥13 years	6	-
≥14 years	2	28
Total (≥1 dose)	1348	4652

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Of note, the starting dose in B1871053 and B1871048 was 400 mg QD and the starting dose in all other CTs (B1871006, B1871008, B1871007 and B1871039) was 500 mg QD.

Table 9. Exposure by Starting Dose and by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Starting Dose	**Persons**	**Person Time (years)**
400 mg	328	1034
500 mg	248	1360
Total (≥1 dose)	576	2393
Indication: CML Chronic Phase Second Line		
Starting Dose	**Persons**	**Person Time (years)**
400 mg	11	71
500 mg	349	1372
600 mg	14	45
Total (≥1 dose)	374	1489
Indication: CML Chronic Phase Third Line		
Starting Dose	**Persons**	**Person Time (years)**
300 mg	1	4
500 mg	185	442
Total (≥1 dose)	186	446
Indication: CML Chronic Phase Fourth Line		
Starting Dose	**Persons**	**Person Time (years)**
300 mg	1	0.2
400 mg	1	3
500 mg	51	110
Total (≥1 dose)	53	113
Indication: CML Accelerated Phase		
Starting Dose	**Persons**	**Person Time (years)**
400 mg	3	3
500 mg	86	171
600 mg	1	0.1
Total (≥1 dose)	90	174

Table 9. Exposure by Starting Dose and by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: CML Blast Phase		
Starting Dose	**Persons**	**Person Time (years)**
500 mg	66	35
Total (≥1 dose)	66	35

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 10. Total Exposure by Starting Dose and by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Starting Dose	**Persons**	**Person Time (years)**
400 mg	328	1034
500 mg	248	1360
Total (≥1 dose)	576	2393
Indication: CML Regardless of Line of Therapy		
Starting Dose	**Persons**	**Person Time (years)**
300 mg	2	4
400 mg	343	1111
500 mg	988	3492
600 mg	15	45
Total (≥1 dose)	1348	4652

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 11. Exposure by Age Group and Gender by Indication – In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly Diagnosed CML Chronic Phase				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	201	137	916	600
≥55 years through 64 years	83	56	373	191
≥65 years	56	43	193	120
Total (≥1 dose)	340	236	1483	911
Indication: CML Chronic Phase Second Line				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	108	91	516	389
≥55 years through 64 years	43	45	174	159
≥65 years	46	41	157	94
Total (≥1 dose)	197	177	847	642

Table 11. Exposure by Age Group and Gender by Indication – In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: CML Chronic Phase Third Line				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	40	39	110	84
≥55 years through 64 years	25	23	72	59
≥65 years	30	29	59	62
Total (≥1 dose)	95	91	240	206
Indication: CML Chronic Phase Fourth Line				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	6	10	15	27
≥55 years through 64 years	7	11	18	16
≥65 years	9	10	13	23
Total (≥1 dose)	22	31	47	66
Indication: CML Accelerated Phase				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	34	20	62	37
≥55 years through 64 years	15	10	29	31
≥65 years	5	6	10	6
Total (≥1 dose)	54	36	101	73
Indication: CML Blast Phase				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	32	15	15	6
≥55 years through 64 years	5	3	2	0.4
≥65 years	7	4	5	7
Total (≥1 dose)	44	22	22	13

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 12. Total Exposure by Age Group and Gender by Indication – In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	201	137	916	600
≥55 years through 64 years	83	56	373	191
≥65 years	56	43	193	120
Total (≥1 dose)	340	236	1483	911

Table 12. Total Exposure by Age Group and Gender by Indication – In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: CML Regardless of Line of Therapy				
Age Group	**Persons**		**Person Time (years)**	
	Male	**Female**	**Male**	**Female**
≥18 years through 54 years	421	312	1633	1143
≥55 years through 64 years	180	148	671	457
≥65 years	154	133	437	312
Total (≥1 dose)	755	593	2741	1911

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 13. Exposure by Ethnic or Racial Origin by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	12	37
Asian	176	686
White	369	1614
Other	19	57
Total (≥1 dose)	576	2393
Indication: CML Chronic Phase Second Line		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	18	44
Asian	105	421
White	225	946
Other	26	78
Total (≥1 dose)	374	1489
Indication: CML Chronic Phase Third Line		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	6	31
Asian	26	56
White	139	316
Other	15	43
Total (≥1 dose)	186	446
Indication: CML Chronic Phase Fourth Line		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	2	0.9
White	47	103
Other	4	9
Total (≥1 dose)	53	113
Indication: CML Accelerated Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	6	4

Table 13. Exposure by Ethnic or Racial Origin by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Asian	29	62
White	48	93
Other	7	15
Total (≥1 dose)	90	174
Indication: CML Blast Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	11	4
Asian	17	11
White	37	20
Other	1	0.0
Total (≥1 dose)	66	35

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 14. Total Exposure by Ethnic or Racial Origin by Indication - In Clinical Trials in Adult Participants with Chronic Myelogenous Leukaemia

Indication: Newly-Diagnosed CML Chronic Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	12	37
Asian	176	686
White	369	1614
Other	19	57
Total (≥1 dose)	576	2393
Indication: CML Regardless of Line of Therapy		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Black	55	120
Asian	353	1235
White	868	3095
Other	72	202
Total (≥1 dose)	1348	4652

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 15. Duration of Exposure by Indication - In Clinical Trials in Paediatric Participants with Chronic Myelogenous Leukaemia

Indication: Resistant/Intolerant Phase I (300mg/m^2) Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥ 1 year	5	-
≥ 2 years	2	-
≥ 3 years	2	-

Table 15. Duration of Exposure by Indication - In Clinical Trials in Paediatric Participants with Chronic Myelogenous Leukaemia

≥ 4 years	1	-
≥ 5 years	1	5
Total person time (≥ 1 dose)	6	14
Indication: Resistant/Intolerant Phase 1 (350mg/m^2) Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥ 1 year	5	-
≥ 2 years	5	-
≥ 3 years	2	7
Total person time (≥ 1 dose)	11	17
Indication: Resistant/Intolerant Phase 1 (400mg/m^2) Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥ 1 year	7	-
≥ 2 years	2	4
Total person time (≥ 1 dose)	11	13
Indication: Newly Diagnosed Phase 2 CP1L (300mg/m^2) Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
≥ 1 year	12	-
≥ 2 years	3	7
Total person time (≥ 1 dose)	24	27
Indication: Resistant/Intolerant Phase 2 R/I (400mg/m^2) Phase		
Duration of Exposure	**Persons**	**Person Time (years)**
Total person time (≥ 1 dose)	3	0.5

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 16. Exposure by Starting Dose and by Indication - In Clinical Trials in Paediatric Participants with Chronic Myelogenous Leukaemia

Indication: Resistant/Intolerant Phase 1 (300mg/m^2) Phase		
Starting Dose	**Persons**	**Person – Time (years)**
150 mg	1	1
200 mg	1	0.8
275 mg	1	4
400 mg	2	7
500 mg	1	2
Total person time	6	14
Indication: Resistant/Intolerant Phase 1 (350mg/m^2) Phase		
Starting Dose	**Persons**	**Person – Time (years)**
250 mg	1	3
275 mg	1	4
300 mg	1	0.1
325 mg	1	0.6

Table 16. Exposure by Starting Dose and by Indication - In Clinical Trials in Paediatric Participants with Chronic Myelogenous Leukaemia

350 mg	1	0.4
375 mg	1	0.8
400 mg	1	2
525 mg	1	3
550 mg	1	0.5
600 mg	2	3
Total person time	11	17
Indication: Resistant/Intolerant Phase 1 (400mg/m^2) Phase		
Starting Dose	**Persons**	**Person – Time (years)**
325 mg	1	0.5
400 mg	1	1
475 mg	1	1
600 mg	8	10
Total person time	11	13
Indication: Newly Diagnosed Phase 2 CP1L (300mg/m^2) Phase		
Starting Dose	**Persons**	**Person – Time (years)**
200 mg	1	2
275 mg	3	2
325 mg	1	0.6
350 mg	1	0.3
400 mg	2	4
425 mg	2	1
450 mg	3	5
475 mg	2	0.6
500 mg	9	12
Total person time	24	27
Indication: Resistant/Intolerant Phase 2 R/I (400mg/m^2) Phase		
Starting dose	**Persons**	**Person – Time (years)**
600 mg	3	0.5
Total person time	3	0.5

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 17. Exposure by Age Group and Gender by Indication - In Clinical Trials with Paediatric Participants with Chronic Myelogenous Leukaemia

Indication: Resistant/Intolerant Phase I (300mg/m^2) Phase				
Age Group	**Persons**	**Persons**	**Person Time (years)**	**Person Time (years)**
	Male	**Female**	**Male**	**Female**
≥ 1 years through 6 years	2	0	2	0

Table 17. Exposure by Age Group and Gender by Indication - In Clinical Trials with Paediatric Participants with Chronic Myelogenous Leukaemia

≥6 years through 12 years	3	0	11	0
≥12 years through 18 years	0	1	0	2
Total	5	1	13	2
Indication: Resistant/Intolerant Phase 1 (350mg/m^2) Phase				
Age Group	**Persons**	**Persons**	**Person Time (years)**	**Person Time (years)**
	Male	**Female**	**Male**	**Female**
≥ 1 years through 6 years	0	2	0	3
≥6 years through 12 years	1	3	0.6	7
≥12 years through 18 years	3	2	2	6
Total	4	7	2	15
Indication: Resistant/Intolerant Phase 1 (400mg/m^2) Phase				
Age Group	**Persons**	**Persons**	**Person Time (years)**	**Person Time (years)**
	Male	**Female**	**Male**	**Female**
≥6 years through 12 years	3	0	3	0
≥12 years through 18 years	4	4	5	4
Total	7	4	8	4
Indication: Newly Diagnosed Phase 2 CP 1L (300mg/m^2) Phase				
Age Group	**Persons**	**Persons**	**Person Time (years)**	**Person Time (years)**
	Male	**Female**	**Male**	**Female**
≥ 1 years through 6 years	1	1	0.8	2
≥6 years through 12 years	2	4	1.0	2
≥12 years through 18 years	12	4	16	6
Total	15	9	18	9
Indication: Resistant/Intolerant Phase 2 R/I (400mg/m^2) Phase				
Age Group	**Persons**	**Persons**	**Person Time (years)**	**Person Time (years)**
	Male	**Female**	**Male**	**Female**
≥12 years through 18 years	2	1	0.3	0.2
Total	2	1	0.3	0.2

The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Table 18. Exposure by Ethnic or Racial Origin by Indication - In Clinical Trials with Paediatric Participants with Chronic Myelogenous Leukaemia

Indication: Resistant/Intolerant Phase I (300mg/m^2) Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
Unknown[a]	6	14
Total	6	14
Indication: Resistant/Intolerant Phase 1 (350mg/m^2) Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
White	5	9
Black or African American	1	0.5
Asian	1	0.1
Unknown[a]	4	7
Total	11	17
Indication: Resistant/Intolerant Phase 1 (400mg/m^2) Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
White	7	9
Black or African American	1	2
Asian	3	2
Total	11	13
Indication: Newly Diagnosed Phase 2 CP1L (300mg/m^2) Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
White	19	21
Black or African American	4	4
Native Hawaiian or Other Pacific Islander	1	3
Total	24	27
Indication: Resistant/Intolerant Phase 2 R/I (400mg/m^2) Phase		
Ethnic/Racial Origin	**Persons**	**Person Time (years)**
White	2	0.5
Black or African American	1	0.0
Total	3	0.5

a. Race and ethnicity were initially not captured in the case report form (included after (CRF v2.1).
The Person Time on treatment for each individual participant is defined as (last dose - first dose + 1)/365.25.
The counts under Person Time column are rounded to whole numbers, when greater than 1. When the counts are less than 1, they are rounded to nearest tenth. This may result in the Total row mismatching the sum of individual counts.

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

There has been limited exposure in special populations in the bosutinib CML CTs and no epidemiologic studies have been conducted. Pregnant/lactating women, paediatric patients (age: ≤17 years), participants with cardiac impairment, and specific subpopulations with genetic polymorphisms were excluded from the CT development programme; PK CTs were conducted in participants with hepatic impairment and in participants with renal impairment.

Table 19. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale
Hepatic impairment	Participants in CTs were required to have adequate hepatic function. In a study on the effect of hepatic impairment, an approximately 2-fold increase in bosutinib exposures was observed in the hepatically impaired (Child-Pugh Classes A, B, and C) participants as compared with healthy participants when administered 200 mg of bosutinib. An increased exposure above that provided with the clinically recommended dose of bosutinib could lead to additional toxicity. The frequency of QTc interval prolongation, defined as a QTc >450 ms, increased with declining hepatic function per grade of hepatic impairment	No	Use of bosutinib in patients with hepatic impairment is contraindicated in the bosutinib SmPC (Section 4.3).
Ph- CML	Primary endpoint of most CT based on CyR.	No	The target of bosutinib is the BCR-ABL non-receptor tyrosine kinase transcript, present in both Ph+ and Ph- CML, and literature supports that patients with both Ph+ and Ph- CML have similar natural history of disease and respond similarly to TKI therapy.[59] These Ph- negative, BCR-ABL+ patients have a similar clinical presentation, response to therapy, and prognosis as Ph+ CML patients.[60,61] Ph- CML accounts for 5% or less of CML patients[62] and there are no large Phase 3 CTs outlining treatment specifics for Ph- patients. It is not possible to assess cytogenetic endpoints in Ph- patients.

Table 19. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale
			However, in recent years, the relevance of cytogenetic endpoints has decreased, and the focus of response assessment has switched to molecular monitoring. Among the limited number of patients with Ph- CML enrolled in the bosutinib CTs, some were able to achieve/maintain molecular responses.
Participants with extramedullary disease only	To ensure uniformity of CT population and exclude participants with restricted disease potentially adversely impacting CT results. Primary endpoint of most CT based on CyR, and response cannot be assessed in patients without marrow disease.	No	Extramedullary disease is associated with BC or impending BC, a later stage of disease. Bosutinib has a positive benefit-risk profile in Ph+ CML patients with BC.
Major surgery or radiotherapy within 14 days of randomisation	To reduce the risk of AEs associated with prior procedures, which may interfere with successful administration of bosutinib and to ensure uniformity of the CT population.	No	A negative benefit-risk profile for bosutinib would not be expected in patients who underwent recent major surgery or radiation therapy, based on the AE profile of bosutinib.
Concomitant use of or need for medications known to prolong the QT interval	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	The SmPC provides recommendation in Sections 4.4 and 4.5 aimed at mitigating the risk of QTc prolongation. These recommendations are considered sufficient, allowing the physician to make an assessment of the benefit-risk for the individual patient without a need for a contraindication.
History of clinically significant or uncontrolled cardiac disease including: history of or active congestive heart failure uncontrolled angina or hypertension within 3 months	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	No available data suggest a negative benefit-risk profile for bosutinib in patients who have uncontrolled cardiac disease. The SmPC notes that caution should be exercised in patients with relevant cardiac disorders (Section 4.2) and has language

Table 19. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale
myocardial infarction (within 12 months) clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsade de pointes) diagnosed or suspected congenital or acquired prolonged QT history of prolonged QTc unexplained syncope			in Sections 4.4 and 4.5 aimed at mitigating the risk of QTc prolongation.
Prolonged QTc (>0.45 ms; average of triplicate readings at screening)	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	The SmPC provides a recommendation in Sections 4.4 and 4.5 aimed at mitigating the risk of QTc prolongation without a need for a contraindication. These recommendations are considered sufficient without a need for a contraindication, allowing the physician to make an assessment of the benefit-risk for the individual patient.
Recent or ongoing clinically significant GI disorders	To ensure uniformity of CT population having adequate GI absorption and exclude participants with significant co-morbidities potentially confounding CT results.	No	Guidance is provided to use bosutinib with caution in patients with recent or ongoing clinically significant GI disorders. There is no evidence these clinical events have led to safety issues and therefore a contraindication is not considered warranted at this time.
Known seropositivity to HIV, current acute or chronic hepatitis B (hepatitis B surface antigen positive), hepatitis C, or cirrhosis	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	It is the potential liver manifestations of these diagnoses that are important. If any of the patients suffering from these diseases have hepatic impairment (eg, cirrhosis) then use of bosutinib would be contraindicated as stated in Section 4.3 of the SmPC. Hepatitis B reactivation has

Table 19. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale
			occurred with BCR-ABL TKIs. The SmPC provides a recommendation in Section 4.8 to test patients for HBV infection before initiating treatment with bosutinib and to closely monitor carriers of HBV for signs and symptoms of active HBV infection during treatment. These recommendations are considered sufficient without a need for a contraindication, allowing the physician to make an assessment of the benefit-risk for the individual patient.
Uncontrolled hypomagnesaemia or uncorrected hypokalaemia due to potential effects on the QT interval	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	The SmPC provides recommendations in Sections 4.4 and 4.5 aimed at mitigating the risk of QTc prolongation including that the presence of hypomagnesaemia or hypokalaemia may further increase the risk. These recommendations are considered sufficient without a need for a contraindication. In a single-dose oral dog cardiovascular safety study of bosutinib, neither abnormal atrial or ventricular arrhythmias nor bosutinib-related prolongation of the PR, QRS, or QTc interval of the electrocardiogram were detected.
Unstable or severe uncontrolled medical condition, evidence of serious active infection, significant psychiatric illness, or any important medical illness or abnormal laboratory finding that would, in the investigator's judgement, increase the risk	To ensure uniformity of CT population and exclude participants with significant co-morbidities potentially confounding CT results.	No	No data exist to suggest a negative benefit-risk profile for bosutinib in patients with severe acute or chronic medical or psychiatric conditions.

Table 19. Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale
associated with the participants participation in the study			

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of ARs such as rare ARs, ARs with a long latency, and ARs caused by prolonged exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 20 lists the patient populations that have been under-represented in CTs in the bosutinib clinical development programme.

Table 20. Exposure of Special Populations Included Or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Elderly Patients[a]	Elderly participants accounted for 287 (21.3%) of the participants enrolled in the 6 pooled leukaemia CTs[b] (N = 1348, total person years exposure = 4579) and received 731 (16.0%) person years exposure.
Paediatric Patients[c]	Not included in the MAH's clinical development programme. However, a Phase 1/2 paediatric CT being conducted by an external cooperative group as part of a clinical research collaboration, with the data to be transferred to the MAH, enrolled its first participant in November 2016.
Pregnant/Lactating Women[d]	Although pregnancy and lactation are exclusion criteria for bosutinib CTs, as of the DLP there were 14 cases in the CT database that reported pregnancy (including 7 that reported exposure via father) in bosutinib CTs.
Patients with Hepatic Impairment	Eighteen (18) participants with mild, moderate, or severe hepatic impairment were administered bosutinib in CT 3160A4-1111-EU which examined the effect of hepatic impairment on the PKs of bosutinib.
Patients with Renal Impairment	Participants with creatinine >1.5 x the ULN were excluded from the CML CTs. In CT B1871020, the PKs, safety, and tolerability of single doses of bosutinib in 26 participants with mild, moderate, or severe renal impairment were investigated.
Patients with Cardiac Impairment	Although Patients with Cardiac Impairment are exclusion criteria for bosutinib CTs, as of the DLP there were 180 cases in the CT database that reported a history of Cardiac Impairment.
Patients with Recent or Ongoing Clinically Significant GI Disorders	Although Patients with Recent or Ongoing Clinically Significant GI Disorders are exclusion criteria for bosutinib CTs, as of the DLP there were 282 cases in the CT database that reported a history of Recent or Ongoing Clinically Significant GI Disorders.

Table 20. Exposure of Special Populations Included Or Not in Clinical Trial Development Programmes

Type of special population	Exposure
Non-White/Non-Asian Patients	In the 6 pooled leukaemia CTs[b] (N = 1348, total person years exposure = 4579), 55 participants were black, 72 participants had an ethnicity reported as different; person years exposure were 120 and 202, respectively.
Patients with Background of Infectious Diseases	Not included in the MAH's clinical development programme.
Subpopulation of Patients Carrying Relevant Genetic Polymorphisms	Not included in the MAH's clinical development programme.

a. age: ≥65 years
b. clinical trials B1871053, B1871008, B1871006, B1871007, B1871039 and B1871048.
c. Age: ≤17 years
d. Includes in utero exposure

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

The methodology for calculating patient exposure from marketing experience has been changed. Pfizer is evolving patient equivalent count methodology to increase data quality and standardize approach across maximum of countries. As most as possible a unique data source of volume and units will be IQVIA MIDAS to improve homogeneity of collected information and avoid integration of inventory and stockage effect.

In addition to moving to a new data source which improves data quality, Pfizer is rationalizing for most products, the patient equivalent calculation to anchor methodology on dose label definition with average duration of therapy best estimation by patient. If no specific patient data is available, an average volume definition is defined by patients to extrapolate patients equivalent on volumes observed in IQVIA MIDAS data source. Those changes will enhance our patient equivalent exposure calculation to ensure standardized and rationalized approach for most of countries (North America and International Developed Markets as defined in Pfizer).

Cumulatively, it was estimated that 93,618 patients worldwide had been exposed to bosutinib commercially since bosutinib was first approved.

The estimates of the numbers of patients worldwide who were exposed to the commercial formulation of bosutinib cumulatively were calculated based on the Pfizer North America, IDM countries and EM countries methodologies presented in Sections SV.1.1, SV.1.2, and SV.1.3, respectively.

In contrast, the cumulative number of CU patients (242) who received bosutinib as of the DLP of this report is not an estimate but rather is known, as CU requests are processed and tracked on an individual basis by the MAH, which provides clinical drug supply to patients meeting the criteria for participation in the CU program. As such, the estimates of patients worldwide who received commercial bosutinib do not include patients receiving clinical drug supply through the CU program.

However, because bosutinib has achieved approval status in a number of countries since its initial approval, it is possible that some of the patients who were initially receiving bosutinib clinical drug supply through the CU program transitioned to receive commercial bosutinib via prescription. The MAH is not able to track individual patients once they have discontinued from the CU program, so it is possible that the cumulative estimate of 93,618 patients worldwide who received commercial bosutinib as of approximately 01 November 2023 may include some former CU patients who went on to receive commercial bosutinib once bosutinib was approved in their countries.

SV.1.1. Cumulative Patient Exposure from Marketing Experience for North America

Cumulatively, as of 01 November 2023, it was estimated that 18,589 patients in North America had been exposed to bosutinib commercially from 01 September 2012 to 01 November 2023.

US patient exposure estimates were derived from the US SPP data. The new patient's data were summed up with the Canada patient exposure obtained from MIDAS to obtain 18,589 patients from 01 September 2012 to 01 November 2023.

SV.1.2. Cumulative Patient Exposure from Marketing Experience for IDM Countries

As per the updated methodology for bosutinib, US SPP data were used to estimate New Patient to TRx Ratio. From the US SPP data, 17,897 total new patients in the cumulative period (01 September 2012 to 01 November 2023) were divided by the total TRx 286,633 to attain 6.24% New Patient TRx Ratio. IDM KG sales data extracted from MIDAS was summed up for all IDM countries till 01 November 2023. The sales have been extrapolated from 01 October 2023 to 01 November 2023 by taking average of the previous 4 quarters. The total KG sales data was divided by 0.015 to attain the TRx values in cumulative period. The Total TRx values were multiplied with the US New Patient TRx Ratio of 6.24% for the cumulative period. The total IDM patient exposure in cumulative period was 26,580 patients. The country wise patient exposure in IDM countries for cumulative reporting period is given in the below Table 21.

Table 21. Country Patient Exposure in IDM Countries

	Cumulative (01 September 2012 to 01 November 2023)
Austria	220
Belgium Luxembourg	432
Denmark	178
France	2483
Germany	1570
Hungary	194
Ireland	124
Italy	1257
Japan	5243
Netherlands	351
Poland market	310
Portugal	191
Romania	132
Russia	1149
Spain	751
Sweden	195
Switzerland	209
Turkey market	622
United Kingdom	10,968
Total (IDM)	**26,580**

*No patient exposure data was available for the following IDM countries: Belarus, Cyprus, Malta, Greece, Korea market, New Zealand, Australia, Israel, Lithuania, Latvia, Estonia, Kazakhstan, Azerbaijan, Georgia, Albania, Kosovo, Macedonia, Finland, Slovakia and Bosnia Herzegovina.

SV.1.3. Cumulative Exposure from Marketing Experience for EM Countries

The EM countries exposure is based on the Sales LCD and Standard Units extracted from Midas database at country and strength level for bosutinib from 3rd quarter 2015 to 3rd quarter 2023 for the cumulative period along with the internal sales data from 2020 to December 2022[2] for the cumulative period.

For the EM countries exposure, the total sales LCD is divided by the total Standard unit sales on a country basis to obtain the country wise unit cost. The average MG is calculated based on the dose information available for each country separately. In order to obtain the Total volume, the internal sales data is divided by the country wise unit cost. Further, the country wise total volume is multiplied with the average MG to obtain MG volume. The country wise total MG volume is divided by AVDOS 500 mg/day to obtain EM countries' patient exposure of 48,449 for the cumulative period.

Cumulative estimated exposure for EM countries based on total patients from launch through 01 November 2023 are summarized in Table 22.

Table 22. Cumulative Estimated Exposure for Bosutinib for EM Countries

Country	Finance Data	Unit Cost	Total Volume	Average MG	MG Volume	Total Patients
Argentina	1,259,821	-	-	-	-	-
Brazil	-	34	-	60	-	-
Central America and Caribbean	-	-	-	-	-	-
Chile	2,625,713	76	34,442	360	12,399,067	24,798
China	-	-	-	-	-	-
Colombia	4,732,880	79	60,062	30	1,801,858	3604
Ecuador	-	-	-	-	-	-
India	-	-	-	-	-	-
Malaysia	-	-	-	-	-	-
Mexico	175,168	32	5508	1820	10,023,823	20,048
Peru	-	-	-	-	-	-
Singapore	207,047	-	-	-	-	-
Taiwan	-	-	-	-	-	-
Thailand	-	-	-	-	-	-
Total (EM)	**9,000,629**	**221**	**100,011**	**2270**	**24,224,748**	**48,449**

SV.1.4. Worldwide Patient Exposure from Compassionate Use

Cumulatively, 242 patients worldwide had been exposed to bosutinib on a CU basis; the patient exposure numbers by region/country are presented in Table 23. Of these 242 patients, 239 were adult patients who received bosutinib for the treatment of Ph+ CML after

[2] Finance data for EM countries is available only till December 2022.

developing resistance or intolerance to, or had contraindications to, at least 1 or more prior TKI; the other 3 patients received bosutinib in the following manner:

- 1 Ph+ CML patient was a 15-year-old female (paediatric patient) from the US who received bosutinib in 2006.
- 2 patients with Ph+ ALL received bosutinib (1 patient from Switzerland received bosutinib in 2012 and 1 patient from Hong Kong received bosutinib in 2015).

Table 23. Worldwide Cumulative Patient Exposure to Bosutinib on a Compassionate Use Basis by Region/Country

Region/Country	Number of Patients
European Union	136
United States	22
Malaysia	18
India	17
Canada	15
Australia	8
Hong Kong	6
South Africa	5
Switzerland	5
Israel	4
Russia	2
New Zealand	1
Nigeria	1
Philippines	1
Ukraine	1
Total	**242**

SV.1.5. Worldwide Patient Exposure from Non-Interventional Studies

Cumulatively, it was estimated that 955 patients worldwide had been exposed to bosutinib in Pfizer-sponsored NISs.

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for Misuse for Illegal Purposes

There is very low potential for misuse for illegal purposes with bosutinib. Bosutinib does not have characteristics that would make it attractive for use for illegal purposes.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no important identified risks, important potential risks, or missing information for bosutinib.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

SVII.2.1. New Important Risks Added to the List of Safety Concerns

None.

SVII.2.2. Important Risks Removed from the List of Safety Concerns

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no important identified risks, important potential risks, or missing information for bosutinib.

Module SVIII. Summary of the Safety Concerns

There are no safety concerns for bosutinib.

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities include ADR reporting and signal detection.

- **Specific adverse reaction follow-up questionnaires for safety concerns:**
  None.
- **Other forms of routine pharmacovigilance activities for safety concerns:**
  None.

III.2. Additional Pharmacovigilance Activities

None.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. Ongoing and Planned Additional Pharmacovigilance Activities

Table 24. 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				
None				

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no post-authorisation efficacy studies being conducted or planned with bosutinib.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Bosulif (bosutinib)

This is a summary of the RMP for Bosulif. The RMP details important risks of Bosulif, how these risks can be minimised, and how more information will be obtained about Bosulif's risks and uncertainties (missing information).

Bosulif's SmPC and its PL give essential information to HCPs and patients on how Bosulif should be used.

This summary of the RMP for Bosulif should be read in the context of all this information including the Assessment Report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Bosulif's RMP.

I. The Medicine and What It Is Used For

Current indication:

Bosulif is authorised for treatment of adult patients with CP, AP, or BP Ph+ CML previously treated with 1 or more TKIs and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options, and for the treatment of adult patients with newly-diagnosed CP Ph+ CML. It contains bosutinib as the active substance and it is given orally.

New indication:

- Adult and paediatric patients aged 6 years and older with newly-diagnosed (ND) chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- Adult and paediatric patients aged 6 years and older with CP 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.
- Adult patients with 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.

See SmPC for the full indications.

Further information about the evaluation of Bosulif's benefits can be found in Bosulif's EPAR, including its plain-language summary, available on the EMA website, under the medicine's webpage:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002373/human_med_001613.jsp&mid=WC0b01ac058001d124

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

There are no important identified risks, important potential risks, or missing information for Bosulif.

Routine risk minimisation activities, which include the use of SmPC and PL are sufficient to manage the product. In addition, information about adverse events is collected continuously analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

There are no important identified risks, important potential risks, or missing information for Bosulif.

II.B. Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for bosutinib.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of this product.

II.C.2. Other Studies in Post-Authorisation Development Plan

None.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, ongoing, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and ongoing studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 2. TABULATED SUMMARY OF PLANNED, ON-GOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 1 Annex II: Planned and on-going studies

Study	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Phase 1/2 to investigate safety and efficacy of bosutinib in the paediatric population (CT ITCC-054/ AAML1921) Category 3 (ongoing)	The Phase 1 main objective is to determine the Recommended Phase 2 Dose of Bosutinib for Resistant/intolerant ($RP2D_{R/I}$) and newly diagnosed chronic phase ($RP2D_{ND}$) 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 last patient first visit (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 on behalf of the MAH by an external cooperative group as part of a Clinical Research Collaboration with the data to be transferred to the MAH. Final study report submission: 31 January 2029.

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
An open-label, single-dose, parallel-group study of the pharmacokinetics and safety of bosutinib in subjects with renal impairment and	The primary objective of this study was to verify that renal impairment did not affect bosutinib pharmacokinetics.	Effect of renal impairment on the pharmacokinetics of bosutinib.	Final study report submission: 12 April 2013 Module 5.3.3.3 B1871020 Final CSR

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
matched healthy adults (B1871020) Category 3			
Study of the effect of bosutinib on growth in juvenile rats (13GR351 [non-clinical]) Category 3	To define the potential impact of bosutinib on growth in paediatric patients.	Evaluate the reported off-target effects on bone growth of tyrosine kinase inhibitors.	Final study report submission: 24 November 2014 Module 4.2.3.5.4 Study 13GR351
Phase 1 drug-drug interaction study of bosutinib with a moderate CYP3A inhibitor (B1871041) Category 3	To evaluate the effect of a single oral dose of aprepitant on the pharmacokinetic profile of a single oral dose of bosutinib in healthy subjects.	Drug interaction with CYP3A inhibitors.	Final study report submission: 06 March 2015 Module 5.3.5.4 B1871041 Final CSR
Phase 1 P-gp drug-drug interaction study (B1871043) Category 3	To evaluate the effect of a P-gp inhibitor on the pharmacokinetic profile of bosutinib in healthy subjects.	Drug interaction with P-gp inhibitors.	Final study report submission: 06 March 2015 Module 5.3.5.4 B1871043 Final CSR
Phase 1 absolute bioavailability study (B1871044) Category 3	To determine the absolute bioavailability of bosutinib.	Fulfilment of EMA post-approval requirement.	Final study report submission: 03 August 2015 Module 5.3.4.1 B1871044 Final CSR
Rat pre- and post-natal development, including maternal function, study (non-clinical) (17GR319) Category 3	To investigate the developmental toxicity of bosutinib in late pregnancy through weaning stages.	Pregnancy	Final study report submission: January 2019 Module 4.2.3.5.3 Study 17GR319
Six-month transgenic rasH2 mouse carcinogenicity study (non-clinical) Category 3	To investigate the potential tumourgenicity of bosutinib.	Carcinogenicity	Final study report submission 19 June 2020 Module 4.2.3.4
Phase 4 safety and efficacy (CT B1871039) Category 2	To estimate the safety and efficacy of bosutinib in subjects with Ph+ CML who have been treated with 1 or more TKI(s).	- Hepatotoxicity - Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting) - QT Prolongation	Module 5.3.5.4 B1871039 Final CSR 25 June 2021

Study	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
		- Renal Dysfunction - Cardiac Toxicity (Excluding QT Prolongation) - Safety in Patients with Cardiac Impairment - Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders	
Open-label rollover/extension CT for subjects with CML who previously received bosutinib in CTs 3160A4-200-WW (B1871006) or 3160A4-3000-WW (B1871008) (CT B1871040) Category 3	To allow for continued long-term bosutinib treatment in subjects with CP or AP Ph+ CML who previously received bosutinib in the Ph+ CML CTs 3160A4-200-WW (B1871006) or 3160A4-3000-WW (B1871008) and who are thought to have the potential, as judged by the investigator, to derive clinical benefit from continued treatment with bosutinib.	- Hepatotoxicity - Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting) - QT Prolongation - Renal Dysfunction - Cardiac Toxicity (Excluding QT Prolongation) - Safety in Patients with Cardiac Impairment - Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders - Long-Term Safety (>365 Days)	Module 5.3.5.4 B1871040 Final CSR Final study report submission: 25 June 2021

ANNEX 3. PROTOCOLS FOR PROPOSED, ON-GOING, AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP: None

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP: None

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority:

Approved protocols:

- ITCC-054/AAML1921: EMEA-000727-PIP01-09-M02; being conducted on behalf of the Marketing Authorisation Holder (MAH) by an external cooperative group as part of a Clinical Research Collaboration with the data to be transferred to the MAH.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None.

ANNEX 5. PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Efficacy studies which are conditions of the marketing authorisation: None

Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES

None.

ANNEX 7. OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIALS)

1 Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: Results of the HAEMACARE project. Blood 2010;116(19):3724-34.

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ANNEX 8. SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Table 1. Significant Changes to the Risk Management Plan Over Time

Version(s)	Approval Date Procedure	Change
1.0, 1.1, 1.2, 1.3	At the time of authorisation: 27 March 2013 Version 1.0 28 June 2011 Procedure number: EMEA/H/C/ 002373//0000 Version 1.1 06 April 2012 Procedure number: EMEA/H/C/ 002373//0000 Version 1.2 01 October 2012 Procedure number: EMEA/H/C/ 002373//0000 Version 1.3 12 December 2012 Procedure number: EMEA/H/C/ 002373//0000	Updated based on interactions with EMA. Version 1.3 represents agreed initial RMP. <u>Important identified risks:</u> • Hepatotoxicity • Gastrointestinal Toxicities • Hypersensitivity Reactions, Including Anaphylaxis • Fluid Retention • Myelosuppression • QT Prolongation • Respiratory Tract Infections • Bleeding Events • Rash • Pancreatitis <u>Important potential risks:</u> • Cardiac Toxicity (Excluding QT Prolongation) • Interstitial Lung Disease • Thyroid Dysfunction • Tumour Lysis Syndrome • Bone Turnover / Bone Mineral Metabolism Disorders • Immunotoxicity <u>Missing information:</u> • Paediatric safety • Safety in elderly patients • Safety in non-white and non-Asian patients • Renal impairment • Safety in patients with hepatic impairment • Safety in patients with cardiac impairment • Safety in patients with recent or ongoing clinically significant gastrointestinal disorders • Pregnancy and lactation • Carcinogenicity • Long-term safety • Interactions of bosutinib with P-gp substrates • Safety in patients with background diseases • Efficacy and safety information in the proposed indication
2.0	22 May 2014 Procedure number: EMEA/H/C/	Maintained initial list of important identified risks and important potential risks. Removed “Carcinogenicity”, “Safety in patients with hepatic impairment”, and “Efficacy and safety information in the proposed indication” from the list of missing information.

Table 1. Significant Changes to the Risk Management Plan Over Time

Version(s)	Approval Date Procedure	Change
	2373/II/0001	Updated data to focus on recent experience in target population (i.e., CTs 3160A4-200-WW [B1871006] and 3160A4- 2203-JA [B1871007]). Added information on planned new safety and efficacy studies.
2.1	22 May 2014 Procedure number: EMEA/H/C/ 2373/II/0001	Added "Renal Dysfunction" as an important identified risk. Included draft SmPC text from Warnings and Precautions section for "Renal Dysfunction".
3.0	13 January 2015 Procedure number: EMEA/H/C/ 002373/IB/0011	Important identified risk "Gastrointestinal Toxicities" was renamed to "Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)"; important identified risk "Pancreatitis and Lipase Increased" was renamed to "Pancreatitis". Data were updated with most recent CT snapshot dates and MedDRA terms for each important identified and important potential risk were revised.
3.1	23 July 2015 Procedure number: EMEA/H/C/ 002373/II/0014/G	Removed "Interaction of bosutinib with P-gp substrates" from missing information.
4.0	22 February 2018 Procedure number: EMEA/H/C/ 002373/II/0025/G	<u>Important identified risks:</u> • Added "Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis" as a new important identified risk. • Reclassified "Tumour Lysis Syndrome" from an important potential risk to an important identified risk. • Removed "Respiratory Tract Infections", "Bleeding Events", "Rash", and "Pancreatitis" from the list of important identified risks. • Revised search criteria for "Hypersensitivity Reactions, Including Anaphylaxis" in order to exclude MedDRA terms in the new important identified risk "Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis". <u>Important potential risks:</u> • Removed "Thyroid Dysfunction" and "Immunotoxicity" from the list of important potential risks. <u>Missing information:</u> • Removed "Safety in non-White and non-Asian Patients", "Long-Term Safety (≥365 days)", and "Safety in Patients with Background Infectious Diseases" from the list of missing information. CTs AV001, B1871039, and B1871040 were added to the pool of CTs. Data were updated with most recent CT snapshot dates.

Table 1. Significant Changes to the Risk Management Plan Over Time

Version(s)	Approval Date Procedure	Change
4.1	22 February 2018 Procedure number: EMEA/H/C/ 002373/II/0025/G	Important identified risks: • Removed "Hypersensitivity Reactions, Including Anaphylaxis", "Fluid Retention", "Myelosuppression", and "Tumour Lysis Syndrome". Important potential risks: • Removed "Interstitial Lung Disease" and "Bone Turnover / Bone Mineral Metabolism Disorders". Important identified interactions: • Removed "Interactions with CYP3A Inhibitors" and "Interactions with CYP3A Inducers". Important potential interaction: • Removed "Interactions with Proton Pump Inhibitors". Missing information: • Added "Carcinogenicity". • Removed "Safety in Elderly Patients" and "Safety in Patients with Renal Impairment"; removed "Lactation" from "Pregnancy and Lactation". Additional pharmacovigilance activities: • Added 2 non-clinical studies ("Carcinogenicity" and "Growth and Development") as Category 3 required additional pharmacovigilance activities. • Recategorised renal function testing in CTs and collection of blood samples in CT B1871048 for genetic testing from routine pharmacovigilance activities to additional pharmacovigilance activities.
4.2	14 February 2018 Not submitted; internally approved only	Missing information: • Added "Long-Term Safety (>365 Days)".
4.3	18 October 2018 Procedure number: EMEA/H/C/ 002373/II/0030	Important identified risks: • Added "Increased Toxicity Due to Interactions with CYP3A4 Inhibitors", "Lack of Efficacy Due to Interactions with CYP3A4 Inducers", and "Lack of Efficacy Due to Interactions with PPIs".
4.4	\ 18 October 2018 Procedure number: EMEA/H/C/ 002373/II/0030	Additional pharmacovigilance activities: • Added NIS B1871052 as a completed additional pharmacovigilance activity for the important identified risks "Increased Toxicity Due to Interactions with CYP3A4 Inhibitors", "Lack of Efficacy Due to Interactions with CYP3A4 Inducers", and "Lack of Efficacy Due to Interactions with PPIs".
4.5		Missing information:

Table 1. Significant Changes to the Risk Management Plan Over Time

Version(s)	Approval Date Procedure	Change
	Procedure number: EMEA/H/C/002373/II/0037 16 May 2019	• Removed "Pregnancy".
5.0	Procedure number: EMEA/H/C/002373/II/0043 03 September 2020	Nonclinical Part of Safety Specification: • Provided results of the 6-month transgenic rasH2 mouse carcinogenicity study. Post-authorisation exposure: • Updated post-marketing exposure with DLP of 03 March 2020 Missing information: • Removed "Carcinogenicity" Additional pharmacovigilance activities • Modified description of UTCC-054/AAML1921 and final clinical study report (CSR) from September 2020 to March 2024 • Changed the due date of the final CSR for CT B1871040 from December 2020 to June 2021
6.0	Procedure number: EMEA/H/C/002373/II/0050/G	Important identified risks: • Proposed removal of 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: • Proposed removal of Cardiac Toxicity (Excluding QT Prolongation). Missing information: • Proposed removal of Safety in Patients with Cardiac Impairment, Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders, and Long-Term Safety (>365 Days). Clinical Trial Exposure and Post-authorisation exposure: • Updated post-marketing exposure with DLP of 01 January 2021 Additional Pharmacovigilance Activities CT B1871039, CT B1871040, CTB1871048 updated to completed studies.
6.1		Removal of the following important identified risks Hepatotoxicity,

Table 1. Significant Changes to the Risk Management Plan Over Time

Version(s)	Approval Date Procedure	Change
	Procedure number: EMEA/H/C/002373/II/0050/G 27 January 2022	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), the following important potential risk of Cardiac Toxicity (Excluding QT Prolongation), and the following missing information Safety in Patients with Cardiac Impairment, Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders, and Long-Term Safety (>365 Days).
6.3	Procedure number: EMEA/H/C/002373/IB/0057 05 March 2024	Additional pharmacovigilance activities • Updated date of final CSR for CT ITCC-054/AAML1921 • References consolidated in Annex 7
7.0	TBD	Proposed new indications and Dosage Form Epidemiology of the Indication(s) and Target Population(s): Updated with paediatric data. Missing Information: Use in paediatric patients age ranged updated to <1 year. Clinical Trial Exposure and Post-Authorisation Exposure: Clinical trial exposure updated with DLP of 27 February 2023 (CT ITCC-054/AAML 1921) and 06 April 2021 (B1871048) and post-marketing exposure updated with DLP of 01 November 2023.
7.1	TBD	Removed CT ITCC-054/AAML 1921 as an additional pharmacovigilance activity.
7.2	TBD	Removal of Use in paediatric patients less than 1 year from missing information.
7.3 /8.0	Procedure	Update paediatric indication. Version updated to 8.0 as per process.

Number: EMEA/H/C/002373/X/0058/G. Approval date 14 April 2025