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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bosulif

International non-proprietary name: bosutinib

Procedure No. EMEA/H/C/002373/II/0025/G

Note

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



Table of contents

1. Background information on the procedure	5
1.1. Type II group of variations	5
1.2. Steps taken for the assessment of the product.....	6
2. Scientific discussion	7
2.1. Problem statement	7
2.1.1. Disease or condition.....	7
2.1.2. Epidemiology	7
2.1.3. Biologic features, Aetiology and pathogenesis	7
2.1.4. Clinical presentation, diagnosis and stage/prognosis	8
2.1.5. Management	8
2.2. Non-clinical aspects	9
2.2.1. Introduction.....	9
2.2.2. Pharmacology	9
2.2.3. Pharmacokinetics.....	9
2.2.5. Ecotoxicity/environmental risk assessment	14
2.2.6. Discussion on non-clinical aspects.....	15
2.2.7. Conclusion on the non-clinical aspects.....	16
2.3. Clinical aspects	17
2.3.1. Introduction.....	17
2.3.2. Pharmacokinetics.....	18
2.3.3. Pharmacodynamics	25
2.3.1. PK/PD modelling.....	27
2.3.2. Discussion on clinical pharmacology	29
2.3.3. Conclusions on clinical pharmacology	31
2.4. Clinical efficacy	31
2.4.1. Dose response studies.....	31
2.4.2. Main study.....	32
2.4.3. Discussion on clinical efficacy	53
2.4.4. Conclusions on the clinical efficacy.....	56
2.5. Clinical safety	56
2.5.1. Discussion on clinical safety	74
2.5.2. Conclusions on clinical safety	76
2.5.3. PSUR cycle	77
2.6. Risk management plan.....	77
2.7. Update of the Product information	85
2.7.1. User consultation.....	85
3. Benefit-Risk Balance	86
3.1. Therapeutic Context	86
3.1.1. Disease or condition.....	86
3.1.2. Available therapies and unmet medical need	86
3.1.3. Main clinical studies	86
3.2. Favourable effects	86

3.3. Uncertainties and limitations about favourable effects	87
3.4. Unfavourable effects	87
3.5. Uncertainties and limitations about unfavourable effects	87
3.6. Effects Table	87
3.7. Benefit-risk assessment and discussion	88
3.7.1. Importance of favourable and unfavourable effects	88
3.7.2. Balance of benefits and risks	89
3.7.3. Additional considerations on the benefit-risk balance	89
3.8. Conclusions	89
4. Recommendations	90
5. EPAR changes	90

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALL	Acute lymphocytic leukemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Accelerated phase
AST	Aspartate aminotransferase
BC	Blast crisis
BCR-ABL	Fusion transcript (or protein) resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia Chromosome
BP	Blast phase
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CI	Confidence interval
CML	Chronic myelogenous leukemia
CP	Chronic phase
CSR	Clinical study report
ECG	Electrocardiogram
ECHO	Echocardiogram
EFS	Event-free survival
eGFR	Estimate glomerular filtration rate
EQ-5D	EuroQol-5 Dimensions
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
HR	Hazard ratio
ITT	Intent-to-treat
MAA	Marketing Authorisation Application
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMR	Major molecular response
MR	Molecular response
MUGA	Multigated acquisition
OS	Overall survival
PCI	Potentially clinically important
Ph	Philadelphia
Ph+	Philadelphia chromosome positive
Ph-	Philadelphia chromosome negative
PK	Pharmacokinetics
PRO	Patient-reported outcome
PSUR	Periodic Safety Update Report
PT	Preferred term
RMP	Risk Management Plan
ROW	Rest of world
SAE	Serious adverse event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
WBC	White blood cell

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 25 July 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Extension of Indication to include treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML) for Bosulif based on study AV001; in addition, the MAH updated the SmPC with safety and efficacy information from studies B1871006 and B1871008. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 4.0 has been submitted, as part of this application. Furthermore, the Annex IIIA is brought in line with the latest QRD template version 10.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Package Leaflet and Labelling and to the Risk Management Plan (RMP).

Bosulif was designated as an orphan medicinal product EU/3/10/762 on 4 August 2010. Bosulif was designated as an orphan medicinal product in the following indication: treatment chronic myeloid leukaemia (CML).

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Following the CHMP positive opinion on this change to the terms of the marketing authorisation at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 16 March 2018 on request of the sponsor. The relevant Withdrawal assessment report – orphan maintenance can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/Find_medicine/Human_medicines/European_public_assessment_reports.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0325/2016 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0325/2016 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Harald Enzmann Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	25 July 2017
Start of procedure	12 August 2017
CHMP Rapporteur's preliminary assessment report circulated on	17 October 2017
PRAC Rapporteur's preliminary assessment report circulated on	16 October 2017
PRAC Rapporteur's updated assessment report circulated on	17 October 2017
PRAC RMP advice and assessment overview adopted by PRAC on	26 October 2017
CHMP Rapporteur's updated assessment report circulated on	3 November 2017
Request for supplementary information and extension of timetable adopted by the CHMP on:	9 November 2017
MAH's responses submitted to the CHMP on	21 December 2017
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on	7 February 2018
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 January 2018
PRAC Rapporteur's updated assessment report on the MAH's responses circulated on	1 February 2018
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on	20 February 2018
PRAC RMP advice and assessment overview adopted by PRAC on	8 February 2018
The CHMP adopted a report on similarity of Bosulif with Tasigna and Iclusig on	22 February 2018

Timetable	Actual dates
CHMP Opinion	22 February 2018

2. Scientific discussion

2.1. Problem statement

Bosutinib was granted conditional approval in the European Union (EU) on 27 March 2013 for the 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.

The current regulatory submission is being made in support of an additional indication for bosutinib to include the treatment of adult patients with newly diagnosed Ph+ CP CML.

Bosutinib was designated as an orphan medicinal product for the treatment of chronic myeloid leukemia on 4 August 2010.

2.1.1. Disease or condition

Bosulif (bosutinib) is proposed for the treatment for adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase (CP) chronic myelogenous leukemia (CML).

2.1.2. Epidemiology

CML accounts for 20% of adult leukemias (Union for International Cancer Control, 2014). The number of new cases of CML has been estimated as 1.8 per 100,000 men and women per year in the United States (US) (SEER Cancer Stat Facts, CML) and 1.2 per 100,000 men and women per year in the UK (Cancer Research UK CML Statistics). CML can occur in all age groups but occurs predominantly among adults and more frequently among males than females (Union for International Cancer Control, 2014). The median age at diagnosis is approximately 65 years.

2.1.3. Biologic features, Aetiology and pathogenesis

CML is a myeloproliferative disorder characterized by a reciprocal t(9;22)(q34;q11) translocation that results in the formation of the Philadelphia (Ph) chromosome containing the p210 BCR-ABL1 (hereafter referred to as BCR-ABL) oncogene (Chereda, 2015). The BCR-ABL oncogene encodes the BCR-ABL kinase that activates several downstream signaling pathways, which mediate myeloproliferation, resistance to apoptosis, and genetic instability.

The BCR-ABL gene fusion translocation 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 (Quintas-Cardama & Cortes, 2006). In most patients with CML, BCR-ABL mRNA transcripts are characterized by b2a2 and/or b3a2 junctions (Faderl et al, 1999).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

CML comprises 3 distinct phases, which are differentiated by clinical characteristics and laboratory findings: a Chronic Phase (CP), an accelerated phase (AP), and a blast phase (BP). CML is usually diagnosed in the CP (Chereda, 2015; Quintas-Cardama & Cortes, 2006; Faderl et al, 1999).

Patients may present with fatigue, anemia, 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 (BC), also termed BP, usually preceded by AP. Disease progression is characterized by a progressive loss of white blood cell (WBC) differentiation and is defined by a blast cell count of 15-29% (peripheral blood) in AP and $\geq 30\%$ (blood and/or marrow) in BP (National Comprehensive Cancer Network [NCCN] 2017). BP CML, which resembles acute leukemia, generally leads to patient death due to infection, thrombosis, or anemia.

2.1.5. Management

The development of tyrosine kinase inhibitors (TKIs) has changed the CML treatment landscape dramatically. Their use has resulted in a marked decrease in the transformation of CP CML to more advanced, lethal phases of CML (Druker et al, 2006) and has improved life expectancy for patients with CML so that it is comparable with the general population (Flynn & Atallah, 2016). The goal of treatment has changed from focusing on delaying disease progression to prolonging life while maintaining as normal a quality of life as possible.

Imatinib mesylate (imatinib) was the first TKI to be approved for adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) CML for whom bone marrow transplantation is not considered as the first line of treatment in the European Union (EU) in 2006.

Other TKIs against the kinase domain of BCR-ABL have been developed as second-generation (dasatinib and nilotinib) and third-generation (ponatinib) TKIs for the treatment of CP CML. In the EU, dasatinib was approved for the treatment of adult patients with newly diagnosed (Ph+) CML in the chronic phase in 2010 and nilotinib was approved for the treatment of adult patients with newly diagnosed (Ph+) CML in the chronic phase in 2010.

About the product

Bosutinib belongs to a pharmacological class of medicinal products known as kinase inhibitors. Bosutinib inhibits the abnormal BCR ABL kinase that promotes CML. Modeling studies indicate that bosutinib binds the kinase domain of BCR ABL. Bosutinib is also an inhibitor of Src family kinases including Src, Lyn and Hck. Bosutinib minimally inhibits platelet derived growth factor (PDGF) receptor and c Kit (SmPC, section 5.1).

Bosulif has been authorised in 2013 for treatment of adult patients with chronic phase, accelerated phase, and blast phase Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Type of Application and aspects on development

The applicant requested the approval for the following indication:

Bosulif is indicated for the treatment of adult patients with: newly -diagnosed chronic phase (CP) Philadelphia chromosome -positive chronic myelogenous leukaemia (Ph+ CML) (SmPC, section 4.1).

The CHMP adopted this indication without changes.

The recommended dose for the newly diagnosed CP Ph+ CML is 400 mg bosutinib once daily (SmPC, section 4.2).

Two phase 3 studies have been conducted in patients with newly diagnosed Ph+ CP CML: pivotal Study AV001 and supportive Study B1871008 (Study 1008). Supportive Study 1008 was conducted prior to the start of pivotal Study AV001 and provided the basis for the design of Study AV001. Both studies support the extension of indication application.

In addition, the MAH submitted an updated SmPC with safety and efficacy data from studies B1871006 and B1871008.

2.2. Non-clinical aspects

2.2.1. Introduction

In support of the development of bosutinib for the treatment of adults patients with newly diagnosed Ph+ CP CML with an oral dose of 400 mg daily, additional pharmacokinetics and toxicology evaluations have been completed. The new pharmacokinetics information includes: systemic exposure to bosutinib and its metabolites in the carcinogenicity study in rats, toxicokinetics of bosutinib in juvenile rats, and in vitro evaluation of the potential for bosutinib to inhibit various drug transporters. The new toxicology information includes: a juvenile toxicity study in rats, a local vascular irritation study in rabbits, in vitro studies of the blood compatibility of IV formulation in rabbit and human blood, and the revision of the comparison of exposures achieved in animals with those in humans to reflect the planned human clinical dose of 400 mg daily.

2.2.2. Pharmacology

No pharmacology studies were conducted.

2.2.3. Pharmacokinetics

For the toxicokinetic evaluation in juvenile rats (131468VSMB_PGC_R1) the former validated and assessed LC/MS/MS method for the quantification of bosutinib a revised LC-MS/MS assay validation was conducted for the determination of pharmacokinetic and toxicokinetic parameters in plasma of the juvenile rats. For this method, using 0.5 mL rat plasma volume, the assay was linear from 1 to 500 ng/mL instead of 5 ng/mL to 500 ng/mL (rat and dog) respectively 10 ng/mL to 500 ng/mL (mouse and rabbit) in the former assay.

In vitro Transporter Inhibition by PF-05208763 (Study PF-05208763)

The purpose of this study was to determine the inhibitory potency of Bosulif (PF-05208763) for human breast cancer resistance protein (BCRP), human organic anion transporter (OAT) 1 and 3, human hepatic organic anion transporting polypeptides (OATP) 1B1 and 1B3, and human organic cation transporter (OCT) 1 and 2 when stably expressed in a mammalian cellular system.

The following stably transfected cell lines and their corresponding probes were used for analysis:

Table 1 stably transfected cell lines and their corresponding probes were used for analysis

Cell line	Probe
MDCKII-LE-BCRP	pitavastatin
HEK293-OAT1	[3H]-para-aminohippuric acid
HEK293-OAT3	[3H]-estrone-3-sulfate
HEK293-OATP1B1, HEK293-OATP1B3	rosuvastatin
HEK293-OCT1, HEK293-OCT2	[14C]-Metformin

Assessments based on the EMA Guidance were conducted for both 400 mg and 500 mg once daily (QD) doses and the risk assessments are summarized in Table 2 and Table 3 respectively.

Table 2 Pharmacokinetics: drug-drug interactions, transporter inhibition risk assessment (400 MG QD)

Summary Results: Assessment of Risk for In Vivo DDIs Between Bosutinib at 400 mg QD and Co-Administered Substrates of Various Transporters, based on the EMA guideline (2012).^a

	Transporter	K_i^b (μM)	$50 \times C_{\text{max,u}}^c$ (μM)	$25 \times I_{\text{u,inlet,max}}^d$ (μM)	$0.1 \times \text{Dose}/250 \text{ mL}^e$	Threshold Cutoff For Potential DDI
Systemic	P-gp	1.0	0.9	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	BCRP	8.7	0.9	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OAT1	>30	0.9	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OAT3	>30	0.9	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OCT2	4.1	0.9	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OATP1B1	8.4	--	4.93	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
	OATP1B3	6.9	--	4.93	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
	OCT1	1.31	--	4.93	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
Intestinal	P-gp	1.0	--	--	302	$K_i \leq (0.1 \times \text{dose}/250)$
	BCRP	8.7	--	--	302	$K_i \leq (0.1 \times \text{dose}/250)$

Notes: molecular weight of bosutinib = 530.46 g/mole.

BCRP = Breast cancer resistance protein; Bosutinib (PF-05208763); CLb = Blood clearance; Cb/Cp = Ratio of drug concentration in blood/plasma; Cmax = Maximum observed steady-state concentration; Cmax,u = Unbound mean steady-state Cmax; DDI = Drug-drug interaction; EMA = European Medicines Agency; F = Absolute bioavailability; Fa = Fraction absorbed; Fg = Fraction escaping gut metabolism; FH = Fraction escaping liver metabolism; fu = Fraction unbound in human plasma; fu,b = Fraction unbound in blood; IC50 = 50% inhibitive concentration; Iu,inlet,max = Maximum unbound hepatic inlet inhibitor concentration; [I]max,b = Maximum concentration in blood; ka = Absorption rate constant; Ki = Inhibition constant; Km = Substrate concentration at half-maximal velocity; OAT = Organic anion transporter; OATP = Organic anion-transporting polypeptide; OCT = Organic cation transporter; P-gp = P-glycoprotein (also known as MDR1); QH = hepatic blood flow; -- = Data not applicable.

a. Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions:

CPMP/EWP/560/95/Rev. 1, Corr. 2. European Medicines Agency; 2012.

b. For OAT1, OAT3, OCT1, and OCT2, $K_i = \text{IC}_{50}$ as probe substrate concentration $\ll K_m$; for the other transporters, $K_i = \text{IC}_{50}/2$.

c. $C_{\text{max,u}} = 0.018 \mu\text{M}$ [9.2 ng/mL]; calculated as $C_{\text{max}} \times f_u$, where $C_{\text{max}} = 0.28 \mu\text{M}$ [146 ng/mL] determined in patients treated with 400 mg QD bosutinib (Study 3160A4-200- WW) and human $f_u = 0.063$ (RPT-54418).

d. $I_{\text{u,inlet,max}} = 0.197 \mu\text{M}$, calculated as $[f_{u,b} \times ([I]_{\text{max,b}} + (F_a \times F_g \times k_a \times \text{Dose}/\text{QH}))]$; where $f_{u,b} = 0.053$, calculated as $[f_u / (\text{Cb}/\text{Cp})]$ where $f_u = 0.063$ and $\text{Cb}/\text{Cp} = 1.2$ (WAY-173606_02Aug10_113243), $[I]_{\text{max,b}} = 0.34 \mu\text{M}$, determined as $(C_{\text{max}} \times \text{Cb}/\text{Cp})$, $F_a \times F_g = 0.723$, calculated as F/FH where $F = 33.85\%$ (B1871044), $\text{FH} = 0.468$ calculated as $(1 - \text{CLb}/\text{QH})$ with $\text{CLb} = 51.58 \text{ L/h}$; determined as $[\text{CLp}/(\text{Cb}/\text{Cp})]$, where $\text{CLp} = 61.89 \text{ L/h}$ after intravenous dosing (B1871044), $\text{Cb}/\text{Cp} = 1.2$ and $\text{QH} = 97 \text{ L/h}$.

e. Calculated using the clinical dose of 400 mg (on a molar basis) in a volume of 250 mL.

Table 3 Pharmacokinetics: drug-drug interactions, transporter inhibition risk assessment (500 mg qd)

Summary Results: Assessment of Risk for In Vivo DDIs Between Bosutinib at 500 mg QD and Co-Administered Substrates of Various Transporters, based on the EMA guideline (2012).^a

	Transporter	K_i^b (μM)	$50 \times C_{\text{max,u}}^c$ (μM)	$25 \times I_{\text{u,inlet,max}}^d$ (μM)	$0.1 \times \text{Dose}/250 \text{ mL}^e$	Threshold Cutoff For Potential DDI
Systemic	P-gp	1.0	1.2	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	BCRP	8.7	1.2	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OAT1	>30	1.2	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OAT3	>30	1.2	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OCT2	4.1	1.2	--	--	$K_i \leq (50 \times C_{\text{max,u}})$
	OATP1B1	8.4	--	6.23	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
	OATP1B3	6.9	--	6.23	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
	OCT1	1.31	--	6.23	--	$K_i \leq (25 \times I_{\text{u,inlet,max}})$
Intestinal	P-gp	1.0	--	--	377	$K_i \leq (0.1 \times \text{dose}/250)$
	BCRP	8.7	--	--	377	$K_i \leq (0.1 \times \text{dose}/250)$

Notes: molecular weight of bosutinib = 530.46 g/mole.

BCRP = Breast cancer resistance protein; Bosutinib (PF-05208763); CLb = Blood clearance; Cb/Cp = Ratio of drug concentration in blood/plasma; Cmax = Maximum observed steady-state concentration; Cmax,u = Unbound mean steady-state Cmax; DDI = Drug-drug interaction; EMA = European Medicines Agency; F = Absolute bioavailability; Fa = Fraction absorbed; Fg = Fraction escaping gut metabolism; FH = Fraction escaping liver metabolism; fu = Fraction unbound in human plasma; fu,b = Fraction unbound in blood; IC50 = 50% inhibitive concentration; Iu,inlet,max = Maximum unbound hepatic inlet inhibitor concentration; [I]max,b = Maximum concentration in blood; ka = Absorption rate constant; Ki = Inhibition constant; Km = Substrate concentration at one-half of the maximal velocity; OAT = Organic anion transporter; OATP = Organic anion-transporting polypeptide; OCT = Organic cation transporter; P-gp = P-glycoprotein (also known as MDR1); QH = hepatic blood flow; -- = Data not applicable.

a. Committee for Human Medicinal Products (CHMP). Guideline on the investigation of drug interactions: CPMP/EWP/560/95/Rev. 1, Corr. 2. European Medicines Agency; 2012.

b. For OAT1, OAT3, OCT1, and OCT2, $K_i = \text{IC}_{50}$ as probe substrate concentration $\ll K_m$; for the other transporters, $K_i = \text{IC}_{50}/2$.

c. $C_{\text{max,u}} = 0.024 \mu\text{M}$ [12.6 ng/mL]; calculated as $C_{\text{max}} \times f_u$, where $C_{\text{max}} = 0.38 \mu\text{M}$ [200 ng/mL] determined in patients treated with 500 mg QD bosutinib (Study 3160A4-200- WW) and human $f_u = 0.063$ (RPT-54418).

d. $I_{\text{u,inlet,max}} = 0.249 \mu\text{M}$, calculated as $[f_{u,b} \times ([I]_{\text{max,b}} + (F_a \times F_g \times k_a \times \text{Dose}/\text{QH}))]$; where $f_{u,b} = 0.053$, calculated as $[f_u / (\text{Cb}/\text{Cp})]$ where $f_u = 0.063$ and $\text{Cb}/\text{Cp} = 1.2$ (WAY-173606_02Aug10_113243), $[I]_{\text{max,b}} = 0.45 \mu\text{M}$, determined as $(C_{\text{max}} \times \text{Cb}/\text{Cp})$, $F_a \times F_g = 0.723$, calculated as F/FH where $F = 33.85\%$ (B1871044), $\text{FH} = 0.468$ calculated as $(1 - \text{CLb}/\text{QH})$ with $\text{CLb} = 51.58 \text{ L/h}$; determined as $[\text{CLp}/(\text{Cb}/\text{Cp})]$, where $\text{CLp} = 61.89 \text{ L/h}$ after intravenous dosing (B1871044), $\text{Cb}/\text{Cp} = 1.2$ and $\text{QH} = 97 \text{ L/h}$.

e. Calculated using the clinical dose of 500 mg (on a molar basis) in a volume of 250 mL.

2.2.4. Toxicology

An Oral (Gavage) Toxicity Study of PF-05208763 in Juvenile Rats (Study Number WIL-655073; Sponsor Number 13GR351)

A juvenile toxicity study (GLP-compliant) was conducted in rats to evaluate the effects of 3, 10, 30, and 75 mg/kg/day bosutinib administered by oral gavage from postnatal day (PND) 7 to PND28. Bosutinib was not tolerated at $\geq 10 \text{ mg/kg}$, with severe body weight loss and mortality leading to termination of these dose groups between PND14 and PND21 (just prior to weaning). No adverse findings were observed in the 3 mg/kg dose group resulting in a no-observable-adverse effect-level (NOAEL). Cmax exposure was 1,160 ng/mL and AUC24 exposure was 20,100 ng h/mL.

Exposures on PND7 were greater than expected based on exposures obtained in adult rats at similar doses on a mg/kg basis in prior studies. This is attributed to the limited liver metabolic capability in pre-weaning rats. The exposures on PND7 at 10 mg/kg were 275x (male) and 56x (female) the exposure in more mature rats at the same dose on a mg/kg basis. Plasma concentrations on PND17 and PND18 indicate these high exposures were maintained through at least the first 10 days of the study. Post-weaning exposures on PND28 in the 3 mg/kg dose group were subtherapeutic.

Local Vascular Irritation Study of bosutinib(PF-05208763) in New Zealand White Rabbits (Study 14LJ062)

The purpose of this non-GLP study was to investigate the local tolerance of bosutinib following single intravenous infusion or perivascular injection in rabbits. Male New Zealand White rabbits (4/group) were administered bosutinib, vehicle (, or 0.9% saline by intravenous infusion and perivascular injection).

Doses were given by intravenous infusion (caudal left marginal ear vein) and perivascular injection (rostral portion of the right ear) to each animal once on Day 1. The dose volumes for intravenous and perivascular administration were constant at 80 mL and 0.05 mL, respectively. Due to the large volume of total drug required, intravenous doses were delivered as an infusion via indwelling catheter over 2-3 hours at a rate of 20 mL/kg/h using an infusion pump. Flow rates were calculated using the lowest animal body weight. Observations and measurements were collected from day1 until day 4. Clinical signs of irritation were evaluated as follows: Day 1: prior to dosing, immediately following, and 1 and 3-4 hours following dosing, Days 2-3: twice daily, Day 4: prior to termination. Tissues were collected on day 4 only.

Dose administration sites were monitored for the following endpoints: redness, swelling, thickening, discoloration, exudation, and sore development. Each endpoint was scored on a scale of 0-4 (0 = no finding; 1 = minimal; 2 = mild; 3 = moderate; 4 = severe finding).

Following intravenous infusion, minimal swelling observed in 2/4 bosutinib-treated animals was considered test article-related because it was not observed in either the saline or vehicle-treated groups. Minimal thickening observed in 1/4 rabbits correlated with microscopic findings of dermal fibrosis and was also considered test-article related.

Following perivascular injection, minimal thickening and minimal fibrinoid necrosis of a vessel wall, each in 1/4 bosutinib-treated animals, were considered test article-related as they were not observed in either the saline or vehicle-treated groups. Increased incidence and/or severity of dermal hemorrhage, dermal fibrin/edema and dermal fibrosis were attributed to vehicle and/or bosutinib. Dermal hemorrhage findings across all groups correlated with irritation scores of discoloration.

Two-Year Oral (Gavage) Carcinogenicity Study in rats (Study RPT-80077)

A 2-year carcinogenicity study was conducted in S-D rats (60/sex/group). Rats were gavaged once daily with 0 (distilled water), 0 (vehicle), 0 (vehicle), and males with 2.5, 7.5, or 25 mg/kg bosutinib for up to 91 weeks and females with 1.5, 5, or 15 mg/kg bosutinib for up to 100 weeks. Based on reduced survival in males at 25 mg/kg/day bosutinib, the dose level was decreased to 15 mg/kg/day on Week 78. Vehicle was a mixture of 0.5% methylcellulose (4000 cps) (w/v), 2.0% polysorbate 80, NF (w/v), 0.06% glacial acetic acid, NF (w/v) and distilled water.

Plasma toxicokinetics of bosutinib and its metabolites M2 and M5 were evaluated in satellite groups on days 182-183 with mean exposures (AUC(0-24) bosutinib) of 14.9, 51, and 313 ng hr/mL in males at 2.5, 7.5, and 25 mg/kg/day, and 18.2, 116, and 645 ng hr/mL in females. Exposure levels were equivalent to 0.1, 0.3, and 1.8-fold the unbound AUC in humans for males and 0.1, 0.7, and 3.8-fold

for females following the 400 mg dose. The exposures to the M5 metabolite in males and females at the highest dose tested (unbound AUC(0-24) of 94 and 15.3 ng·hr/mL, respectively) were 2.7x and 0.4x the predicted M5 unbound AUC in humans following the 400 mg dose. The exposure to the M2 metabolite in males (total AUC(0-24) of 175 ng·hr/mL; unbound fraction not available for M2) was 0.3x the predicted M2 total AUC in humans following the 400 mg dose, while negligible exposures were measured in female rats.

In high dose males (25/15 mg/kg/day) survival was significantly lower compared to control groups. Dosing for this group was stopped on Week 79 when the surviving animals were reduced to 20. Surviving males in this group were euthanized on Week 86. Remaining groups of males were euthanized on Weeks 90-91. Reduced survival in female high dose group resulted in cessation of dosing in Week 92. All female groups were euthanized in weeks 97-100. In females, there were no statistically significant differences at termination in survival in treated groups versus controls. Decreases in absolute body weight and body weight gain were observed in high dose males (25/15 mg/kg/day) and females (15 mg/kg/day). Statistically significant decreases were evident beginning Week 6 in males and Week 53 in females. Decreased body weight and bodyweight gains in high dose groups correlated with decreased food consumption.

Main non-neoplastic findings were erosions/ulceration and inflammation/edema/hemorrhage in the forestomach of high dose females (15 mg/kg/day), mucosal congestion/hemorrhage/erosions/ulceration and mucosal necrosis in the small and large intestine of mid and high dose males and females and collagen deposition in lamina propria at all treated groups. Chronic progressive nephropathy was observed in mid and high dose males and tubular atrophy in the kidney of high dose males and females. Epithelial hyperplasia/hyperkeratosis of the squamous epithelium of the forestomach was seen in mid and high dose males and high dose females. Lymphatic vessel proliferation, ectasia and fibrosis in the mesenteric lymph nodes were observed in all dosed males and mid and high dose females. Multifocal lobular atrophy with inflammation and fibrosis in the exocrine pancreas in mid and high dose males and high dose females were also seen as well as sinus erythrocytosis/erythrophagocytosis of the mesenteric lymph nodes in all treated male groups and mid and high dose females.

Based on effects seen at all dose levels in this study no NOAEL for nonneoplastic findings was derived. There were no neoplastic findings resulting from administration of bosutinib at dose levels up to 25/15 mg/kg/day (males) and 15 mg/kg/day (females) for up to 2 years.

In Vitro Comparability of the IV Formulation of bosutinib (PF-05208763) with Rabbit Blood (Study Number 14LJ047)

The hemolytic potential of 0.5 mg/mL bosutinib (two different IV formulations) and its vehicle () were evaluated with rabbit blood using the modified Dacie method of erythrocyte fragility. Both test formulations containing 0.5 mg/mL of bosutinib and its vehicle caused toxicologically significant hemolysis in vitro (see Table 4).

Table 4: Mean Percent Hemolysis

Compound or Vehicle Concentration (v/v%)	100%	50%	25%	10%	Positive Control
Mean % Hemolysis (PF-05208763)	95	95	59	45	100
Mean % Hemolysis (Vehicle)	96	95	54	4	100

In Vitro Comparability of the IV Formulation of PF-05208763 with Human Blood (Study Number 14LJ048)

The hemolytic potential of 0.5 mg/mL of bosutinib IV formulation and its vehicle [] were evaluated with human blood using the Reed and Yalkowsky method. Formulation containing 0.5 mg/mL of bosutinib did not cause significant hemolysis at [1:4], [1:6], [1:10] and [1:20]. In a similar manner, vehicle did not cause significant hemolysis at [1:6], [1:10] and [1:20]. However, 2% hemolysis was observed with the Vehicle at [1:4] which is considered negligible. No precipitation was observed with bosutinib (PF-05208763) IV formulation and the vehicle in all the dilutions tested.

Table 5: Mean Percent Hemolysis

Formulation Tested	[1:20] Formulation or Vehicle	[1:10] Formulation or Vehicle	[1:6] Formulation or Vehicle	[1:4] Formulation or Vehicle
Mean Percent Hemolysis Vehicle	0	0	0	2
Mean Percent Hemolysis 0.5 mg/mL PF-05208763	0	0	0	0

2.2.5. Ecotoxicity/environmental risk assessment

Table 6: Summary of main study results

Substance Bosutinib			
CAS-number (if available):918639-08-4			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	log D: pH 5: 1.09 pH 8: 3.34 pH 9: not provided	no PBT, since BCF- Study provided. Result: BCF < 2000
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}		No conclusion
	BCF	60	not B
Persistence	DT50 or ready biodegradability	DT ₅₀ whole system (20°C) 1260 d (FOMC recalculated)	vP
Toxicity	NOEC or CMR	NOEC (fish)00.034 mg/l	Not T
PBT-statement :		Not PBT	
Phase I			
Calculation	Value	Unit	Conclusion
PEC surfacewater , default or refined (e.g. prevalence,	PEC surfacewater refined 0.019	µg/L	> 0.01 threshold Y

literature)			
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate

Study type	Test protocol	Results	Remarks
Adsorption-Desorption	OECD 106 or ...	<u>Activated sludge:</u> 10 164 L/kg <u>Silty clay loam sediment:</u> 98 704 L/kg <u>Sand sediment:</u> 272 530 L/kg	List all values
Ready Biodegradability Test	OECD 301	not provided	not necessary since OECD 308 provided
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT _{50, water} (20°C)=0,7-4,3 d (dissipation) DT _{50, sediment} (20°C)= stable, no Dt50 calculable DT _{50, whole system} (20°C)=1260 d (FOMC-best fit) % shifting to sediment => 35% parent compound on day 14	persistent

Phase IIa/b Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Pseudokirchneriella subcapitata</i>	OECD 201	NOEC	30	µg/L	
<i>Daphnia</i> sp. Reproduction Test/ <i>Daphnia magna</i>	OECD 211	NOEC	145	µg/L	
Fish, Early Life Stage Toxicity Test/ <i>Pimephales promelas</i>	OECD 210	NOEC	34	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	>10 ⁶	µg/L	

Phase II TierB studies

Bioaccumulation	OECD 305	BCF	60	L/kg	5% lipid normalized
Soil microorganisms, nitrogen transformation test	OECD 216	10 x PEC	8,92	µg/kg	
Terrestrial plants	OECD 208	EC50	> 10	mg/kg	
Earthworm, Acute toxicity test	OECD 207	EC 50	>10	mg/kg	
Collembola, Reproduction Test <i>Folsomia candida</i>	ISO 11267	NOEC	250	mg/kg	
Sediment dwelling organism <i>Chironomus riparius</i> .	OECD 218	NOEC	10	mg/kg	

2.2.6. Discussion on non-clinical aspects

In order to develop potential DDI of bosutinib, the inhibitory potency of bosutinib for human breast cancer resistance protein (BCRP), human organic anion transporter (OAT) 1 and 3, human hepatic

organic anion transporting polypeptides (OATP) 1B1 and 1B3, and human organic cation transporter (OCT) 1 and 2 was evaluated according to the EMA Guidance and at the clinically relevant concentrations of 400 and 500 mg QD. The data indicated that bosutinib has the potential to inhibit BCRP in the GI-tract but showed a low systemic DDI. The potential of bosutinib to cause DDI by inhibiting OAT1, OAT3, and OCT2 is considered to be low. The analysis of the potential to inhibit OCT1 was not performed according to the EMA Guidance. According to the EMA guidelines there is the possibility that bosutinib has the potential to inhibit OCT1.

In conclusion the *in vitro* studies indicated that bosutinib has a low potential to inhibit breast cancer resistance protein (BCRP, systemically), organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2 at clinically relevant concentrations, but may have the potential to inhibit BCRP in the gastrointestinal tract and OCT1 (SmPC section 4.5).

The analysis of TK data in the newly performed juvenile rat study showed greater exposures on PND7 than expected based on exposures in adult rats at similar doses in prior studies. It is not expected that these findings are of clinical relevance because of the possible immature metabolic pathway of bosutinib in the juvenile rats. Furthermore, the high exposures observed in PND7 rats do not translate into the clinical setting since the known metabolic pathway for bosutinib is fully mature by one year of age in humans (Lacroix et al, 1997; Stevens et al, 2003).

A pre- and postnatal development rat study will be completed post approval of bosutinib in first-line therapy. The MAH will submit the results of the study as soon as they become available (see Risk Management Plan).

The local tolerance study in rabbits showed that perivascular injection was less tolerated compared to intravenous injection.

Data of the 2-year carcinogenicity study have already be performed and assessed during the original submission of Bosulif in 2012. Since the posology the new application is intended with an oral dose of 400 mg daily instead of 500 mg of the original indication, this study was reassessed for underlining the dose of 400 mg. No relevant treatment related increases in neoplastic lesion were observed.

A 6-month transgenic rasH2 mouse carcinogenicity study will be completed post approval of bosutinib for first line therapy. The MAH will submit the results of the study as soon as they become available (see Risk Management Plan).

The hemolytic potential of bosulif was evaluated in two *in vitro* studies. These comparability studies showed that bosutinb lead to toxicologically significant hemolysis in vitro in rabbit blood but showed no toxicologically relevant hemolysis in vitro in human blood. Therefore, it is unlikely that bosulif will cause hemolysis *in vivo* in human blood.

The active substance bosutinib is not expected to pose a risk to surface water, groundwater, sediment and soil compartments.

2.2.7. Conclusion on the non-clinical aspects

The pharmacokinetic and toxicology studies evaluated so far support the proposed new indication from a non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 7 Overview of clinical studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group) (No. of Subjects)	Duration of Treatment	Study Start/Status
STUDY REPORTS OF CLINICAL STUDIES PERTINENT TO CLINICAL EFFICACY AND SAFETY						
Pivotal phase III trial in the applied indication of Ph+CP-CML (first line CP-CML)						
AV001 (Multinational)	A Multicenter Phase 3 Randomized, Open-Label Study of Bosutinib versus Imatinib in Adult	Bosutinib (Route: Oral; Dose Regimen: 400 mg once daily)	Randomized: 268 (ITT Population) 246 (mITT Population) Treated: 268 (Safety Population)	mITT Population: Sex: 142 M/104 F Median Age (min/max): 52 (18/84) years Race: W/B/A/O: 191/10/30/14	Safety Population: Median: 14.1 months	FSFV: 15 Jul 2014 PCD: 11 Aug 2016 Ongoing Core Analysis Phase completed
		Imatinib (Route: Oral; Dose Regimen: 400 mg once daily)	Randomized: 268 (ITT Population) 241 (mITT Population) Treated: 265 (Safety Population)	mITT Population: Sex: 135 M/106 F Median Age (min/max): 53 (19/84) years Race: W/B/A/O: 186/10/30/14	Safety Population: Median: 13.8 months	
Supportive Trials (Previously pivotal trial for the applied indication, PEP failed)						
B1871008 (Multinational) = 1008-3000WW	A Phase 3, Randomized, Open-Label Study of Bosutinib Versus Imatinib in Subjects With Newly Diagnosed CP-PH+-CML	Bosutinib (Route: Oral; Dose Regimen: 500 mg once daily)	Randomized: 250 (ITT Population) Treated: 248 (Safety Population)	ITT Population: Sex: 149 M/101 F Median Age (min/max): 48 (19/91) years Race: W/B/A/O: 160/2/65/23	Safety Population: Median: 55.4 months	FSFV: 05 Feb 2008 LSLV: 27 May 2015 Completed

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects (by Treatment Group)	Demographics (by Treatment Group) (No. of Subjects)	Duration of Treatment	Study Start/Status
		Imatinib (Route: Oral; Dose Regimen: 400 mg once daily)	Randomized: 252 (ITT) Treated: 251 (Safety Population)	ITT Population: Sex: 135 M/117 F Median Age (min/max): 47 (18/89) years Race: W/B/A/O: 164/3/57/28	Safety Population: Median: 49.7 months	
Pivotal trial most relevant for the current conditional approval						
B1871006 (Multinational) =200WW	A Phase 1/2 Study of Bosutinib (SKI-606) in PH+ Leukemias	Bosutinib (Route: Oral; Dose Regimen (Part 2): 500 mg once	Treated: 570 (Safety Population)	Safety Population: Sex: 300M/270F Median Age (min/max): 53 (18-91) years	Safety Population: Median: 11.1 months	FSFV: 18 Jan 2006 LSLV: 06 Aug 2015 Completed
Other supportive trials						
B1871007 (Japan)	A Phase 1/2 Study of SKI-606 Administered as A Single Agent in Japanese Subjects with PH+- Leukemia	Bosutinib (Route: Oral; Dose Regimen: Part 1: 400-600 mg once daily Part 2: 500 mg once daily)	Treated: 63 (Safety Population)	NA	Median: 131.4 weeks	FSFV 03 Dec 2007 LSLV 17 Jun 2015 Completed

2.3.2. Pharmacokinetics

This submission included bosutinib PK data for 267 patients with newly diagnosed CP CML (Ph+ and Philadelphia chromosome negative [Ph-]) in Study AV001 based on a data cutoff date of 11 August 2016.

An updated population PK analysis was conducted based on 4 studies (Study 1006, 1008, 1012, and Study AV001). In addition, an exposure-response analysis of key safety and efficacy endpoints was conducted based on 2 Phase 3 first-line studies in adult CML patients (Study 1008 and Study AV001).

Methods

A method (Report TRTPR14-036) was validated for measuring bosutinib in human plasma (K₃EDTA) in study AV001. Samples were analysed using a 100 µL aliquot volume and a liquid/liquid extraction procedure followed by liquid chromatography/tandem mass spectrometry (LC/MS/MS). Bosutinib concentrations were calculated with a 1/x² linear regression over a concentration range of 1.00-200 ng/mL using bosutinib-d8 as an internal standard. An API 4000 was operated in the Multiple Reaction Monitoring (MRM) mode under optimized conditions for detection of bosutinib and bosutinib-d8 positive ions formed by electrospray ionization. The method met the acceptance criteria as specified in SOP LABOP105 (Table 8).

Table 8 Bosulif validation results (report TRTPR14-036) for study AV001

Bosutinib Validation Results	
Internal Standard:	Bosutinib-d ₈
LLOQ and ULOQ:	1.00 ng/mL and 200 ng/mL
Calibration Standard Concentrations:	1.00, 2.00, 5.00, 10.0, 20.0, 60.0, 160 and 200 ng/mL
Inter-Assay Accuracy (%Bias):	-7.5% to 5.0%
Inter-Assay Precision (%CV):	2.2% to 8.9%
Regression and Weighting:	Linear 1/x ²
Quality Control Levels:	1.00, 3.00, 15.0, 80.0 and 150 ng/mL
LLOQ QC	
Intra-Assay Accuracy (%Bias):	-7.8% to 1.0%
Intra-Assay Precision (%CV):	2.9% to 7.9%
Inter-Assay Accuracy (%Bias):	-2.4%
Inter-Assay Precision (%CV):	4.1%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as the result from the ANOVA calculations.	
Low, Low-Mid, Mid, and High QC	
Intra-Assay Accuracy (%Bias):	-12.0% to 3.7%
Intra-Assay Precision (%CV):	3.7% to 11.4%
Inter-Assay Accuracy (%Bias):	-8.0% to 2.0%
Inter-Assay Precision (%CV):	0.0% to 2.4%
Intra-Assay results are reported as ranges from the A/P runs.	
Inter-Assay results are reported as ranges from the ANOVA calculations.	
Ability to Dilute:	2000 ng/mL (DF=20)
Dilution Linearity:	10000 ng/mL (DF=100)
Carryover of Analyte:	Carryover within acceptable limits
Carryover of Internal Standard:	Carryover within acceptable limits
Method Selectivity:	Evaluated using 6 Lots of Blank Matrix
Selectivity Blanks:	No interference greater than acceptable limits detected at the retention times of interest.
Matrix Effects	
LLOQ Reproducibility in Matrix:	Accuracy (%Bias): -14.7% Precision (%CV): 4.6%

Bosutinib Validation Results	
Matrix Factor Test:	<u>Matrix Factor (Low)</u> Analyte = 1.09 Internal Standard = 1.10 <u>Matrix Factor (High)</u> Analyte = 1.01 Internal Standard = 1.05 A matrix factor greater than 1 indicates ionization enhancement. A matrix factor less than 1 indicates ionization suppression.
IS-Normalized Matrix Factor Test:	IS-Normalized MF (Low) = 0.992 IS-Normalized MF (High) = 0.960
Interference	
Analyte Only:	No significant interference found at the retention time of interest for Analyte Only samples.
Internal Standard Only:	No significant interference found at the retention time of interest for IS Only samples.
IS Recovery:	106.0%
Analyte Recovery:	68.5% (Low) 76.0% (Mid) 76.3% (High)
Solution Stability	
IS Solution Stability	
Bench-Top:	19 Hours in solution stored in a glass container at room temperature and protected from light.
Analyte Solution Stability	
Bench-Top:	19 Hours in solution stored in a glass container at room temperature and protected from light.
Long-Term Stock:	Highest Conc. (1000000 ng/mL): 28 Days in solution stored in a glass container at 5 °C and protected from light.
Long-Term Working:	Lowest Conc. (20.0 ng/mL): 28 Days in solution stored in a glass container at 5 °C and protected from light. Any additional stability conducted for this study will be added either as an addendum or appendix to this report
Stability in Matrix	
Freeze-Thaw:	5 Cycles; stored at -70 °C and thawed at room temperature
Bench-Top:	28 Hours at room temperature
Long-Term:	27 Days at -70 °C 37 Days at -20 °C
Reinjection Reproducibility:	141 Hours at room temperature
Extract Stability:	45 Hours at room temperature
Whole Blood Stability:	2 Hours at room temperature and 1 to 8 °C
Hemolysis:	No significant impact in samples evaluated with up to 2.0% hemolysis
Hyperlipidemia:	No significant impact in samples with hyperlipidemia (Triglycerides >300 mg/dL; Total Cholesterol >250 mg/dL)
Batch Size Evaluation:	Sample analysis runs may include up to 96 samples (including Standards, QCs, Blanks, Unknowns, etc.)

The experimentally determined recovery of the analyte, bosutinib, was approximately 68-76% across the low, mid, and high QC levels, while the recovery determined for the isotopically labelled internal standard was around 100%. Since the chemical nature of both compounds is similar, recovery of both

would be expected also to be similar. The raw documentation for this experiment was reviewed, but no error is apparent.

Pharmacokinetic data analysis

Study AV001 / Population modelling PMAR-EQDD-B187j

In the phase III study AV0001 pharmacokinetic profiles of bosutinib were determined using sparse sampling and population PK analysis approach. 4 PK samples per patient were drawn. All patients in the bosutinib treatment group provided pre-dose blood samples on days 1, 28, 56 and 84. Per protocol, the PK samples were collected within 180 minutes before study drug administration. Samples taken at Day 1 were not used in the analysis as they were taken before any drug had been administered.

The PK population in study AV001 included all subjects, regardless of Philadelphia chromosome status, who received at least 1 dose of study medication and had sufficient plasma results collected in order to create reliable PK parameter results. The PK population was used for all PK analyses (n=267).

Unless otherwise specified, continuous variables were summarized by descriptive statistics (sample size [n], mean, standard deviation, median, minimum, maximum and 95% confidence interval). Categorical variables were summarized in frequency tables (n, frequencies, and percentages).

In addition, the concentration of study drug was analysed using population PK methodology. Population mean values of PK parameters (e.g., clearance [CL/F], volume of distribution [V/F]) were estimated. PK relationships between plasma study drug concentration and selected outcome measures were characterized using a population approach.

Pharmacokinetics in target population

Study AV001

A summary of trough bosutinib plasma levels over time is provided in Table 9. The median bosutinib trough concentration averaged over Days 28, 56, and 84 was 61.10 ng/mL (range: 0.50-453.00 ng/mL).

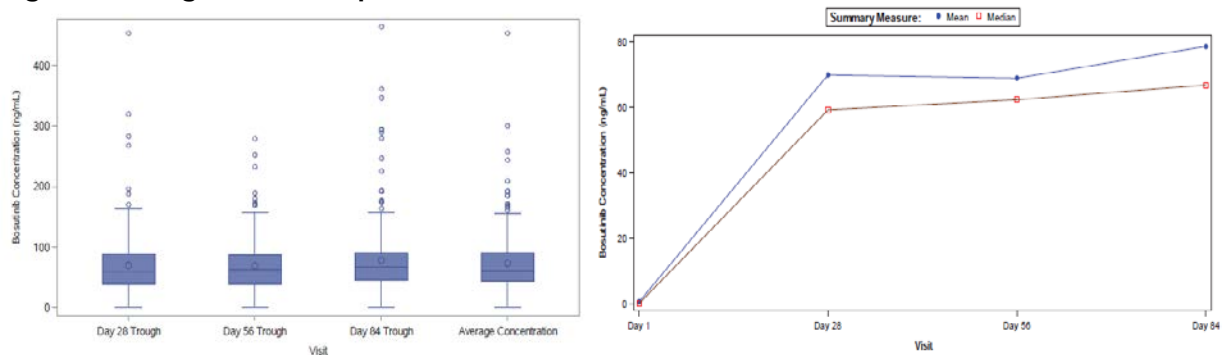
Table 9 Summary of trough bosutinib plasma levels (ng/mL) - PK population

Visit	Statistic	Total (N=267)
Day 1	N	261
	Mean (SD)	0.489 (6.9441)
	95% CI	-0.4, 1.3
	Median	0.000
	Min, Max	0.00, 111.00
Day 28	N	248
	Mean (SD)	69.903 (53.1211)
	95% CI	63.3, 76.5
	Median	59.200
	Min, Max	0.50, 453.00
Day 56	N	243
	Mean (SD)	68.924 (44.1065)
	95% CI	63.4, 74.5
	Median	62.300
	Min, Max	0.50, 279.00
Day 84	N	239
	Mean (SD)	78.628 (61.1245)
	95% CI	70.8, 86.4
	Median	66.800
	Min, Max	0.50, 464.00
Average Concentration	N	261
	Mean (SD)	73.780 (49.8590)
	95% CI	67.7, 79.9
	Median	61.100
	Min, Max	0.50, 453.00

Source: Table 14.7.1

Note: Concentrations that were BLQ and reported as less than the lower limit of quantification (BLQ<LLOQ) were replaced with zero for Day 1. For Days 28, 56 and 84 values of BLQ (<LLOQ) were replaced with LLOQ/2. Average concentration=mean of Day 28, 56 and 84 trough concentrations. Abbreviations: BLQ=below limit of quantification; LLOQ=lower limit of quantification.

Figure 1 Trough bosutinib plasma concentrations (ng/mL)



From Day 56, there was a difference (2-sided $p=0.002$, ANCOVA) in the trough bosutinib plasma concentrations between the <65 years (mean: 67.07 ng/mL) and ≥ 65 years (mean: 77.32 ng/mL) age group categories and remained at Day 84 (2-sided $p=0.026$).

Figure 2 Trough bosutinib concentrations (ng/mL) per subgroup

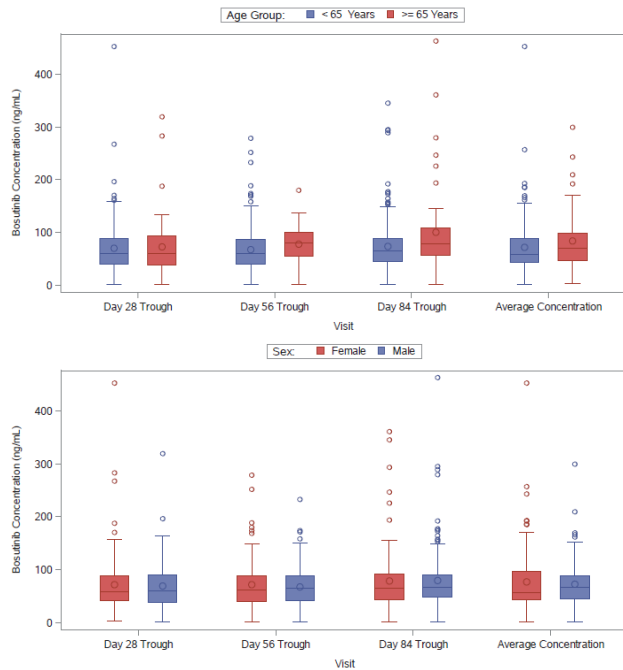


Figure 3 Trough bosutinib concentrations (ng/mL) by creatinine clearance

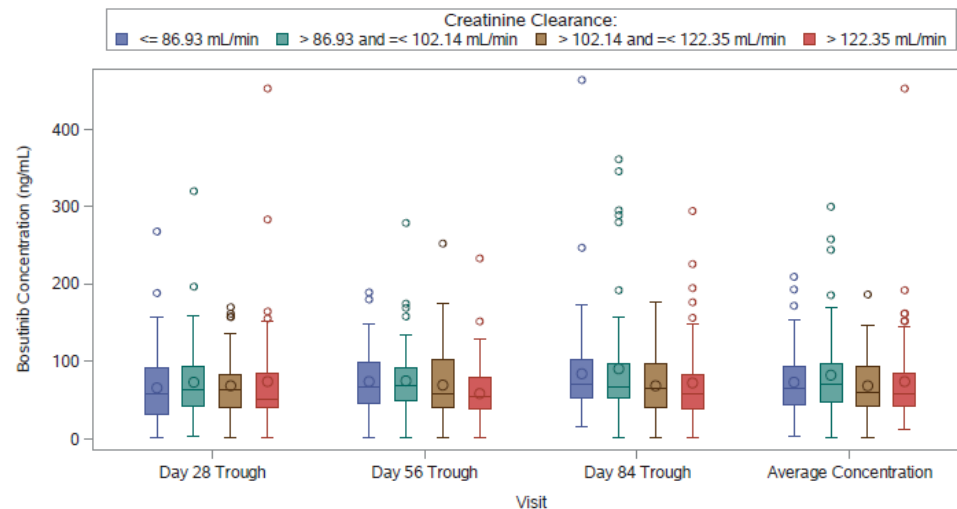


Table 10 Trough bosutinib concentrations (ng/mL) by creatinine clearance

Visit	Statistic	Creatinine Clearance				Spearman Correlation Coefficient Estimate (95% CI)
		Quartile 1 (<= 86.93 mL/min) (N=67)	Quartile 2 (> 86.93 and <= 102.14 mL/min) (N=66)	Quartile 3 (> 102.14 and <= 122.35 mL/min) (N=66)	Quartile 4 (> 122.35 mL/min) (N=66)	
Day 28	n	64	60	61	61	-0.0010 (-0.1260, 0.1241)
	Mean (SD)	65.173 (49.0493)	73.057 (51.1397)	68.162 (41.3662)	73.675 (68.9335)	
	95% CI	52.9, 77.4	59.8, 86.3	57.6, 78.8	56.0, 91.3	
	Median	56.850	62.900	62.100	51.300	
	Min, Max	0.50, 268.00	3.18, 320.00	0.50, 170.00	0.50, 453.00	
Day 56	n	61	61	61	58	-0.1485 (-0.2698, -0.0225)
	Mean (SD)	73.346 (41.8369)	74.510 (45.8292)	69.057 (48.8936)	58.386 (38.9630)	
	95% CI	62.6, 84.1	62.8, 86.2	56.5, 81.6	48.1, 68.6	
	Median	66.100	68.800	58.200	54.650	
	Min, Max	0.50, 189.00	0.50, 279.00	0.50, 252.00	0.50, 233.00	
Day 84	n	57	63	60	57	-0.1339 (-0.2569, -0.0065)
	Mean (SD)	83.963 (65.3426)	90.133 (76.5654)	68.288 (40.7347)	71.895 (55.0072)	
	95% CI	66.6, 101.3	70.8, 109.4	57.8, 78.8	57.3, 86.5	
	Median	70.700	67.300	65.250	57.100	
	Min, Max	14.70, 464.00	0.50, 361.00	0.50, 177.00	0.50, 294.00	

Table 11 Individual and Mean pharmacokinetic parameters after once daily oral doses of Bosunitib 400 mg, 500 mg, or 600 mg in subjects with leukemia on Day 15 (Study B1871006)

Treatment = Bosutinib 400 mg (Dose Day = 15)						
Subject	C _{max} (ng/mL)	t _{max} (hour)	AUC _{ss} (ng*h/mL)	CL/F (L/hour)	t _{1/2} (hour)	R
1	167	3.08	3210	125	37.52	1.8
2	145	6.08	2340	171	18.71	3.1
4	127	4.05	2610	153	81.64	4.5
N	3	3	3	3	3	3
Mean	146	4.41	2720	150	45.96	3.1
SD	20.0	1.53	442	23.2	32.30	1.4
Min	127	3.08	2340	125	18.71	1.8
Median	145	4.05	2610	153	37.52	3.1
Max	167	6.08	3210	171	81.64	4.5
CV%	14	35	16	16	70	43
Geometric Mean	145	4.24	2700	148	38.56	2.9

AUC_{ss}= steady-state mean area under the concentration -time curve; C_{max}=peak concentration; CL/F=apparent oral dose clearance; CV=coefficient of variation; R =accumulation ratio (AUC_{ss} on day 15/AUC₀₋₂₄ on day 1); SD=standard deviation; t_{1/2}=terminal-phase elimination half-life; t_{max}=time to peak concentration

Table 12 Summary of Mean Pharmacokinetic Parameters of Bosutinib Following a Single Oral Dose of 400 mg Bosutinib Administered Under Fasting and Fed Conditions in Healthy Subjects (Study B1871025)

Mean±SD	Plasma Bosutinib	
	Fasting	Fed
N	24	23
C _{max} (ng/mL)	55.9 ± 29.6	89.5 ± 24.1
t _{max} ^a (h)	6.02 (3.02 - 8.02)	6.02 (2.02 - 8.02)
t _{1/2} (h)	35.50 ± 11.24	31.93 ± 5.93
AUC _T (ng•h/mL)	1160 ± 570	1860 ± 409
AUC (ng•h/mL)	1310 ± 598	2060 ± 448
λ _z (1/h)	0.0220 ± 0.0104	0.0224 ± 0.00401
Cl/F (L/h)	369 ± 168	204 ± 45.2
V _z /F (L)	19200 ± 12700	9460 ± 3400

Abbreviations: SD=standard deviation; C_{max}=peak concentration; t_{max}=time to peak concentration; t_{1/2}=terminal-phase elimination half-life (0.693/λ_z); AUC_T=area under the concentration-time curve to the last measurable concentration at time T (C_T); AUC=total area under the concentration-time curve (AUC_T + C_T/λ_z for single dose); λ_z (1/h)=terminal-phase disposition rate constant; Cl/F=apparent oral dose clearance (dose/AUC); V_z/F=apparent volume of distribution.

a. Median (Minimum-Maximum).

2.3.3. Pharmacodynamics

Study AV001

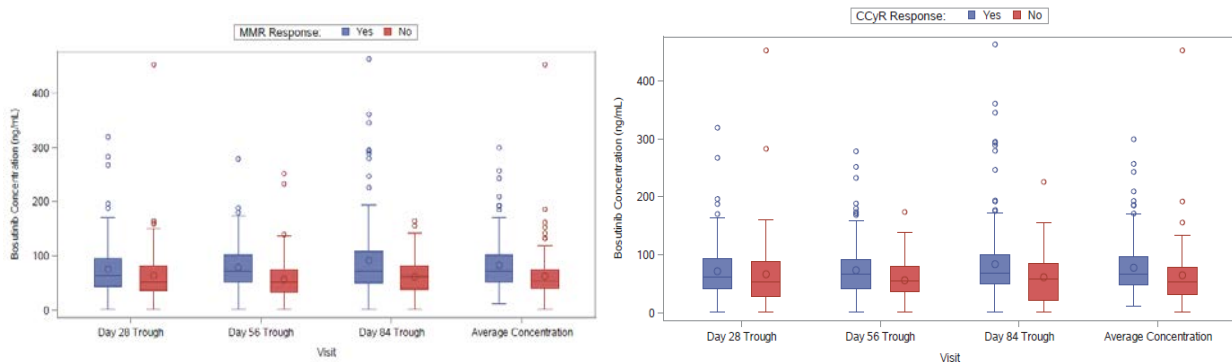
Relationship between plasma concentration and effect – efficacy endpoints

Median trough plasma bosutinib concentrations were higher at each time-point in subjects with MMR compared to those without MMR at 12 months. Plasma bosutinib concentrations were also higher at Day 56, Day 84, and overall in subjects with CCyR vs. without CCyR by 12 months.

Figure 4 Trough bosutinib plasma concentrations (ng/mL)

a by MMR response

b by CCyR response



Logistic regression was used to analyse the probability of achieving MMR at 12 months and CCyR by 12 months for subjects in the PK Population. The Day 84 trough bosutinib concentration was associated with a probability of achieving CCyR by 12 months (2-sided $p=0.006$).

Relationship between plasma concentration and effect – safety

At Day 28, there was a difference in bosutinib concentration between subjects with (median concentration: 44.6 ng/mL) and without (median concentration: 59.7 ng/mL) Grade ≥ 3 thrombocytopenia. There was also a difference in bosutinib concentration between subjects with (median concentration: 3.9 ng/mL) and without (median concentration: 59.4 ng/mL) Grade ≥ 3 vomiting at Day 28; this is based on 3 subjects with Grade ≥ 3 vomiting in the PK Population. Logistic regression was used to analyse the probability of experiencing specific AEs for subjects in the PK Population. The Day 56 trough bosutinib concentration was associated with a probability of rash (2-sided $p=0.031$) and nausea (2-sided $p<0.001$) AEs.

Relationship between efficacy and safety

The probability to experience specific ADRs was separately analysed for MMR and CCyR responders.

Figure 5 Probability of diarrhoea: grade ≥ 1 (left) and grade ≥ 3 (right)

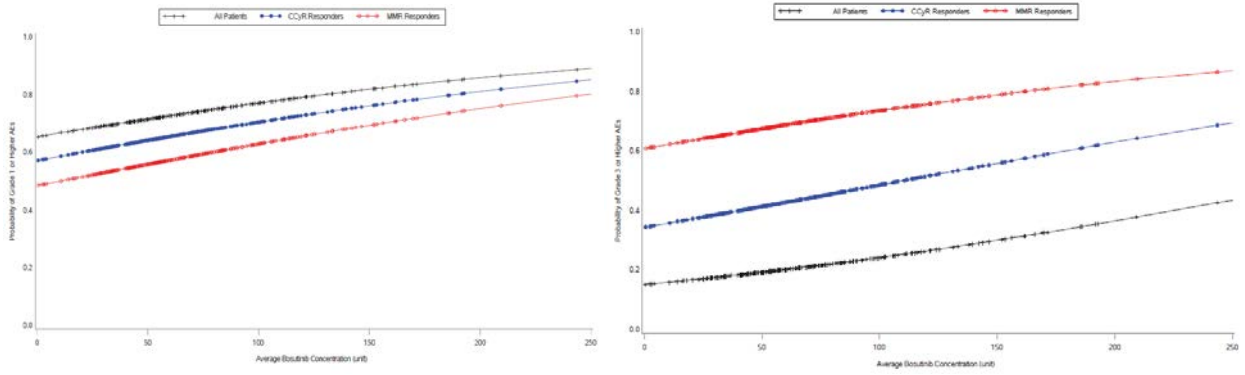


Figure 6 Probability of thrombocytopenia: grade ≥ 1 (left) and grade ≥ 3 (right)

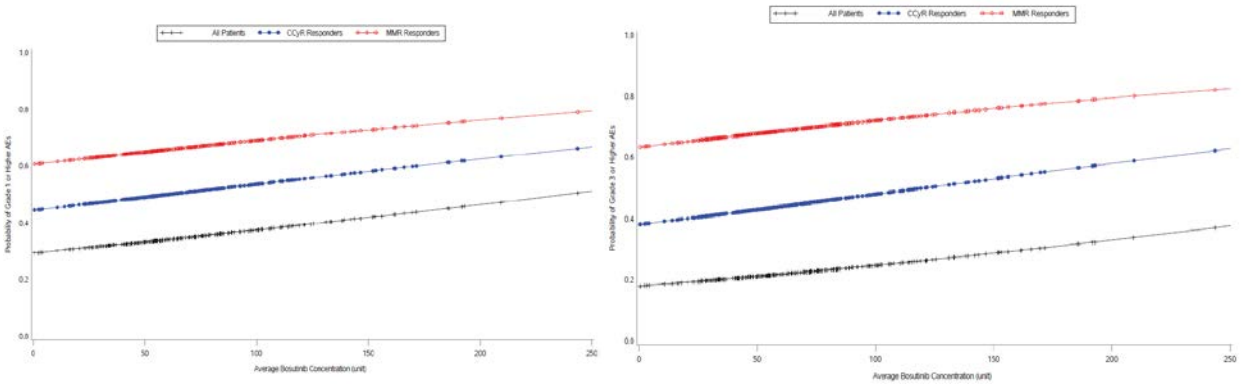


Figure 7 Probability of rash: grade ≥ 1 (left) and grade ≥ 3 (right)

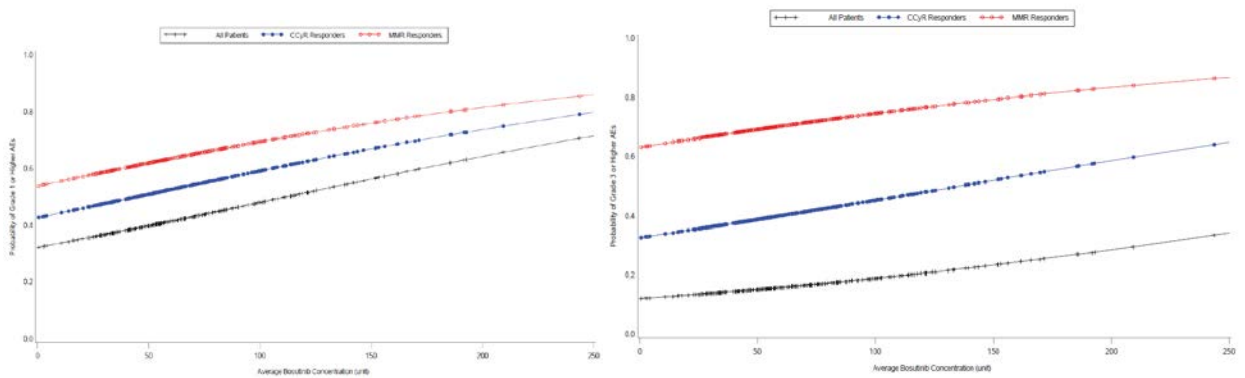
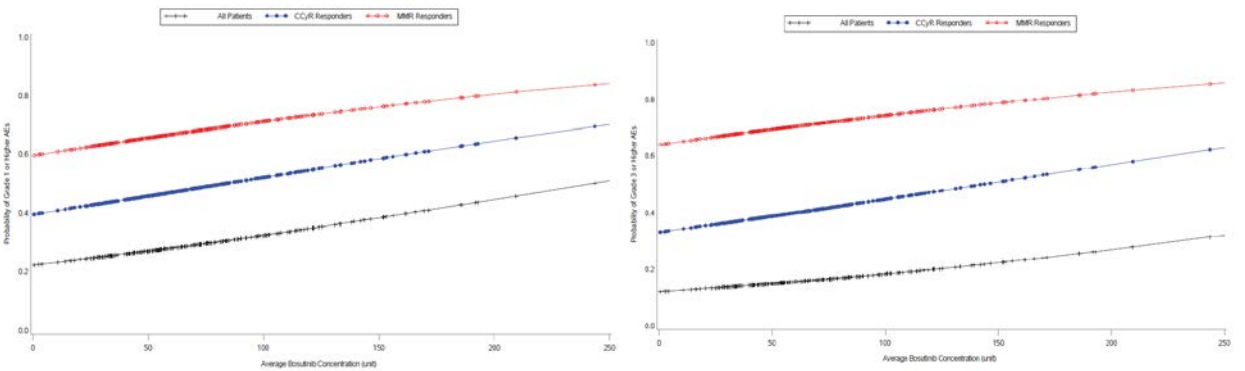


Figure 8 Probability of vomiting: grade ≥ 1 (left) and grade ≥ 3 (right)



2.3.1. PK/PD modelling

Relationship between plasma concentration and effect –efficacy endpoints

The efficacy endpoints were MMR, CCyR, and CHR. Efficacy endpoint MMR was assessed at 48 weeks. If patients discontinued bosutinib treatment before the 48 weeks assessment, they were counted as a non-responder (-). For efficacy endpoints CCyR and CHR, the assessment was cumulative, ie, any on-treatment response (+) was counted as a response if it occurred by 48 weeks. For the E-R analysis, each patient was required to have an estimated parameter of bosutinib exposure. A total of 512 patients were included in the E-R analysis of MMR and CHR. For endpoint CCyR, the E-R analysis was conducted in Ph+ patients only (N=493).

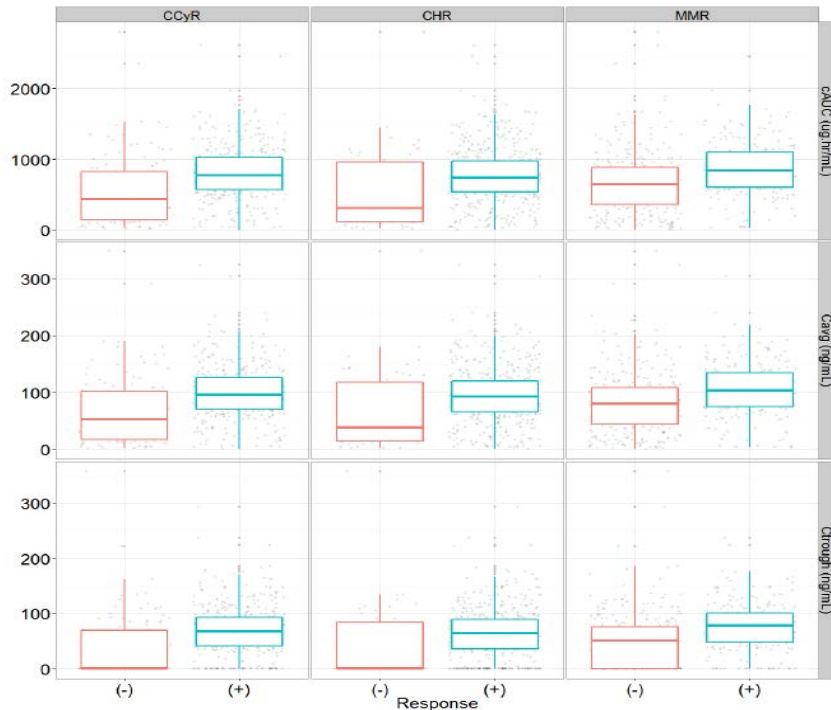
Table 13 Patients included in the model efficacy analysis

Efficacy Endpoint	Study B1871008	Study AV001	Total
N	246	266	512
MMR(-)	151 (61%)	142 (53%)	293 (57%)
MMR(+)	95 (39%)	124 (47%)	219 (43%)
CCyR(-)	58 (24%)	57 (23%)	115 (23%)
CCyR(+)	188 (76%)	190 (77%)	378 (77%)
CHR(-)	29 (12%)	22 (8%)	51 (10%)
CHR(+)	217 (88%)	244 (92%)	461 (90%)

Exploratory plots of the bosutinib exposures (

Figure 9) suggest E-R relationship between the efficacy endpoints of interest for this analysis and bosutinib exposures.

Figure 9 Efficacy endpoints vs bosutinib exposures prior to event (C_{avg} , C_{trough} , $cAUC$)



Both time on treatment and bosutinib exposure were statistically significant predictors of the probability of achieving MMR at 48 weeks. However, time on treatment appears to play a bigger role than bosutinib exposure. A longer time on treatment leads to a higher probability of achieving MMR at

48 weeks.

Bosutinib exposure is a statistically significant predictor of the probability of achieving CCyR and CHR by 48 weeks. The predicted probability curves are close to plateau (**Figure 11**) at the exposure expected from a daily dose of 400 mg, which suggests that differences in doses (400 mg versus 500 mg once daily) will likely not translate into a clinically relevant difference in CCyR and CHR by 48 weeks.

Figure 10 Predicted probability of achieving a Major Molecular Response

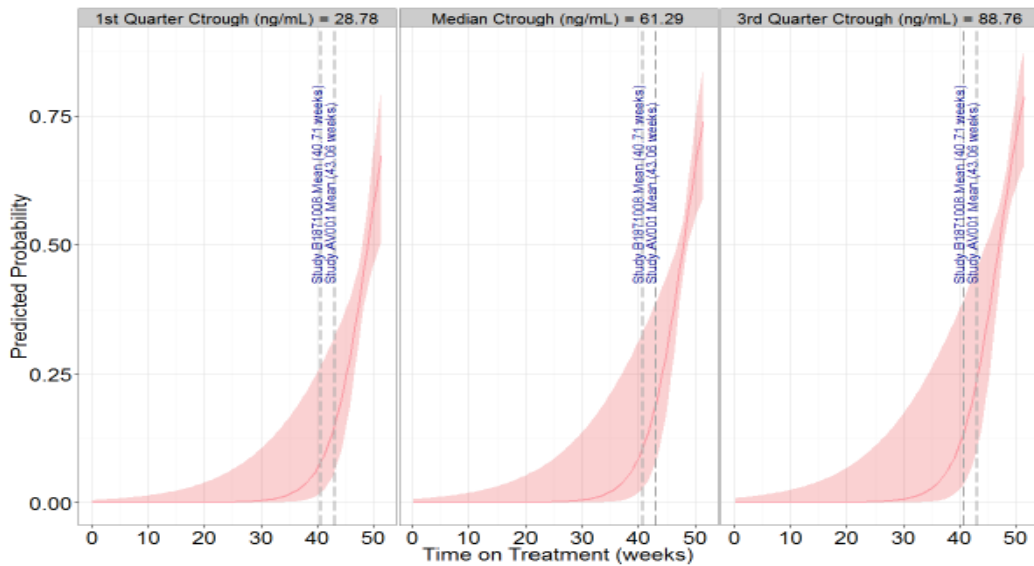
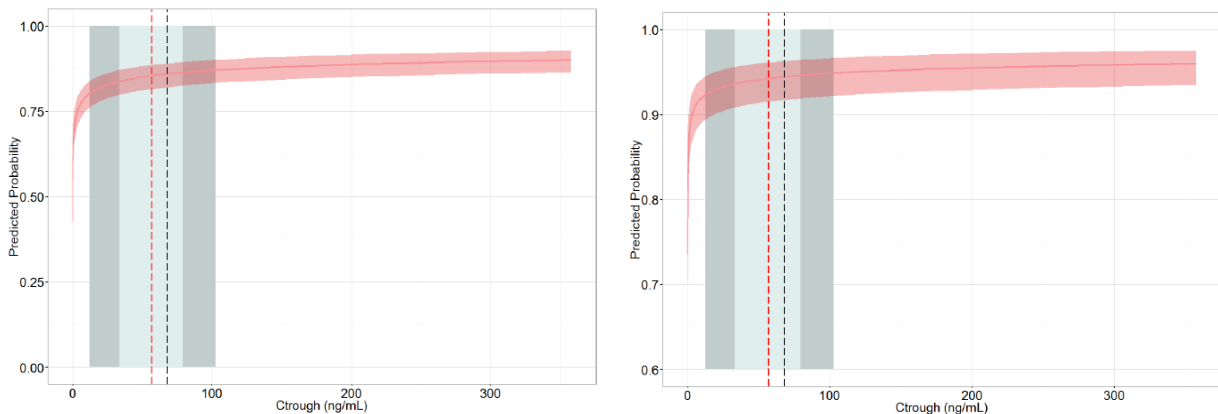


Figure 11 Predicted probability of achieving a CCyR (left) and CHR (right)



Relationship between plasma concentration and effect –safety

The E-R for safety was performed in newly diagnosed CP CML patients from Studies B1871008 and AV001. Only the first occurrence of the highest observed AE grade in the first year of bosutinib treatment (366 days) for each patient was used for the analysis.

An E-R relationship was identified for AE diarrhoea, nausea, and vomiting with time to event. In the final model, time to event and $\log(C_{avg})$, C_{trough} , and C_{avg} were found to be statistically significant predictors ($p < 0.05$) for diarrhoea, nausea, and vomiting, respectively. No demographic covariates

were found to be statistically significant on any of these safety endpoints.

The predicted probabilities of patients experiencing diarrhoea and nausea Grade>0 are shown in Figure 12. The plots show that patients have a lower probability of moving from one AE grade to the subsequent higher AE grade as time goes on; however the probability of moving from one AE grade to the subsequent higher one earlier in treatment (one week) is higher as bosutinib exposure increases.

Figure 12 Predicted probability of diarrhoea grade

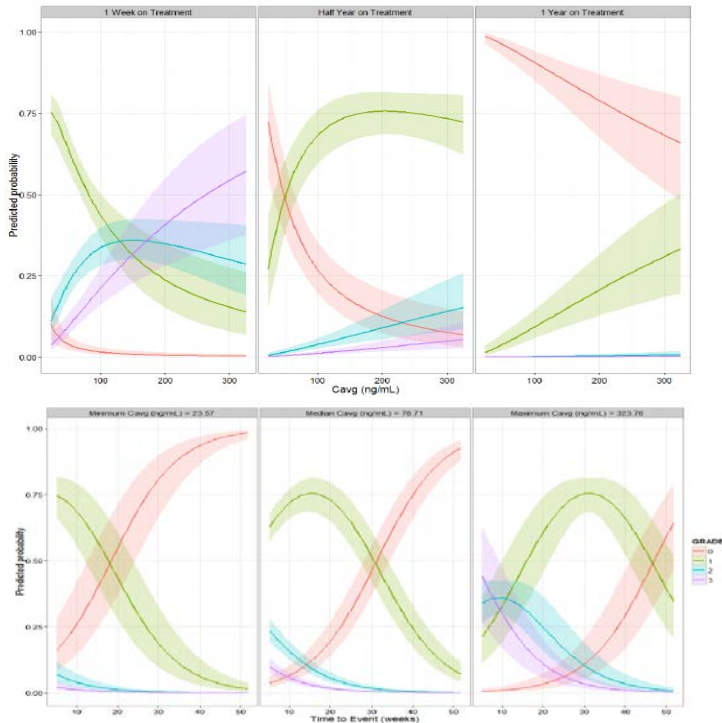
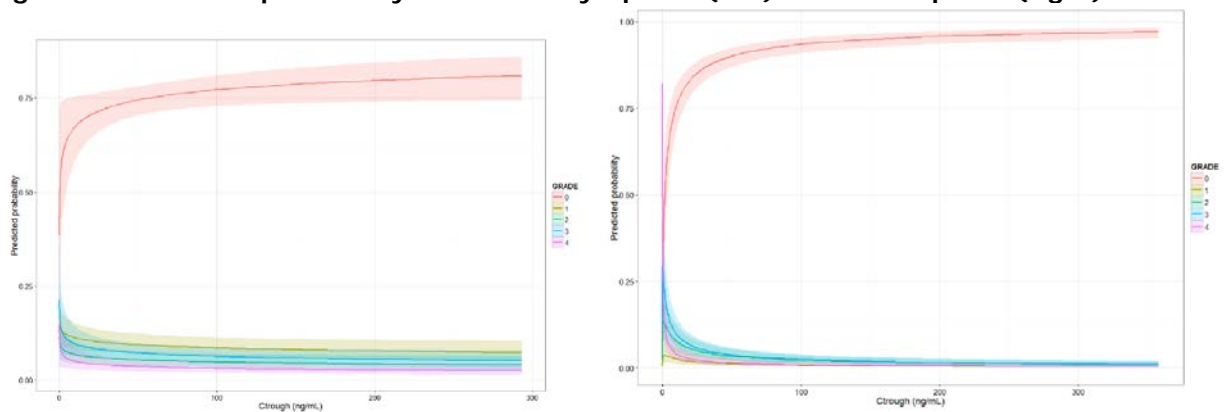


Figure 13 Predicted probability of thrombocytopenia (left) and neutropenia (right)



2.3.2. Discussion on clinical pharmacology

The PK population in the pivotal phase III study AV001 included all subjects, regardless of Philadelphia chromosome status, who received at least 1 dose of study medication and had sufficient plasma results collected in order to create reliable PK parameter results. The PK population was used for all PK analyses (n=267).

In study AV001 the average geo-mean bosutinib trough concentration was 59.4 ng/mL, as calculated from sparse blood sampling and was in the same range as the estimates in the submitted new population pharmacokinetic model estimations. The bosutinib trough concentrations suggest differences between e.g. age groups and groups of creatinine clearance which became more pronounced the longer the patients were on treatment.

An updated popPK model for bosutinib was built on a pooled dataset based on the previous model assumptions (PMAR-219, submitted with initial MAA dossier) and, specifically, on studies B1871006, B1871008, B1871012 and AV001 under the assumption that the PK of bosutinib would not change between patients treated with first-line or second-line bosutinib therapy. This assumption is acceptable. The MAH was asked for an explanation of the apparent approx. 20-fold higher median AUC estimates in the new model and it was clarified that in the new model AUC_T had been reported over a 28-day interval. The newly estimated geo-mean values for AUC_T on Day 140 are ~2.4 and 3.2 µg*hr/mL for the 400 mg and 500 mg dose levels, respectively, which are in the same range as those previously reported and stated in the SmPC.

For renal impairment, the previous model was already updated once by inclusion of data from the renal impairment study B1871020 to be able to provide reliable dosing recommendations for renally impaired patients. These 'Alldata' model PK data resulted in the current approved dose adjustment recommendations for 500mg. The proposed new dose adjustment recommendations in section 4.2 of the SmPC for moderate and severe renally impaired patients in first line CML for the 400mg dose are considered sufficiently justified and hence acceptable.

The modelling approach did not include a covariate analysis of the full dataset. A covariate analysis is considered necessary, in order to provide information on the potential for dose adjustments. The MAH is planning to develop a more comprehensive population PK model and further identify sources of variability, including the patient data from AV001. The MAH should investigate in the new model covariates that might have an influence on the plasma concentrations to improve dosing. In addition, the MAH should further address the following issue: The lines representing the median and percentiles for the observed data do not always follow the depicted observed data, e.g. at time points around 150 to 200 h after first dose for the 500 mg dose plot, the data seem to be excluded from the analyses. Finally, confidence intervals for the observed data should be submitted. The MAH proposed to submit the population modelling analysis report by the fourth quarter of 2018. This is endorsed.

Similar to what was revealed for first-line CML patients with 500mg during the initial MAA procedure, in study AV001 with 400mg responders had higher bosutinib trough plasma concentrations than non-responders (at least 25% higher for responders) so that C_{trough} was a predictor of CHR, CCyR and MMR. The deeper the response was (CHR < CCyR < MMR) the higher was C_{trough} already after 28 days. In addition for MMR, longer time on treatment predicted higher probability for response, though only predictable at 48 weeks from the underlying dataset. Derived from this model it seems more important to stay on treatment than to receive a higher dose. However, the potential to increase concentrations in patients not responding in order to improve therapy outcome should be evaluated and in this respect, the investigation of covariates in the popPK analyses could provide potential to improve dosing. But as the MAH committed to submit an updated popPK model in Q4/2018, this aspect will be further analysed therein.

In addition, section 4.4 of the SmPC has been updated with new data from long-term treatment in studies 200-WW and 3000-WW concerning eGFR decline over time, which is overall acknowledged.

A statistically significant and positive exposure-response relationship between bosutinib exposure and incidence of rash, elevated ALT, and elevated aspartate amino transferase (AST) (Grade >0) was

observed. A statistically significant and inverse exposure-response relationship between bosutinib exposure and incidence of thrombocytopenia and neutropenia (Grade>0) was observed.

Lower bosutinib exposure is predicted to decrease the probability of AEs earlier on treatment for diarrhoea, nausea, and vomiting, and at any time on treatment for rash, elevated ALT, and AST. Comparing the 2 Phase 3 study results, 38 patients (14.2%) in Study AV001 (starting dose of 400 mg once daily) permanently discontinued treatment due to a AE compared to 52 patients (21.0%) who permanently discontinued treatment due to a AE in Study 1008 (starting dose of 500 mg once daily). The MMR at 48 weeks in Study AV001 was 47.2% versus 38.0% in Study 1008, suggesting that a lower dose did not compromise efficacy, but rather reduced the risk of permanent discontinuations due to AEs. These findings suggest that a lower starting dose of bosutinib may allow patients to remain on treatment longer, and that time on treatment plays a bigger role in efficacy than dose.

Differences in bosutinib concentration between subjects with and without Grade ≥ 3 thrombocytopenia and between subjects with and without Grade ≥ 3 vomiting at Day 28 were observed. Logistic regression was used to analyse the probability of experiencing specific AEs for subjects in the PK Population. The Day 56 trough bosutinib concentration was associated with a probability of rash and nausea AEs.

The probability of experiencing certain ADRs (diarrhoea, nausea, vomiting, rash and thrombocytopenia) was separately analysed for 'All patients' vs. MMR responders vs. CCyR responders in study AV001. Except for diarrhoea \geq grade 1, patients who were responders for MMR and CCyR experienced more ADRs independently of lower or higher bosutinib concentrations. Generally, the higher the trough plasma concentrations were, the higher was the probability of ADRs in all cases.

A statistically significant and positive exposure-response relationship between bosutinib exposure and incidence of rash, elevated ALT, and elevated aspartate amino transferase (AST) was revealed. In contrast, significant statistical results suggest an inverse exposure-response relationship between bosutinib exposure and incidence of thrombocytopenia and neutropenia (Grade>0).

2.3.3. Conclusions on clinical pharmacology

The relevant changes in the overall bosutinib clinical pharmacology profile that were identified based on the new PK and PD data submitted in this variation application have been reflected in the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response studies

Prior clinical studies with bosutinib in CML used a starting dose of bosutinib of 500 mg daily, both in first-line (BELA/Study 1008-3000WW) and in later lines of treatment (Study 200WW). In both studies, a considerable number of subjects reported toxicities which were managed in most of the cases by treatment interruption and/or dose reduction.

In first-line CP CML patients recruited in BELA/Study 3000, a total of 92/250 (37%) patients treated with bosutinib had a dose reduction from 500 mg to 400 mg of bosutinib/day as of the 15 months' follow-up. The median time to first dose reduction to 400 mg was 53.5 days with a range from 2 to 612 days.

The incidence of TEAEs overall as well as unique TEAEs were lower following dose reduction from 500 mg to 400 mg. The overall incidence of Grade 3/4 TEAEs decreased from 88% to 71%. All of the most frequently reported TEAEs (all grades) also decreased: diarrhea (70% to 40%), ALT increased (39% to 30%), nausea (38% to 23%), vomiting (33% to 24%), AST increased (33% to 23%), and thrombocytopenia (30% to 21%). It is notable that the median time on treatment for patients prior to dose reduction was 53.5 days (range: 2-612 days) while the median time on treatment for patients post dose reduction was 449 days (range: 0-1142 days).

The efficacy of bosutinib in patients who received dose reductions to 400 mg remained favorable with 46% of patients achieving a CCyR after the dose reduction to 400 mg (compared to 58% in the ITT Population) and 16% of patients maintaining a previously attained CCyR. In addition, 40% of patients were able to achieve a MMR while on 400 mg of bosutinib (compared to 45% in the ITT Population). Of those dose reduced to 400 mg and who attained a CCyR and MMR, the majority of patients (68% and 71% respectively), were still on treatment and retaining their response at the time of the 24-month follow-up analysis.

The starting dose of imatinib selected in this study (400 mg) is in accordance with the approved product label for CML patients.

2.4.2. Main study

Study AV001

A multicentre, phase 3, randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed chronic phase Chronic Myelogenous Leukemia.

Methods

Study participants

Eligible subjects were expected to meet the following criteria:

1. Molecular diagnosis of CP CML of ≤ 6 months (from initial diagnosis).
 - Diagnosis of CP CML with molecular confirmation by detection of BCR-ABL rearrangement at screening (cytogenetic assessment for Ph was not required for enrollment); diagnosis of CP CML was defined as all of the following per ELN definitions:
 - a. $< 15\%$ blasts in peripheral blood and bone marrow;
 - b. $< 30\%$ blasts plus promyelocytes in peripheral blood and bone marrow;
 - c. $< 20\%$ basophils in peripheral blood;
 - d. $\geq 100 \times 10^9/L$ platelets ($\geq 100,000/mm^3$);
 - e. No evidence of extramedullary disease except hepatosplenomegaly; AND
 - f. No prior diagnosis of AP or BP-CML.
 - Ph status was identified at screening. Both Ph+ and Ph- subjects could be included.
2. Adequate hepatic and renal function defined as: AST/ALT $\leq 2.5 \times$ upper limit of normal (ULN) or $\leq 5 \times$ ULN if attributable to liver; involvement of leukemia; Total bilirubin $\leq 2.0 \times$ ULN (unless associated with Gilbert's syndrome); Creatinine $\leq 1.5 \times$ ULN.

3. Able to take oral tablets.
4. ECOG performance status of 0 or 1.
5. Age ≥ 18 years.
6. Negative serum pregnancy test within 2 weeks of the first dose of study drug if the subject was a woman of childbearing potential.
7. Ability to provide written informed consent prior to any study related screening procedures being performed.

Subjects were ineligible to participate in this study if any of the following criteria were met:

1. Any prior medical treatment for CML, including TKIs, with the exception of hydroxyurea and/or anagrelide treatment, which were permitted for up to 6 months prior to study entry (signature of ICF) if suitably approved for use in the subject's region.
2. Any past or current central nervous system involvement, including leptomeningeal leukaemia.
3. Hypersensitivity to the active substance or to any of the following excipients: microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201), magnesium stearate (E470b), polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, Talc (E553b), iron oxide yellow (E172).
4. Extramedullary disease only.
5. Major surgery or radiotherapy within 14 days of randomization.
6. Concomitant use of, or need for, medications known to prolong the QT interval.
7. History of clinically significant or uncontrolled cardiac disease including: History of, or active, congestive heart failure; Uncontrolled angina or hypertension within 3 months; Myocardial infarction (within 12 months). Clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes); Diagnosed or suspected congenital or acquired prolonged QT history or prolonged QTc (QTcF should not exceed 500 msec); Unexplained syncope.
8. Known seropositivity to human immunodeficiency virus (HIV), current acute or chronic hepatitis B (hepatitis B surface-antigen positive), hepatitis C, cirrhosis or evidence of decompensated liver disease. Subjects with resolved hepatitis B could be included.
9. Recent or ongoing clinically significant GI disorder, eg Crohn's Disease, Ulcerative Colitis, or prior total or partial gastrectomy.
10. History of another malignancy within 5 years with the exception of basal cell carcinoma or cervical carcinoma in situ or stage 1 or 2 cancer that was considered adequately treated and currently in complete remission for at least 12 months.
11. Uncontrolled hypomagnesemia or uncorrected hypokalemia due to potential effects on the QT interval.
12. Current, or recent (within 30 days, or 5 half-lives of investigational product) participation in other clinical trials of investigational agents and/or containing interventional procedures deemed contrary to the objectives and conduct of this study.
13. Women who were pregnant, planning to become pregnant during the study or were breastfeeding a child, or men who were planning to father a child during the study.

Treatments

The starting dose for all subjects was 400 mg once daily of either bosutinib or imatinib, orally, recommended to be taken in the morning with a meal and 200 mL of water. Patients were permitted to have their dose increased for suboptimal response to a maximum of 600 mg for bosutinib and 800 mg for imatinib or reduced due to toxicity as necessary in accordance with existing CML guidelines (eg, NCCN Guidelines Version 2.2017).

Objectives

The primary objective of Study AV001 was to compare the proportion of patients demonstrating MMR at 12 months (48 weeks) in the bosutinib arm with that of the imatinib arm in newly diagnosed Ph+ CP CML patients harboring b2a2 and/or b3a2 transcripts and baseline BCR-ABL copies >0 in order to demonstrate statistically significant superiority.

Secondary objectives/endpoints were to:

- Evaluate MMR by 18 months in the bosutinib treatment arm compared with the imatinib treatment arm.
- Evaluate the duration of MMR in the bosutinib arm compared to the imatinib arm.
- Estimate the proportion of patients demonstrating CCyR by 12 months in both treatment arms.
- Evaluate the duration of CCyR in both treatment arms.
- Evaluate EFS in both treatment arms.
- Evaluate overall survival (OS) in both treatment arms.
- Assess the population PK of bosutinib administered once daily.
- Assess correlations between trough concentrations of bosutinib and key efficacy and safety parameters.
- Evaluate the safety profile of bosutinib and imatinib treatment.

Exploratory objectives were to:

- Evaluate MMR at 3, 6, 9, and 18 months in both treatment arms.
- Evaluate MMR at 12 months in both treatment arms in the Ph chromosome unrestricted (ie, Ph+ and Ph-) population.
- Evaluate MR4 and MR4.5 at 3, 6, 9 and 12 months in both treatment arms.
- Evaluate time to MMR in the bosutinib arm compared to the imatinib arm.
- Evaluate time to CCyR in both treatment arms.
- Time to transformation to AP and BP on treatment in both treatment arms.

- Evaluate patient-reported outcomes (PRO), including quality of life (QoL), using Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) and EuroQoL: -5 dimensions (EQ-5D), in both treatment arms.

Outcomes/endpoints

Primary endpoint

The primary endpoint was MMR defined as $\leq 0.1\%$ BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardized baseline) by RQ-PCR with at least 3,000 ABL transcripts analyzed by the central laboratory.

In this study, a MMR at 12 months (48 weeks) was counted only if the response was demonstrated at the 12 month (48 week) visit; a MMR gained and lost before the 12 month (48 week) visit was deemed a nonresponse.

Secondary endpoints

- Duration of MMR was defined as the time from the first date of MMR until the date of the loss of MMR or of progressive disease (earliest date in case of multiple events). Progressive disease was captured in the database as disease progression to AP/BP CML on the treatment discontinuation form.
- Duration of CCyR was defined as the time from the first date of CCyR until the date of the loss of CCyR or of progressive disease (or earliest date in case of multiple events).
- EFS was defined as the time from randomization to the occurrence of the earliest of the following events while on treatment: death due to any cause; transformation to AP or BP at any time on treatment; loss of CHR (defined as a hematologic assessment of non-CHR [CP, AP, or BP confirmed by 2 assessments at least 4 weeks apart); loss of CCyR (defined as ≥ 1 Ph+ out of < 100 metaphases confirmed by a follow-up cytogenetic analysis > 1 month later); for subjects not achieving a CHR: doubling of WBC count at least 1 month apart with the second value $> 20 \times 10^9/L$ and maintained in subsequent assessments for at least 2 weeks; subjects without an event were censored at the last cytogenetic or hematologic assessment.
- OS, defined as the time from randomization to the occurrence of death due to any cause. Subjects without death documented were censored at the last date on which they were known to be alive.

Exploratory endpoints

- MMR at 3, 6, 9 and 18 months.
- MMR at 12 months in the Ph unrestricted (ie, Ph+ and Ph-) subject population.
- MR1 and MR2 at 3 months and 6 months, respectively.
- MR4 and MR4.5 at 3, 6, 9 and 12 months.
- MR4 and MR4.5 (≥ 4 and ≥ 4.5 log reduction in BCR-ABL transcripts) were defined as a 4 and 4.5 log reduction in the BCR-ABL from the standardized baseline or ≤ 0.01 and ≤ 0.0032 BCR-ABL/ABL %, respectively, on the IS, measured by RQ-PCR.
- Time to MMR (data collection not complete, but available results presented in this CSR) measured from randomization to the first date of MMR. Subjects without response were censored at the last molecular assessment.
- Cumulative confirmed CHR in both Ph+ and Ph unrestricted (ie, Ph+ and Ph-) subject population.

- Time to CCyR in both treatment arms (data collection not complete, but available results presented in this CSR) measured from randomization to the first date of CCyR (or MMR if MMR was achieved and no valid cytogenetic assessment was available). Subjects without response were censored at the last cytogenetic assessment.
- Time to on-treatment transformation to AP or BP measured from randomization to the first date of transformation. Subjects without transformation were censored at the last hematologic assessment.
- Presence of newly observed BCR-ABL mutations in subjects post-baseline and correlation with response to treatment in imatinib and bosutinib treatment arms.

Sample size

A total sample size of 500 Ph+ subjects harboring b2a2 and/or b3a2 transcripts was required for the study to provide $\geq 90\%$ power to detect at least 15% difference (assuming 25% in the imatinib vs 40% in the bosutinib arm) in the MMR rates at 12 months using a 1-sided alpha of 2.5% and figuring in two interim futility analyses at 33% of patients and at 66% of subjects with adequate follow-up. Early stopping was intended for futility only (nonbinding, O'Brien-Fleming analog beta spending function). Nonbinding for the futility implied that the futility boundary would be constructed in such a way that it could be overruled if desired by the Sponsor and/or IDMC without inflating the type-1 error rate and without decreasing the power. Since Ph status was not needed for randomization, as CML diagnosis was instead confirmed by presence of BCR-ABL transcript, Ph- was identified retrospectively after enrolment, a total of approximately 530 Ph+ and Ph- patients were expected to be randomized in 1:1 ratio.

Randomisation

Upon completion of the screening evaluation and confirmation of eligibility, patients were randomly assigned to 1 of the 2 treatment groups in a 1:1 ratio. Randomization was done no more than 3 business days prior to first dose of treatment. Randomization of patients into each arm were prospectively stratified based on the patient's Sokal score at screening (Low risk: Sokal score < 0.8 vs Intermediate risk: Sokal score 0.8 to 1.2 vs High risk: Sokal score > 1.2) and geographical region (Region 1: United States, Canada, and Western Europe vs Region 2: Eastern Europe, Latin America and South America vs Region 3: Rest of World) in which the patient is enrolled.

Blinding (masking)

This is an open-label study.

Statistical methods

Analysis Populations

The modified Intent-to-treat (mITT) Population was the primary analysis population and was used for the primary efficacy comparison. The mITT Population included all randomized subjects with Ph+ CP CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL copies > 0 with study drug assignment designated according to initial randomization. All efficacy analyses were based on the mITT Population, with the exception of the duration of response (based on responders) and selected secondary/exploratory endpoints.

The Intent-to-treat (ITT) Population included all randomized subjects (ie, Ph+ and Ph) with study drug assignments designated according to initial randomization. The ITT Population was only used for additional selected secondary efficacy analyses of time to event (OS) and additional selected exploratory efficacy analyses.

The Safety Population included all subjects, regardless of Ph status, who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received. The Safety Population was the population used for all safety analyses.

The Evaluable Population was comprised of subjects who met criteria (randomized and received at least one dose of a test article; no major protocol deviations.; and at least 1 adequate post-baseline disease assessment). Supportive analyses of the primary and secondary endpoints were also performed in the Evaluable Population.

Primary Analysis

The primary efficacy analysis was based on the Cochran-Mantel-Haenszel (CMH) test stratified by Sokal score and geographic region as baseline factors at time of randomisation. The asymptotic 95% confidence intervals (CIs) for the adjusted odds ratio (OR), rates and rate difference along with asymptotic 95% CI of MMR at 48 weeks were also calculated. Efficacy was demonstrated if there was a statistically significant difference in the proportion of subjects with MMR at 48 weeks, when comparing the treatment arms at the 1-sided 0.025 significance level.

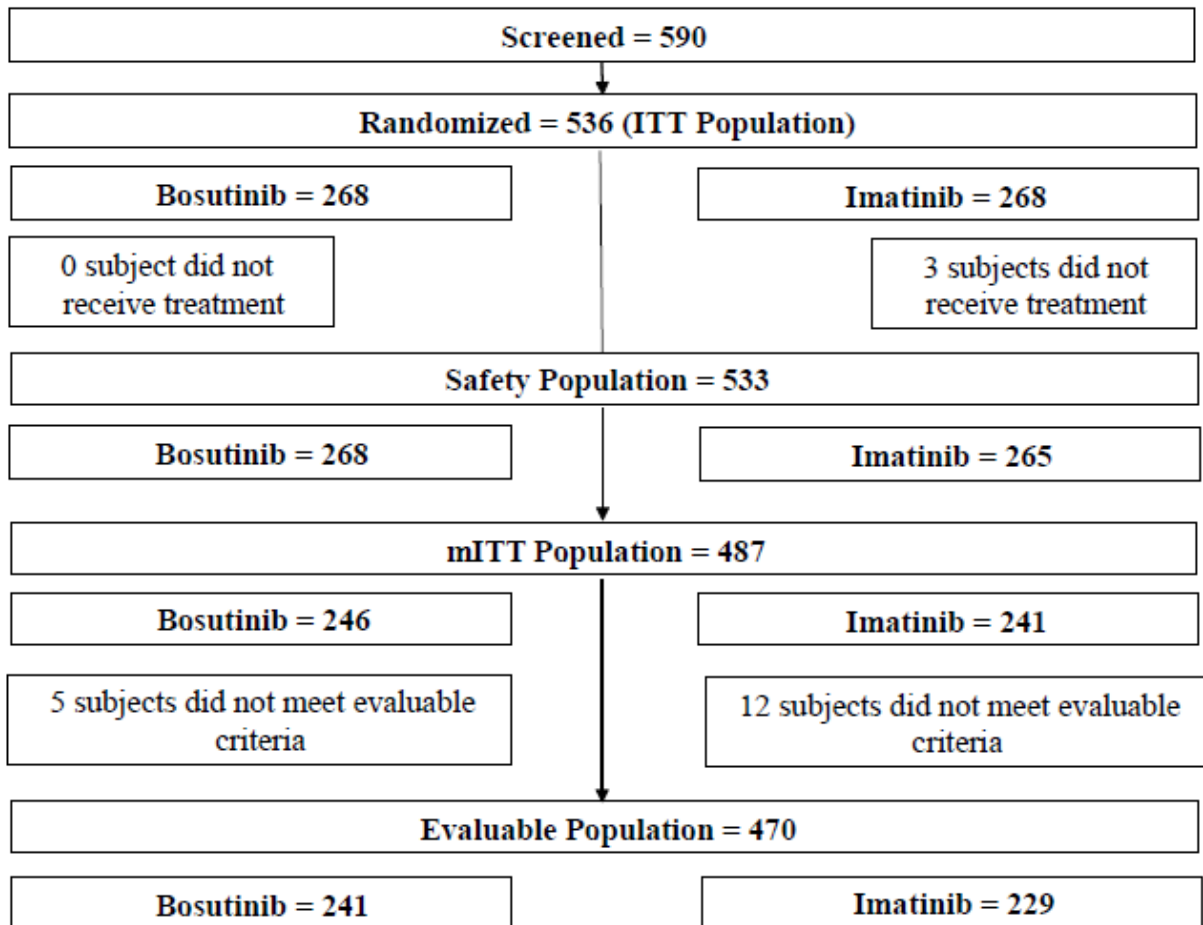
Interim analyses

Two interim futility analyses were performed based on the MMR status of approximately the first 33% and the first 66% of the randomized Ph+ subjects, who were Ph+ harboring b2a2 and/or b3a2 transcripts (ie, the mITT Population). The IA allowed stopping the study for reasons of futility. The provision to stop for futility was nonbinding.

Results

Participant flow

Figure 14. Overall Subject Disposition (Study AV001)



Note: ITT population included all randomized subjects (ie, Ph+ and Ph- CML) with study drug assignment designated according to initial randomization. mITT population included all ITT subjects with Ph+ (baseline Ph+ metaphases >0) chronic phase CML harboring the b2a2 and/or b3a2 transcript and baseline BCR-ABL>0. Safety Population included all ITT subjects who received at least 1 dose of study medication with treatment assignments designated to actual study treatment received. Evaluable population included all subjects in the mITT Population who received at least 1 dose of test article and had no major protocol deviations and at least 1 adequate post-baseline disease assessment.

Abbreviations: ITT=intent-to-treat; mITT=modified intent-to-treat.

Recruitment

In study AV001, a total of 183 sites were initiated but 37 of these sites did not randomize any subjects (including 32 sites that did not screen any subjects). Thus, of the 151 sites that screened subjects, 5 sites had screen failures. The study randomized subjects at 146 centres in Australia, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Norway, Poland, Singapore, Slovakia, South Africa, South Korea, Spain, Sweden, Taiwan, Thailand, Ukraine, UK and USA.

The first subject first visit was on 15 July 2014 and the last subject last visit in core phase was on 11 August 2016.

Conduct of the study

An overview of the changes included for Protocol Amendments is provided in Table 14.

Table 14 Overview of protocol amendments (Study AV001)

Protocol Amendment Number/Version	Date of Amendment	Overview of the Changes	Primary Reason for the Amendments
1.0	06 March 2014	Updated information for assessments of vital signs, inclusion/exclusion criteria, laboratory assessments, timing of efficacy endpoints, exploratory efficacy endpoints, study durations, timing of assessments, terms and definitions, study populations, adverse event assessments, and administrative information.	Clarifications, clerical errors/inconsistencies, and additional information resulting from discussions with regulatory agencies
2.0	14 January 2015	Updated information for contact details, study duration, subject populations, inclusion/exclusion criteria definitions, bosutinib formulation details, assessment timings (eg, schedule of events, pre-randomization Sokal score assessment), timing of assessments, timing for collection of adverse events/reporting, study drug dosing requirements, compliance recording, statistical analysis (primary and secondary efficacy analysis), pharmacokinetic analysis, and administrative information.	Clarifications, updated information and inconsistencies related to protocol requirements.
3.0	09 September 2016	Updated information for sample size, study populations, efficacy analysis, interim analyses, time to response description, and administrative information.	Country-specific amendment due to US-specific regulatory authority standard requirements. Changes included clarifications and updated information. Updated information to align with Statistical Analysis Plan; clarifications and updated information.
3.1	07 December 2016	Updated information for change of Sponsor details, sample size, study populations, methodology for statistical analyses, efficacy analysis, interim analyses, time to response description, Extension phase visit window, sample drug diary cards, and administrative information.	

Baseline data

Table 15 Summary of Demographics - mITT Population (Study AV001)

	Bosutinib (n=246)	Imatinib (n=241)	Overall (N=487)
Age (Years)			
n	246	241	487
Mean	50.8	51.2	51.0
Standard Deviation	15.51	14.03	14.78
Minimum	18	19	18
Maximum	84	84	84
Median	52.0	53.0	53.0
Age Category, n (%)			
Age <65	198 (80.5)	199 (82.6)	397 (81.5)
Age ≥65	48 (19.5)	42 (17.4)	90 (18.5)
Gender, n (%)			
Male	142 (57.7)	135 (56.0)	277 (56.9)
Female	104 (42.3)	106 (44.0)	210 (43.1)
Race, n (%)			
Asian	30 (12.2)	30 (12.4)	60 (12.3)
Black or African-American	10 (4.1)	10 (4.1)	20 (4.1)
White	191 (77.6)	186 (77.2)	377 (77.4)
Other	14 (5.7)	14 (5.8)	28 (5.7)
Missing	1 (0.4)	1 (0.4)	2 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	17 (6.9)	16 (6.6)	33 (6.8)
Not Hispanic or Latino	228 (92.7)	221 (91.7)	449 (92.2)
Missing	1 (0.4)	4 (1.7)	5 (1.0)
Weight (kg)			
n	245	241	486
Mean	76.97	76.64	76.81
Standard Deviation	18.027	18.570	18.280
Minimum	35.0	35.2	35.0
Maximum	125.0	147.0	147.0
Median	74.60	76.20	75.75
Missing	1	0	1
Height (cm)			
n	243	239	482
Mean	169.54	169.74	169.64
Standard Deviation	10.905	10.530	10.710
Minimum	147.0	139.0	139.0
Maximum	195.0	198.0	198.0
Median	170.00	170.00	170.00
Missing	3	2	5
Body Mass Index (kg/m²)			
n	243	239	482
Mean	26.64	26.46	26.55
Standard Deviation	5.429	5.568	5.494
Minimum	15.4	13.4	13.4
Maximum	44.0	51.5	51.5
Median	25.71	25.49	25.57
Missing	3	2	5

Abbreviations: CML=chronic myelogenous leukemia; mITT=modified intent-to-treat; Ph+=Philadelphia chromosome-positive.

Table 16 Baseline Characteristics Summary - mITT Population (Study AV001)

	Bosutinib n=246		Imatinib n=241		Overall N=487	
	n	(%)	n	(%)	N	(%)
Sokal Risk at Randomization						
Low Risk: (<0.8)	94	(38.2)	95	(39.4)	189	(38.8)
Intermediate Risk: (0.8-1.2)	101	(41.1)	95	(39.4)	196	(40.2)
High Risk: (>1.2)	51	(20.7)	51	(21.2)	102	(20.9)
Sokal Risk at Screening						
Low Risk: (<0.8)	86	(35.0)	95	(39.4)	181	(37.2)
Intermediate Risk: (0.8-1.2)	107	(43.5)	92	(38.2)	199	(40.9)
High Risk: (>1.2)	53	(21.5)	54	(22.4)	107	(22.0)
Region						
Region 1: United States, Canada, Western Europe	137	(55.7)	135	(56.0)	272	(55.9)
Region 2: Eastern Europe, Latin America, South America	74	(30.1)	73	(30.3)	147	(30.2)
Region 3: Rest of World	35	(14.2)	33	(13.7)	68	(14.0)
ECOG Performance Status^a						
0	174	(70.7)	170	(70.5)	344	(70.6)
1	72	(29.3)	70	(29.0)	142	(29.2)
Missing	0		1	(0.4)	1	(0.2)
Philadelphia Chromosome Status						
Ph (+)	246	(100.0)	241	(100.0)	487	(100.0)
Ph (-)	0		0		0	
BCR-ABL Transcript Type^b						
Typical	246	(100.0)	241	(100.0)	487	(100.0)
Atypical	0		0		0	
Extramedullary Disease						
Yes	14	(5.7)	8	(3.3)	22	(4.5)
No	231	(93.9)	230	(95.4)	461	(94.7)
Missing	1	(0.4)	3	(1.2)	4	(0.8)
History of Cardiac Disease^c						
Yes	28	(11.4)	29	(12.0)	57	(11.7)
No	218	(88.6)	212	(88.0)	430	(88.3)
History of Cardiac Disease Procedures						
Yes	15	(6.1)	16	(6.6)	31	(6.4)
No	231	(93.9)	225	(93.4)	456	(93.6)

a. ECOG: 0=Fully active; 1=Restricted in physically strenuous activity. b. Typical transcript type is a BCR-ABL transcript with b2a2 and/or b3a2. c. Per Case Report Form collected at Screening if the subject had history of coronary disease. Note: Sokal risk at Randomization was from the Interactive Voice Response System. Sokal risk at Screening was the corrected score from the clinical database. Ph status at Screening is derived from clinical database. The primary analysis was based on the Sokal score at randomization. Abbreviations: CML=chronic myelogenous leukemia; ECOG: Eastern Cooperative Oncology Group; mITT=modified intent-to-treat; Ph+=Philadelphia chromosome-positive.

Numbers analysed

- ITT Population: 536 patients (268 in the bosutinib arm and 268 in the imatinib arm).
- mITT Population: 487 patients (246 in the bosutinib arm and 241 in the imatinib arm).
- Safety Population: 533 patients (268 in the bosutinib arm and 265 in the imatinib arm).
- Evaluable Population: 470 patients (241 in the bosutinib arm and 229 in the imatinib arm).

Outcomes and estimation

Primary Efficacy Endpoint – Comparison of MMR at 12 Months (48 Weeks)

The results of the comparison of MMR at 12 month (48 weeks) in the mITT Population are summarized in Table 17 and Table 18.

Table 17: Comparison of Major Molecular Response (MMR) at month 12 by treatment arm - mITT Population (Study AV001)

Outcome at Month 12 Molecular Response	Bosutinib (n=246) (n, %)	Imatinib (n=241) (n, %)
mITT (PEP)		
MMR	116 (47.2)	89 (36.9)
Not MMR ^a	130 (52.8)	152 (63.1)
1-sided p-value ^b	0.0100	
ITT (exploratory)		
MMR	125 [46.6%]	97 [36.2%]
1-sided p-value ^b	0.0063	

a. Not MMR included subjects not having a MMR at the Month 12 (Week 48) assessment.

b. The p-value was based on a CMH test for general association between treatment and response with stratification by Sokal risk group (low, intermediate, high) and Region (1-3) as determined at time of randomization. If odds ratio of bosutinib vs imatinib >1 then the 1-sided p-value=1-probnorm (square root (CMH statistic)). If the odds ratio is ≤1 then the 1-sided p-value=1-probnorm (-square root (CMH statistic)), where probnorm=normal distribution function. Note: Percentages were based on number of subjects in each treatment arm. MMR was defined as ≤0.1% BCR-ABL ratio on international scale (corresponding to ≥3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts assessed by the central laboratory.

Table 18: 95% Confidence Intervals for MMR at Month 12 and associated odds ratio by treatment arm - mITT Population (Study AV001)

	Bosutinib (n=246)	Imatinib (n=241)
MMR at Month 12		
Rate of Response % (95% CI)	47.2 (40.9, 53.4)	36.9 (30.8, 43.0)
Rate Difference % (95% CI) ^a	10.2 (1.5, 18.9)	
Adjusted Odds Ratio (95% CI) ^b	1.547 (1.072, 2.233)	

Data for MMR at 12 months in the Ph unrestricted (ie, Ph+ and Ph-) subject population (ITT Population) were similar to the Ph+ mITT Population: a higher proportion of subjects achieved MMR in the bosutinib arm compared to the imatinib arm (125 [46.6%] subjects vs 97 [36.2%] subjects, respectively; 1-sided p-value=0.0063 based on CMH test stratified by Sokal score and Region (data not shown).

Secondary Efficacy Endpoint: CCyR by 12 months (48 weeks)

The results from the comparison of CCyR are presented in Table 19 and Table 20.

Table 19: Comparison of Complete Cytogenetic Response (CCyR) by month 12 by treatment arm - mITT Population (Study AV001)

CCyR by 12 months (48 weeks)	Bosutinib (n=246)	Imatinib (n=241)
CCyR	190 (77.2)	160 (66.4)
Not CCyRa	56 (22.8)	81 (33.6)
1-sided p-value ^b	0.0037	

Table 20: 95% Confidence Intervals for CCyR by Month 12 and Associated Odds Ratio by Treatment Arm - mITT Population (Study AV001)

Cumulative CCyR by Month 12	Bosutinib (n=246)	Imatinib (n=241)
Rate of Response % (95% CI)	77.2 (72.0, 82.5)	66.4 (60.4, 72.4)
Rate Difference % (95% CI) ^a	10.8 (2.9, 18.8)	
Adjusted Odds Ratio (95% CI) ^b	1.740 (1.160, 2.610)	

a. Rate difference was calculated as response rate of bosutinib minus response rate of imatinib.

b. Adjusted for Sokal risk group (low, intermediate, high) and region (1-3) as determined at time of randomization by the center. 95% CI for the odds ratio based on asymptotic Wald confidence limits.

Secondary Efficacy Endpoint: Major Molecular Response (MMR) at Month 18

The results for the analysis of the exploratory endpoint, MMR at Month 18 based on a database snapshot date of 30 March 2017 (data cutoff date of 02 February 2017 were provided as supplementary information to the results of the primary endpoint analysis based on a database snapshot date of 02 November 2016 (data cutoff date of 11 August 2016). Whereas the MMR rate increased in both treatment arms between the 12-month and 18-month time points, the MMR rate at Month 18 in the mITT Population remained higher in the bosutinib arm (56.9%, 95% CI: 50.7, 63.1) than in the imatinib arm (47.7%, 95% CI: 41.4, 54.0), with a 1-sided p-value (CMH test stratified by Sokal score and geographic region) = 0.0208.

The results in the ITT Population were consistent with the results in the mITT Population: the MMR rate was higher in the bosutinib arm (56.7%, 95% CI: 50.8, 62.6) than in the imatinib arm (46.6%, 95% CI: 40.7, 52.6), with a 1-sided p-value (CMH test stratified by Sokal score and geographic region) = 0.0099

Table 21: Major Molecular Response (MMR) at Month 18 – (mITT Population) (Study AV001)

	Bosutinib N=246	Imatinib N=241
Patients with a MMR, n (% [95% CI])	140 (56.9 [50.7, 63.1])	115 (47.7 [41.4, 54.0])
p-value ^a	0,0208	

Abbreviations: CI=confidence interval; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number of patients.

^a. The 1-sided p-value is based on a Cochran-Mantel-Haenszel test for general association between treatment and being a responder with stratification by Sokal risk group (low, intermediate, high) and region (1-3) as determined at time of randomization.

Secondary Efficacy Endpoint: Duration of MMR and CCyR

Data for duration of MMR and CCyR were not mature at the data cut-off date. Of the 142 (57.77%) patients in the bosutinib arm and 122 (50.6%) patients in the imatinib arm that achieved MMR anytime on-treatment in the mITT Population, 4 patients (3 patients in the bosutinib arm and 1 patient in the imatinib arm) had events at the time of data cut-off (events defined as confirmed loss of response, treatment discontinuation due to disease progression to AP/BP CML, and deaths that occurred due to disease progression within 28 days after last dose).

Of the 197 (80.1%) subjects in the bosutinib arm and 175 (72.6%) subjects in the imatinib arm that achieved CCyR anytime on-treatment in the mITT Population, 6 patients (3 patients in each treatment arm) had events at the time of the data cut-off (data not shown).

Secondary Efficacy Endpoint: Event-free Survival

Data for on-treatment EFS was not mature at the data cut-off date; 4 on-treatment deaths were reported (0 death in the bosutinib treatment arm and 4 deaths in the imatinib arm). Of 246 patients in the bosutinib arm, 10 (4.1%) patients had events of interest (defined as either death, transformation to AP or BP, doubling of WBC without CHR, loss of CCyR or loss of CHR) and 49 (19.9%) patients had competing risk events (treatment discontinuation without an EFS event). Of the 241 (49.5%) patients in the imatinib arm, 15 (6.2%) patients had events of interest with competing risk events reported for 56 (23.2%) subjects. The cumulative incidence (95% CI) of EFS events at week 48 was 3.7% (1.8, 6.7) in the bosutinib arm and 6.4% (3.7, 10.0) in the imatinib arm in the mITT Population (data not shown).

Secondary Efficacy Endpoint: Overall Survival

Data for OS was not mature at the data cut-off date; at this time-point 7 patients had died during the study. The K-M estimate of OS at Week 48 was 99.6% (95% CI: 97.0, 99.9) in the bosutinib arm and 97.9% (95% CI: 95.0, 99.1) in the imatinib arm in the mITT Population (data not shown).

Secondary Efficacy Endpoints: Updated results

Updated efficacy results from study AV001 are presented after a minimum of 24 months of follow-up (time from last patient enrolled to data cutoff of 12 July 2017).

Table 22 Efficacy Results in Newly Diagnosed Patients With Chronic Phase CML, mITT Population (study AV001)

	Bosutinib 400 mg (N=246)	Imatinib 400 mg (N=241)	p-value ^{Error!} Reference source not found.
Cumulative CCyR ^{Error!} Reference source not found., % (95% CI) any time on treatment	80.1 (75.1, 85.1)	72.6 (67.0, 78.2)	n/a
Cumulative MMR ^{Error!} Reference source not found., % (95% CI) any time on treatment	69.5 (63.8, 75.3)	61.0 (54.8, 67.2)	n/a
MMR ^{Error!} Reference source not found., % (95% CI) At 12 months At 24 months	47.2 (40.9, 53.4) 61.8 (55.7, 67.9)	36.9 (30.8, 43.0) 53.1 (46.8, 59.4)	0.0200 0.0498
MR ^{4, Error!} Reference source not found., % (95% CI) At 12 months At 24 months	20.7 (15.7, 25.8) 33.3 (27.4, 39.2)	12.0 (7.9, 16.1) 26.6 (21.0, 32.1)	0.0104 0.104
MR ^{4,5, Error!} Reference source not found., % (95% CI) At 12 months At 24 months	8.1 (4.7, 11.5) 12.6 (8.5, 16.7)	3.3 (1.1, 5.6) 11.2 (7.2, 15.2)	0.0238 0.635
Time to CCyR, hazard ratio ^{Error!} Reference source not found., ^{Error!} Reference source not found., (95% CI)	1.34 (1.10, 1.63)	n/a	0.003
Time to MMR, hazard ratio ^{Error!} Reference source not found., ^{Error!} Reference source not found., (95% CI)	1.34 (1.08, 1.66)	n/a	0.007
On-treatment transformation to accelerated (AP) or blast phase (BP) CML ^{Error!} Reference source not found., n (%)	6 (2.4)	7 (2.9)	n/a

Cumulative incidence of on-treatment EFS events <small>Error! Reference source not found.</small> , % (95% CI) At 24 months	5.3 (3.0, 8.7)	7.1 (4.3, 10.8)	n/a
K-M estimate of OS, % (95% CI) At 24 months	99.2 (96.7, 99.8)	96.6 (93.4, 98.3)	n/a

No adjustment was made for multiple testing except for the primary endpoint MMR at Month 12.

ABL=Abelson; BCR=breakpoint cluster region; CI=confidence interval; CCyR=complete cytogenetic response; CML=chronic myelogenous leukaemia; EFS=event-free survival; ITT=intent to treat; MMR=major molecular response; n/a=not available; OS=overall survival.

a. Analyses were stratified by Sokal-risk group (low, intermediate, high) and region using a CMH test for response rates and Gray's test for time-to-response. All p-values are 2-sided.

b. CCyR is defined as 0% Ph+ chromosome present with ≥ 20 metaphases or MMR.

c. MMR (3 log sensitivity) is defined as [(BCR copies/ABL copies)IS] ≤ 0.001 and ABL copies $\geq 3,000$; MR4 (4 log sensitivity) is defined as [(BCR copies/ABL copies)IS] ≤ 0.0001 and ABL copies $\geq 9,800$; MR4.5 (4.5 log sensitivity) is defined as [(BCR copies/ABL copies)IS] ≤ 0.00032 and ABL copies $\geq 30,990$.

d. Hazard ratio (95% CI) from a stratified proportional subdistributional hazards model and p-value from a stratified Gray's test for exploratory comparisons of cumulative incidence curves (bosutinib versus imatinib) adjusting for the competing risk of treatment discontinuation without the event.

e. Criteria for AP: 15% to 29% blasts or blasts $< 15\%$ with $\geq 30\%$ blasts + promyelocytes or $\geq 20\%$ basophils, all in either the blood or bone marrow findings; criteria for BP: $\geq 30\%$ blast in blood or bone marrow or extramedullary blast proliferation, other than in spleen.

f. Cumulative incidence curves adjusting for the competing risk of treatment discontinuation without the event.

g. EFS is defined as death due to any cause, transformation to AP or BP at any time on treatment, loss of CHR (defined as a hematologic assessment of non-CHR [CP, AP, or BP] confirmed by 2 assessments at least 4 weeks apart), loss of CCyR (defined as ≥ 1 Ph+ out of < 100 metaphases confirmed by a follow-up cytogenetic analysis > 1 month later), and for subjects not achieving a CHR: doubling of WBC count at least 1 month apart with the second value $> 20 \times 10^9/L$ and maintained in subsequent assessments for at least 2 weeks.

Exploratory Endpoints

Table 23: Overview of the results of the exploratory endpoints (Study AV001)

	Bosutinib (n=246)		Imatinib (n=241)	
MMR at 3, 6, 9 and 18 months	Month 3	10 (4.1 [1.6, 6.5])	4 (1.7 [0.0, 3.3])	p=0.0578
	Month 6	86 (35.0 [29.0, 40.9])	44 (18.3 [13.4, 23.1])	p=<0.0001
	Month 9	104 (42.3 [36.1, 48.4])	71 (29.5 [23.7, 35.2])	p=0.0015
	Month 18	140 (56.9 [50.7, 63.1])	115 (47.7 [41.4, 54.0])	p=0.0208
MMR at 12 months in the Ph chromosome unrestricted (ie, Ph+ and Ph-) subject population =ITT	Patients with an event, n (%) ^a	142 (57.7)	122 (50.6)	
	Patients with a competing risk event, n(%) ^b	51 (20.7)	65 (27.0)	
	Censored patients, n (%) ^c	53 (21.5)	54 (22.4)	
MR1 and MR2 at 3 months and 6 months				
MR4 and MR4.5 at 3, 6, 9 and 12 months	Month 6	9.8%	4.6%	
	Month 9	13.8%	8.3%	

	Month 12	20.7%	12.0%
Time to MMR [=Median time to MMR (responders only)]	24.7 weeks (range: 11.9 to 96.4).		36.3 weeks (range: 12.1 to 85.7)
Time to CCyR in both treatment arms	23.9 weeks (range: 11.4 to 68.9)		24.3 weeks (range: 11.4 to 73.1)
Time to on-treatment transformation to AP and BP	1.6% * (4/246)		2.5%* (6/241)
Cumulative CHR in both Ph+ and Ph chromosome unrestricted (ie, Ph+ and Ph-) subject population (ITT)	228 [92.7%; 95% CI: 89.4, 95.9]		225 [93.4%; 95% CI: 90.2, 96.5]

* Of the 10 transformation events reported, 5 were not considered to be true transformation events. Three (3) of the bosutinib arm patients and 2 of the imatinib arm patients had CP CML that transformed to AP/BP CML within 2 weeks after randomization, and none of the 5 patients permanently discontinued treatment due to disease progression or death. It was considered that these events were not true transformation events, since their clinical courses were not consistent with AP/BP. The remaining 5 patients had CP CML that transformed to AP/BP CML during Weeks 12 to 36, and all 5 patients permanently discontinued treatment due to disease progression (1 patient in each treatment arm had CP CML that transformed to BP CML). One patient in each treatment arm who had CP CML that transformed to AP/BP CML by Week 2 achieved MMR after transformation.

Type of BCR-ABL mutations present at treatment completion/discontinuation or suboptimal response in each treatment arm and presence of newly observed BCR-ABL mutations in subjects post-baseline, and correlation with response to treatment in imatinib and bosutinib treatment arms:

Of the 173 subjects with mutation testing at the end of treatment visit, a similar proportion of subjects (1.6%, 4/246 subjects) in the bosutinib arm had an emergent mutation compared to subjects (4.1%, 10/241) in the imatinib arm.

Subject Reported Outcomes

Patient-reported HRQoL was assessed by the FACT-Leu. All subscales showed either improvement (Emotional Well-Being, Leukemia symptoms, FACT-total score) or maintenance (Physical, Functional, and Social Well-Being, FACT-General, and the Trial Outcome Index) of HRQoL at 12 months (48 weeks) for both bosutinib and imatinib, with no differences observed between the treatment arms at any time-point, up to and including Month 12.

Functional health status as measured by the EQ-5D utility score, was maintained up to Month 12 for bosutinib, and was improved with imatinib at Month 12, however, there were no differences between bosutinib and imatinib at any time-point up to Month 12 (data not shown).

Ancillary analyses

N/A

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as

well as the benefit risk assessment (see later sections).

Table 24 Summary of Efficacy results from the pivotal trial AV001

Title: A multicenter phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed chronic phase chronic myelogenous leukemia				
Study identifier	AV001			
Design	Multicenter, Phase 3, 2-arm, randomized (1:1 ratio), open label			
	Duration of main phase:	12 months		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	~ 5 years (240 weeks) after the last subject is randomized = ~ 6 years in total		
Hypothesis	Superiority			
Treatments groups	Bosutinib	400 mg once daily , N=268 randomized		
	Imatinib	400 mg once daily, N=268 randomized		
Endpoints and definitions	Primary Endpoint	MMR at 12 months (48 weeks)	MMR was defined as $\leq 0.1\%$ BCR-ABL (corresponding to ≥ 3 log reduction from standardized baseline) with a minimum of 3000 ABL transcripts as assessed by the central laboratory. MMR was counted only if the response was demonstrated at the Week 48 visit; an MMR gained and lost before the Week 48 visit was deemed a non-response.	
	Secondary Endpoint	CCyR by 12 months	CCyR: defined as having 0% Ph+ chromosome present based on analysis of 20 to 99 metaphases from bone marrow or if 0 Ph+ out of <20 metaphases were available, then CCyR was imputed only if MMR was observed on that assessment date.	
	Secondary Endpoints	(MMR by 18 months) , duration of CCyR, EFS and OS	Cumulative incidence (95% CI) of EFS events at Week 48 in the mITT Population,	
Database lock	02 November 2016 / 30 March 2017 for MMR by 18 months			
Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	mITT (and ITT are available); at months 12			
Descriptive statistics and estimate variability	Primary Endpoint:	Parameter	Bosutinib (n=246) (n, %)	Imatinib (n=241) (n, %)
	MMR at Month 12			
	mITT (Primary Endpoint)			
		MMR	116 (47.2)	89 (36.9)
		Not MMR ^a	130 (52.8)	152 (63.1)
		1-sided p-value ^b	0.0100	
	ITT (exploratory)			
			<i>Bosutinib (N=268)</i>	<i>Imatinib (N=268)</i>
	MMR	125 [46.6%]	97 [36.2%]	
	1-sided p-value ^b	0.0063		

Effect estimate per comparison	Key Secondary endpoint CCyR by 12 months (48 weeks)		<i>Bosutinib</i> (n=246) (n, %)	<i>Imatinib</i> (n=241) (n, %)	
		CCyR	190 (77.2)	160 (66.4)	
		Not CCyR^a	56 (22.8)	81 (33.6)	
		1-sided p-value^b	0.0037		
			<i>Bosutinib</i> (N=246)	<i>Imatinib</i> (N=241)	
	Secondary endpoint MMR at 18 months (Cut-off: 30 March 2017)	Patients with MMR, n (%) [95% CI]	140 (56.9 [50.7, 63.1])	115 (47.7 [41.4, 54.0])	
		1-sided p-value^b	0.0208		
	Secondary endpoint Duration of MMR and CCyR	Duration of MMR			
		Data not mature at the data cut-off date	Of the 142 (57.77%) subjects in the bosutinib arm and 122 (50.6%) subjects in the imatinib arm that achieved MMR anytime on-treatment in the mITT Population, only 4 subjects (3 subjects in the bosutinib arm and 1 subject in the imatinib arm) had events at the time of data cut-off		
		Duration of CCyR			
Data not mature at the data cut-off date		Of the 197 (80.1%) subjects in the bosutinib arm and 175 (72.6%) subjects in the imatinib arm that achieved CCyR anytime on-treatment in the mITT Population, only 6 subjects (3 subjects in each treatment arm) had events at the time of the data cut-off			
Secondary endpoint Event-free Survival	Cumulative incidence (95% CI) of EFS events at Week 48 in the mITT Population.				
	Event is defined as either death, transformation to AP or BP, doubling of WBC without CHR, loss of CCyR or loss of CHR;	<i>Bosutinib</i> (N=246)	<i>Imatinib</i> (N=241)		
		3.7% (CI 1.8 , 6.7)	6.4% (CI 3.7, 10.0)		
Data not mature at the data cut-off date					
Secondary endpoint Overall Survival	K-M estimate of OS at Week 48 in the mITT Population.				
		<i>Bosutinib</i> (N=246)	<i>Imatinib</i> (N=241)		
		99.6% (95% CI: 97.0, 99.9)	97.9% (95% CI: 95.0, 99.1)		
Data not mature at the data cut-off date					

Analysis description	Other analysis: [Exploratory endpoints]				
		Bosutinib (n=246)		Imatinib (n=241)	
MMR at 3, 6, 9 and 18 months	Month 3	10 (4.1 [1.6, 6.5])	4 (1.7 [0.0, 3.3])	p=0.0578	
	Month 6	86 (35.0 [29.0, 40.9])	44 (18.3 [13.4, 23.1])	p=<0.0001	
	Month 9	104 (42.3 [36.1, 48.4])	71 (29.5 [23.7, 35.2])	p=0.0015	
	Month 18	140 (56.9 [50.7, 63.1])	115 (47.7 [41.4, 54.0])	p=0.0208	
MMR at 12 months in the Ph chromosome unrestricted (ie, Ph+ and Ph-) subject population =ITT	Patients with an event, n (%) ^a	142 (57.7)	122 (50.6)		
	Patients with a competing risk event, n(%) ^b	51 (20.7)	65 (27.0)		
	Censored patients, n (%) ^c	53 (21.5)	54 (22.4)		
MR1 and MR2 at 3 months and 6 months					
MR4 and MR4.5 at 3, 6, 9 and 12 months	Month 6	9.8%	4.6%		
	Month 9	13.8%	8.3%		
	Month 12	20.7%	12.0%		
Time to MMR [=Median time to MMR (responders only)]	24.7 weeks (range: 11.9 to 96.4).		36.3 weeks (range: 12.1 to 85.7)		
Time to CCyR in both treatment arms	23.9 weeks (range: 11.4 to 68.9)		24.3 weeks (range: 11.4 to 73.1)		
Time to on-treatment transformation to AP and BP	1.6% * (4/246)		2.5%* (6/241)		
Cumulative CHR in both Ph+ and Ph chromosome unrestricted (ie, Ph+ and Ph-) subject population (ITT)	228 [92.7%; 95% CI: 89.4, 95.9]		225 [93.4%; 95% CI: 90.2, 96.5]		
Subject Reported Outcomes [FACT-Leu, EQ-5D utility score]: no differences observed between the treatment arms at any time-point, up to and including Month 12.					

Analysis performed across trials (pooled analyses and meta-analysis)

Table 25: Summary of Key Efficacy Results in Pivotal Phase 3 Study AV001 (mITT Population) and Supportive Phase 3 Study 1008 (ITT Population) After a Minimum of 12 Months of Follow-up

Study Number (n)	MMR at 1 Year % (95% CI)	CCyR by 1 Year % (95% CI)	Comparison of Cumulative Incidence Curves for Time to Response		Time to AP/BP Cumulative Incidence at 1 Year (95% CI)
			MMR	CcyR	
Study AV001			HR (95% CI)	HR (95% CI)	
Bosutinib 400 mg (N=246)	47.2 (40.9, 53.4)	77.2 (72.0, 82.5)	1.34 (1.06, 1.69)	1.38 (1.13, 1.69)	1.6 (0.5, 3.9)
Imatinib 400 mg (N=241)	36.9 (30.8, 43.0)	66.4 (60.4, 72.4)			2.5 (1.0, 5.1)
Study 1008-3000WW					
Bosutinib 500 mg (N=250)	38.0 (32.0, 44.0)	75.6 (70.3, 80.9)	1.57 (1.22, 2.03)	1.34 (1.10, 1.63)	1.2 (0.4, 3.7)
Imatinib 400 mg (N=252)	25.4 (20.0, 30.8)	67.1 (61.3, 72.9)			3.2 (1.6, 6.3)

Note: Final results for Study 1008 are presented.

Abbreviations: AP=accelerated phase; BP=blast phase; CCyR=complete cytogenetic response; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number of patients.

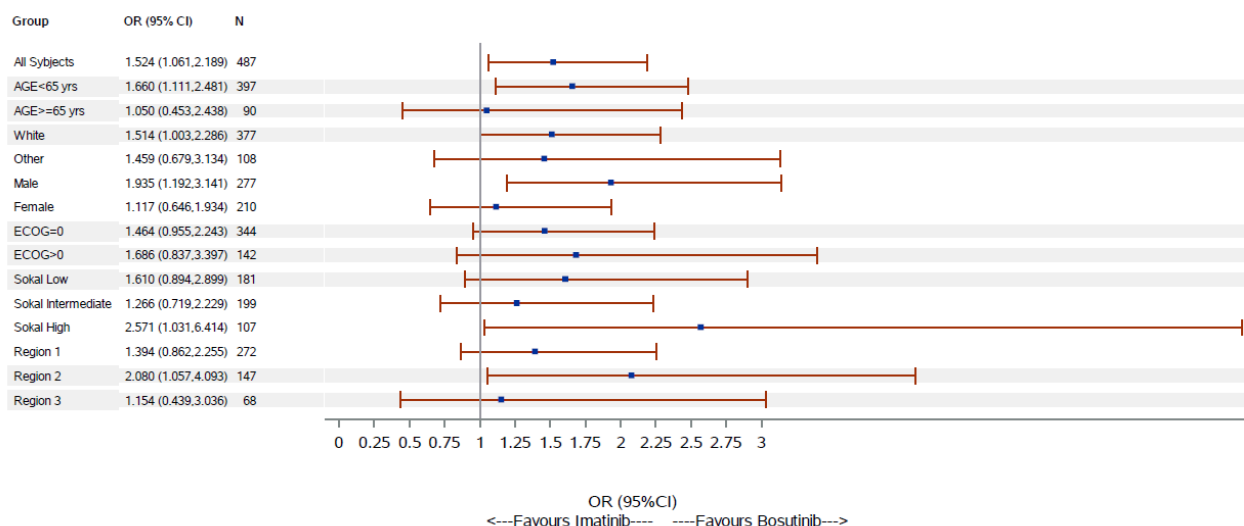
The cumulative incidence of EFS events by 48 weeks was 3.7% (95% CI: 1.8, 6.7) and 6.4% (95% CI: 3.7, 10.0) in the bosutinib and imatinib arms, respectively, in Study AV001 and 3.2% (95% CI: 1.6, 6.4) and 6.8% (95% CI: 4.3, 10.7) in the bosutinib and imatinib arms, respectively, in Study 1008.

The Kaplan-Meier estimate (95% CI) of OS at Week 48 was 99.6% (95% CI: 97.0, 99.9) and 97.9% (95% CI: 95.0, 99.1) in the bosutinib and imatinib arms, respectively, in Study AV001 and 99.6% (95% CI: 97.0, 99.9) and 96.8% (95% CI: 93.6, 98.4) in the bosutinib and imatinib arms, respectively, in Study 1008.

Clinical studies in special populations

Subgroup comparisons in Study AV001 were undertaken to evaluate whether treatment differences in MMR rates at 1 year varied according to baseline characteristics. Characteristics included age (<65 vs ≥65 years), race (white vs non-white [including Asian, Black or African American, or other]), gender (male vs female), ECOG performance status at baseline (0 vs >0), Sokal risk (low, intermediate, high), and geographic region (Region 1: US, Canada, and Western Europe; Region 2: Eastern Europe and Latin America; Region 3: ROW).

Figure 15: Plot of Odds Ratio (Bosutinib/Imatinib) for MMR at Month 12 – Study AV001 (mITT Population)



The results of the MMR rates at 1 year, which were calculated for the specific characteristics of age, race, gender, Sokal score, and geographic region along with a test for interaction to evaluate whether the difference between treatment arm varied according to subgroup characteristics are presented in Table 26.

Table 26: MMR Rate at 1 Year by Characteristic – Study AV001 (mITT Population)

	Bosutinib	Imatinib
Age		
<65 years	N=198	N=199
Patients with MMR at Month 12, n (%)	96 (48.5)	72 (36.2)
≥65 years		
Patients with MMR at Month 12, n (%)	20 (41.7)	17 (40.5)
2-sided p-value for interaction	0.3356	
Race		
Asian	N=30	N=30
Patients with MMR at Month 12, n (%)	17 (56.7)	10 (33.3)
(%) Black or African American	N=10	N=10
Patients with MMR at Month 12, n (%)	2 (20.0)	3 (30.0)
(%) White	N=191	N=186
Patients with MMR at Month 12, n (%)	89 (46.6)	68 (36.6)
(%) Other	N=11	N=11
2-sided p-value for interaction	0.4287	
Sex		
Male	N=142	N=135
Patients with MMR at Month 12, n (%)	71 (50.0)	46 (34.1)
(%) Female	N=104	N=106
Patients with MMR at Month 12, n (%)	45 (43.3)	
2-sided p-value for interaction	0.1412	
Sokal Risk at Screening		
Low	N=86	N=95
Patients with MMR at Month 12, n (%)	50 (58.1)	44 (46.3)
(%) Intermediate	N=107	N=92
Patients with MMR at Month 12, n (%)	48 (44.9)	36 (39.1)
(%) High		
2-sided p-value for interaction	0.4285	
Geographic Region		

Region 1 (US, Canada, and Western EU)	N=137 66 (48.2)	N=135 54 (40.0)
Region 2 (Eastern EU, Latin America, and South America) Region 3 (Rest of World)	N=74 35 (47.3)	N=73 22 (30.1)
2-sided p-value for interaction	0.5315	

Note: The p-value is based on the Breslow-Day test for the homogeneity of the odds ratios across the strata.
Abbreviations: EU=Europe; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number; US=United States.

Supportive study

The following table summarises the efficacy outcome at 12 months observed in the previous pivotal trial 1008-3000WW which was submitted in 2012 for the same target population; however, the primary objective / endpoint failed mainly due to early discontinuation in the bosutinib arm.

Title: A bphase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed chronic phase philadelphia chromosome positive chronic myelogenous leukemia 1008-3000ww			
Study identifier	Protocol No.: 3160A4-3000-WW (L-Wyeth); Pfizer B1871008		
Design	multinational, multicenter, randomized, open-label, parallel-arm, phase 3		
	Duration of main phase:	2008-2-5 to 2009-6 (16 months)	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	ongoing	
Hypothesis	Superiority (effective with superior benefit-risk profile)		
Treatments groups	Bosutinib	500 mg oral daily continuous treatment until progression or toxicity	
	Imatinib	400 mg oral daily continuous treatment until progression or toxicity	
Endpoints and definitions	Primary endpoint	Complete cytogenetic remission at one year	Attainment of Complete Cytogenetic Remission in patients with CML, proven by repetitive Cytogenetic analysis
	Short –term Secondary endpoint	Major Molecular remission	Reduction of the bcr/abl gene product in patients with CML by a 3 fold tenth power (0 reduction a t1/1000 level) proven by repetitive polymerase chain reaction (PCR)
	long-term Secondary endpoints	Duration of Cytogenetic, MMR and CHR Remission	Time of attainment and ongoing Cytogenetic remission as defined above until loss of Cytogenetic remission..
Database lock	August 31 2010		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat, at one year treatment duration		
Descriptive statistics and estimate variability	Treatment group	Bosutinib	Imatinib
	Number of subjects	250	252
	CCyR	197	188

		70,1%	68.0%	
		95% CI	95% CI	
		64,3-75,7	62,1- 73,6	
Effect estimate per comparison	Primary endpoint CCyR at one year	Comparison groups	Bosutinib vs Imatinib	
		test statistic	Cochran –Mantel-Haenszel Test for association of treatment and response	
		variability statistic	Odd ratio: 1,10 95% CI 0,74-1,63	
		P-value	0,601	
	Primary endpoint: (in non-pivotal population) CCyR at one year in <u>evaluable patients</u>	Comparison groups	Evaluable patients in Bosutinib and Imatinib group (with 1 year CCyR status available)	
		test statistic	Cochran –Mantel-Haenszel Test for association of treatment and response	
		variability statistic	95% CI not attained	
		P-value	0,026	
	P endpoint: duration of CCyR	Comparison groups	Bosutinib vs Imatinib	
		test statistic	Kaplan Meier estimate	
		variability statistic	192 in bosutinib ar vs 187 in Imatinib arm	
		P-value	Not stated	
	MMR rate at 1 year based on ITT population	Comparison groups	Bosutinib vs Imatinib	
N=98 (39.2%)		N: 66 (26.2%)		
P-value		0.002		
Notes	It is of interest, that the efficacy in terms of attaining CCyR in female patients seems to be less than in males (OR 1,083 in females vs 3,192 in males)			

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Study AV001 was designed to evaluate the efficacy of bosutinib 400 mg compared with imatinib 400 mg in the treatment of newly diagnosed patients with Ph+ CP CML. The design of Study AV001 was generally similar to that of the previously conducted Study 1008 in which bosutinib 500 mg was compared with imatinib 400 mg in the treatment of newly diagnosed patients with Ph+ CP CML. However, in the approximately 5.5 years between the start of Study 1008 and Study AV001, MMR has replaced CCyR as the standard method of disease assessment, and physicians have improved their handling of AEs secondary to bosutinib therapy due to the growing experience with the drug.

The bosutinib dose of 400 mg was chosen for Study AV001 based on the safety experience with bosutinib 500 mg per day in Study 1008. Imatinib was chosen as the active comparator because it was the first TKI approved for the treatment of CML and is the most frequently used agent of those approved for first-line treatment of patients with Ph+ CP CML. The use of imatinib as the active comparator in both studies is in accordance with the NCCN guidelines (NCCN 2017) and the European Leukemia Net Recommendations (Baccarani, 2013), in which imatinib, dasatinib, and nilotinib are all considered standard of care in newly diagnosed patients with Ph+ CML who are not eligible for stem

cell transplant. Moreover, imatinib was also used as the active comparator in investigations of both dasatinib and nilotinib. In conclusion, the selection of the comparator as well as the 400 mg dose of bosutinib is well justified and was agreed during the study planning.

Study AV001 employed an open-label design due to the complexity of the dosing regimens allowed (due to the different doses and different steps for dose escalation and dose reduction that were used). This is fully acceptable due to the use of objective efficacy outcome measures such as MMR and CCyR which minimize potential bias created by the open-label design. Moreover, an open design was also used in other pivotal trials in CML and the differences in safety profile (high incidence of diarrhoea in bosutinib) would have additionally affected any blinding attempt. The CHMP considered that the open trial design was acceptable, taken into account the applicant's efforts to reduce bias and considering that nilotinib and dasatinib also were investigated in unblinded pivotal clinical trials.

Both Ph+ and Ph- CP CML patients were eligible for inclusion in Study AV001. This was done to facilitate enrollment and improve access to treatment for newly diagnosed patients. Cytogenetic assessment for the Ph chromosome was not required for enrollment into Study AV001, but Ph chromosome status was identified at screening. The CHMP agreed with the selection of the patient population based on the presence of BCR-ABL RNA transcripts reflects the current approach to the diagnosis of CML (NCCN 2017) and is consistent with the choice of primary endpoint (MMR at 12 months) in Study AV001.

Stratification was performed based on known prognostic characteristics. Patient characteristics were comparable across treatment arms in Study AV001 and were consistent with those for both treatment arms in Study 1008. They were generally reflective of the population of newly diagnosed patients with Ph+ CP CML expected to receive treatment with bosutinib, ie, older adults.

The efficacy outcome measures used in Study AV001 are standard measures used in the evaluation of the treatment of CML (NCCN 2017; Baccarani, 2013). MMR at 12 months was chosen as the primary endpoint in Study AV001 rather than CCyR at 12 months, which was used in the previously designed Study 1008. The achievement and maintenance of MMR has become increasingly recognized as an important endpoint in CML therapy as it appears to be predictive of long-term EFS (Hanfstein, 2012; Hughes, 2014). MMR at 12 months was the primary endpoint in ENESTnd, a Phase 3, randomized, open-label, multicenter study comparing the efficacy and safety of nilotinib with imatinib in patients with newly diagnosed CML (Saglio, 2010; Saglio, 2013).

The primary endpoint of MMR at 12 (and 18 months) has now replaced CCyR as the standard method of disease assessment in CP-CML and is the most relevant accepted surrogate endpoint for overall survival in the target population. This is reflected by the recent change in the relevant EMA guideline document on CML which recommends that superiority versus a licensed comparator should be shown for the primary endpoint of major molecular response at 18 months. However, MMR at 12 months is also acceptable since MMRs at 12 months, compared with no MMRs at this time point, is associated with superior progression-free survival and superior overall survival after 36 months.

Exploratory endpoints in Study AV001 included MMR at 3 months and also MR4 and MR4.5, which represent deep and stable molecular responses, as these are considered predictive of long-term outcomes (Fava, 2015). Depth of response is an important clinical objective for patients with CML; patients who achieve complete molecular response (MR4 and MR4.5) have better event-free and failure-free survival which confers a better outcome (Jabbour, 2011; Hanfstein, 2012; Etienne, 2014).

CCyR was included as a secondary endpoint in Study AV001 which was acceptable. Moreover, the

applicant analysed also MMR at 18 months as a key secondary endpoint. Results for MMR at 18 months were included as supplementary information in this regulatory submission based on a later data cutoff date than the one that was used for the 12-month analysis. This is reasoned due to the fact that this slightly more conservative endpoint is recommended in the relevant CHMP guideline document as primary endpoint for superiority trials in the EU. It is welcomed to have this result for confirming the robustness of the clinical outcome of the pivotal trial.

The mITT Population was the pre-specified primary efficacy analysis population in the protocol and was chosen to align the populations for the molecular and cytogenetic endpoints as CCyR is only assessable for Ph+ CP CML patients. Inclusion into the mITT Population was based on baseline transcript and Ph status determined at screening, and thus introduced minimal bias as a subgroup ITT analysis.

In conclusion, the CHMP discussed the study design, the primary and secondary endpoints, the inclusion and exclusion criteria, as well as the statistical approach, and concluded that there are no relevant concerns regarding the design of study.

Efficacy data and additional analyses

In Study AV001, treatment with bosutinib 400 mg once daily resulted in a statistically significant and clinically meaningful improvement in the primary endpoint of MMR at 12 months (48 weeks) compared to imatinib (47.2% vs 36.9%, 1-sided p-value=0.0100). Therefore, the pivotal trial reached its primary objective and demonstrated adequately the claimed superiority over imatinib in the intended first line CP-CML target population. Consistent with the results of Study AV001, the MMR rate at 12 months (48 weeks) was also higher in the bosutinib arm than in the imatinib arm of supportive Study 1008 which might be a chance finding, but also could reflect the more constant drug levels in trial AV001 due to a better tolerability of the 400 mg dose in comparison to the previously administered 500 mg bosutinib. This may be caused due to a change in the treatment paradigm from 2008 to 2017 whereby more patients had their dose escalated on imatinib allowing them to achieve a better response. The improvement in MMR at 12 months in favor of bosutinib was maintained in the sensitivity analysis in the ITT Population and the subgroup analysis (Sokal score, geographic region, age, gender, and race).

With respect to secondary endpoint MMR at 18 months the superiority seems to be also robust in both analysis populations: 56.9% in the bosutinib arm vs 47.7% in the imatinib arm, 1-sided p-value=0.0208 in the mITT Population and 56.7% in the bosutinib arm vs 46.6% in the imatinib arm, 1-sided p-value=0.0099 in the ITT Population).

The efficacy of bosutinib in Study AV001 was further supported by the analysis of the secondary endpoint of CCyR by 12 months (48 weeks), which was statistically significantly higher in the bosutinib arm than in the imatinib arm (77.2% vs 66.4%, 1-sided p value= 0.0037). In Study 1008, the CCyR at 12 months (48 weeks) was similar in both treatment arms likely due to the higher and earlier rate of permanent discontinuations due to AEs in the bosutinib arm vs the imatinib arm; however, the CCyR by Month 12 rates were consistent with Study AV001. Moreover, other secondary endpoints as duration of MMR (57.7% vs. 50.6%), duration of CCyR (80.1% vs 72.6%), event-free survival (3.7% vs. 6.4%) and overall survival (99.6 vs 97.9%) were also consistently in favour for bosutinib. However, it should be considered that results for these endpoints are not mature at 12 months and long term experience is necessary. As requested the applicant has provided an update of efficacy outcome after 24 months. In conclusion, the updated 24 months results indicated no clinical relevant change in the efficacy benefit shown for bosutinib at 12 months; the benefits of bosutinib over imatinib continued to be clinically meaningful at 24 months and remain stably in both the mITT and ITT populations.

On-treatment transformations events to AP or BP CML were low for both treatment arms in both Study AV001 and Study 1008, and were numerically lower in patients in the bosutinib arm vs imatinib in both studies. These results further support the suggestion of a more beneficial long-term outcome with bosutinib.

As would be expected with effective therapies used over a long period of time, few EFS (defined as death, transformation to AP or BP, doubling of WBC without CHR, loss of CCyR, or loss of CHR) were observed in either treatment arm after a minimum of 12 months of follow-up. Although data for this endpoint were not mature at the data cutoff date it is reported that patients in the bosutinib arm had less events on treatment [(B: 10 (4.1%) vs I: 15 (6.2%)] and remains consistent in favour also after longer observation times; at 24 months B:5.3% vs I: 7.1% were reported.

With respect to patient-reported outcome HRQoL was maintained for up to 12 months. All subscales showed either improvement (EWB, Leukemia symptoms, FACT-total score) or maintenance (PWB, FWB, and SWB, FACT-General, and the TOI) of HRQoL at 12 months (48 weeks) for both bosutinib and imatinib, with no statistically significant differences observed between treatments. This is consistent with the long-term maintenance of HRQoL observed in Study 1008-3000WW.

In Study AV001 onset of CCyR and MMR was more rapid and showed deeper levels of molecular response in patients treated with bosutinib, as reflected in higher percentages of patients obtaining an MR4 and MR 4.5, than imatinib. This might indicate a better long-term outcome.

As seen for other second generation TKIs after longer periods (24 months) the difference regarding the efficacy outcomes becomes smaller, which is deemed to indicate rather a well known difference in reponse kinetic for imatinib compared with other second generation CML TKIs than a lost of efficacy.

2.4.4. Conclusions on the clinical efficacy

In Study AV001 bosutinib 400 mg has demonstrated a robust statistical significant superiority in efficacy comparare to imatinib in terms of the primary endpoint MMR in newly diagnosed CP Ph+ CML adult patients. Therefore, a significant clinical benefit in this patient population was convincingly demonstrated.

2.5. Clinical safety

Introduction

The safety results for individual studies and pooled sets of studies are presented as follows:

- Safety Set 1 Results from the pivotal Phase 3 Study AV001 conducted in newly diagnosed Ph+ CP CML to evaluate the safety profile of bosutinib 400 mg in this target population. In addition, safety of bosutinib 400 mg given once daily is compared with imatinib 400 mg given once daily.
- Safety Set 2 Comparison of Study AV001 versus Study 1008-3000WW. An evaluation of the safety of bosutinib 400 mg/daily in Study AV001 with that of bosutinib 500 mg/daily in Study 1008-3000WW (12-Month Analysis) was conducted in order to evaluate differences in safety between the 2 doses of bosutinib in the newly diagnosed CML patient population. For this analysis, the studies were not pooled together and results are given at 12 months analysis, respectively. Imatinib arms are not included in the analysis.

Safety Set 3 Newly diagnosed CP CML pool. An evaluation of the bosutinib safety profile from a pooled analysis of Studies AV001, 1008 (5 year data), and 1040 (Study 1008 first line patients only with an additional 2 years of data) was conducted in order to identify any potential safety issues specific to the target population of newly diagnosed CML patients regardless of starting dose. This pool is described as “Patients with Newly diagnosed CP CML” in the SCS.

Safety Set 4 All Leukemia Pool. An evaluation of the bosutinib safety profile, regardless of diagnosis, line of therapy, and starting dose, in patients with CML and Ph+ ALL from a pooled analysis of Studies AV001, 1006, 1007, 1008, 1039, and 1040 (all patients regardless of line of therapy) was conducted to potentially identify any adverse events associated with bosutinib that may not have been evident from the individual studies or a smaller pool.

This pool includes long-term safety information from 4 and 5 years of follow-up in Studies 1006 and 1008, respectively, and approximately 6 and 7 years of follow-up from Studies 1006 and 1008 patients, respectively, who rolled over to Study 1040.

Safety Analyses

All safety variables were summarized using the Safety Population. AE summaries included incidence of treatment-emergent AEs (TEAEs) by treatment and system organ class (SOC) and preferred term, SAEs, AEs that led to study drug discontinuation, AEs by maximum severity and relationship to study drug were also summarized by treatment, SOC and preferred term. AEs and AESI categories including cardiac, hemorrhage, effusion, edema, myelosuppression, anemia, thrombocytopenia, liver function, infection, rash, hypersensitivity, gastrointestinal toxicity, diarrhea, nausea, vomiting and renal toxicity were summarized.

AE summaries included the number and percentage of subjects having each event and the number of events. Subjects with multiple occurrences of the same event were counted only once for a specific PT. Comparisons among treatment arms were performed using Fisher's exact test for AESI and AE incidence of $\geq 5\%$, $\geq 10\%$, and $\geq 20\%$ and other AE summaries as deemed appropriate. No adjustments for multiple comparisons were made. Digital ECG data were collected (in triplicate and averaged) at screening and on Days 1, 28, 56 and 84 pre-dose and at the treatment completion visit. ECHO or MUGA scans were performed at Screening (within 2 weeks of starting treatment) and at end of treatment or at 2 years, whichever was soonest and as clinically indicated.

Mean change from baseline to each visit were analyzed for ECG parameters QT, RR, PR, and QTc, using a fixed-effects analysis of variance (ANOVA) model, adjusted for baseline, with term of treatment on the raw and/or rank transformed values, as appropriate. The RR interval was analyzed for change from baseline only. Digital ECG data were collected (in triplicate and averaged) at screening and on Days 1, 28, 56 and 84 pre-dose and at the treatment completion visit. ECHO or MUGA scans were performed at Screening (within 2 weeks of starting treatment) and at end of treatment or at 2 years, whichever was soonest and as clinically indicated. Mean change from baseline to each visit were analyzed for ECG parameters QT, RR, PR, and QTc, using a fixed-effects analysis of variance (ANOVA) model, adjusted for baseline, with term of treatment on the raw and/or rank transformed values, as appropriate. The RR interval was analyzed for change from baseline only.

Patient exposure

The safety population of Set 1 consisted of patients with newly diagnosed CP CML who received at

least 1 dose of either bosutinib (N=268) or imatinib (N=265). Exposure to study drug is summarized in Table 27.

Table 27: Exposure to Bosutinib and Imatinib (Safety Population) (Study AV001)

	Bosutinib 400 mg (N=268)	Imatinib 400 mg (N=265)
Number of doses		
n	268	265
Mean	400.41	406.74
SD	174.35	162.77
Median	421.50	421.00
Minimum	8.00	21.00
Maximum	741.00	710.00
Total exposure (mg)		
n	268	265
Mean	157764.18	177085.66
SD	73733.55	82741.29
Median	165600.00	174600.00
Minimum	3200.00	8400.00
Maximum	375800.00	406000.00
Missed doses		
n	268	265
Mean	20.78	9.15
SD	35.23	15.85
Median	10.50	0.00
Minimum	0.00	0.00
Maximum	367.00	133.00
Dose intensity (mg/day)		
n	268	265
Mean	357.40	414.50
SD	82.38	82.21
Median	391.82	400.00
Minimum	39.02	188.89
Maximum	556.74	679.17
Relative dose intensity (%)		
n	268	265
Mean	89.35	103.62
SD	20.59	20.55
Median	97.95	100.00
Minimum	9.76	47.22
Maximum	139.19	169.79
Duration of treatment (months)		
n	268	265
Mean	13.67	13.56
SD	5.59	5.35
Median	14.06	13.83
Minimum	0.26	0.69
Maximum	24.70	23.49
Dose Delays due to Adverse Events n (%)		
None	117 (43.7)	170 (64.2)
1	68 (25.4)	55 (20.8)
2	43 (16.0)	25 (9.4)
3	21 (7.8)	10 (3.8)
4	12 (4.5)	4 (1.5)
>4	7 (2.6)	1 (0.4)
At least 1 dose delay	151 (56.3)	95 (35.8)
Dose Reductions due to Adverse Events n		

	Bosutinib 400 mg (N=268)	Imatinib 400 mg (N=265)
None	175 (65.3)	219 (82.6)
At least 1 dose reduction	93 (34.7)	46 (17.4)
Number of patients with Adverse Events		
Any Adverse Event	38 (14.2)	28 (10.6%)

Dose Intensity: Total exposure divided by time from first dose date to last zero/non-zero dose date.

Relative Dose Intensity: Dose intensity divided by first dose administered for single arm studies or randomized dose for randomized studies.

Dose Delay is defined as a temporary stop due to an adverse event. A patient is considered to have a dose reduction when decreased due to adverse event is selected as reason of dose change.

Data cutoff date: 11 August 2016.

Adverse events

The following Table 28 shows the general safety outcome of the pivotal trial AV001 in which patients were treated with 400 mg bosutinib od. Moreover the table allows a direct comparison to the results observed in the supportive trial 1008-3000WW in which the 500 mg bosutinib dose was used in the same population.

Table 28: Comparison of Adverse Event Profile of 400 mg and 500 mg Bosutinib in both CP-CML trials

Event	Study 1008-3000WW Bosutinib 500 mg o.d.		Study AV001 Bosutinib 400 mg o.d.	
	Bosutinib 500mg N=248 n (%)	Imatinib 400mg N=251 n (%)	Bosutinib 400 mg (N=268) n (%)	Imatinib 400 mg (N=265) n (%)
Any treatment-emergent adverse event (TEAE)	237 (95.6)	238 (94.8)	263 (98.1)	257 (97.0)
Drug-related TEAEs	(91.5)	(86.9)	250 (93.3)	235 (88.7)
Grade 3 or 4 TEAEs	159 (64.1)	119 (47.4)	150 (56.0)	111 (41.9)
Serious adverse events (SAEs)	63 (25.4)	34 (13.5)	54 (20.1)	45 (17.0)
Adverse events leading to discontinuation	48 (19.4)	14 (5.6)	38 (14.2)	28 (10.6)
Adverse events leading to reduction in test article dose	92 (37.1)	40 (15.9)	152 (56.7)	98 (37.0)
Adverse events leading to temporary stop in test article dose	150 (60.5)	106 (42.2)	54 (20.1)	45 (17.0)
Deaths on study treatment (within 28 days of last dose 1)	1 (0.4)	3 (1.2)	1 (0.4)*	4 (1.5)

*The SAE began during study treatment; however, death occurred 28 days after the last dose. Note: Table presents number and percentages of patients (n [%]). Percentages were based on (N) the number of patients treated in each arm. TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of the study drug up to 28 days after last dose of study drug. Abbreviations: N/n=number of patients; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Treatment-Emergent Adverse Events

The most commonly reported TEAEs of any toxicity grade (incidence \geq 20%) were diarrhoea (70.1%), nausea and thrombocytopenia (35.1% each), ALT increased (30.6%), and AST increased (22.8%) for patients receiving bosutinib compared with nausea (38.5%), diarrhoea (33.6%), muscle spasms (26.4%), and neutropenia (20.8%) for patients receiving imatinib.

Table 29 provides an overview on the TEAEs reported from trial AV001.

Table 29: Summary of All-Causality, Treatment-Emergent Adverse Events by Preferred Term Experienced by ≥ 10% of Patients in the Total Column for Either Arm (by Decreasing Order for Bosutinib Arm) - (Safety Population 1) (Study AV001)

Preferred Term (MedDRA 19.0) Toxicity	Bosutinib (N=268)					Imatinib (N=265)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhoea	115	52 (19.4)	21 (7.8)	0	188 (70.1)	71	16 (6.0)	2 (0.8)	0	89 (33.6)
Nausea	75 (28.0)	19 (7.1)	0	0	94 (35.1)	85(32.1)	17 (6.4)	0	0	102 (38.5)
<i>Thrombocytopenia</i>	36 (13.4)	21(7.8)	26 (9.7)	11 (4.1)	94 (35.1)	17 (6.4)	20 (7.5)	10 (3.8)	5 (1.9)	52 (19.6)
Alanine aminotransferase increased	9 (3.4)	22 (8.2)	45 (16.8)	6 (2.2)	82 (30.6)	6 (2.3)	5 (1.9)	3 (1.1)	1 (0.4)	15 (5.7)
Aspartate aminotransferase increased	21 (7.8)	14 (5.2)	25 (9.3)	1 (0.4)	61 (22.8)	10 (3.8)	2 (0.8)	5 (1.9)	0	17 (6.4)
Rash	33 (12.3)	19 (7.1)	1 (0.4)	0	53 (19.8)	25 (9.4)	7 (2.6)	3 (1.1)	0	35 (13.2)
Fatigue	39 (14.6)	12 (4.5)	1 (0.4)	0	52 (19.4)	42	5 (1.9)	0	0	47 (17.7)
<i>Anaemia</i>	18 (6.7)	23 (8.6)	8 (3.0)	1 (0.4)	50 (18.7)	18 (6.8)	20 (7.5)	12 (4.5)	0	50 (18.9)
Headache	39 (14.6)	8 (3.0)	3 (1.1)	0	50 (18.7)	23 (8.7)	8 (3.0)	3 (1.1)	0	34 (12.8)
Abdominal pain	32 (11.9)	11 (4.1)	5 (1.9)	0	48 (17.9)	8 (3.0)	10 (3.8)	1 (0.4)	0	19 (7.2)
Vomiting	36 (13.4)	9 (3.4)	3 (1.1)	0	48 (17.9)	36	7 (2.6)	0	0	43 (16.2)
Lipase increased	6 (2.2)	4 (1.5)	20 (7.5)	6 (2.2)	36 (13.4)	4 (1.5)	4 (1.5)	12 (4.5)	2 (0.8)	22 (8.3)
Pyrexia	24 (9.0)	9 (3.4)	2 (0.7)	0	35 (13.1)	18 (6.8)	4 (1.5)	0	0	22 (8.3)
Platelet count decreased	10 (3.7)	8 (3.0)	12 (4.5)	3 (1.1)	33 (12.3)	6 (2.3)	10 (3.8)	3 (1.1)	1 (0.4)	20 (7.5)
Arthralgia	19 (7.1)	9 (3.4)	2 (0.7)	0	30 (11.2)	26 (9.8)	9 (3.4)	0	0	35 (13.2)
Asthenia	23 (8.6)	7 (2.6)	0	0	30 (11.2)	12 (4.5)	5 (1.9)	0	0	17 (6.4)
<i>Neutropenia</i>	1 (0.4)	11 (4.1)	14 (5.2)	4 (1.5)	30 (11.2)	5 (1.9)	18 (6.8)	25 (9.4)	7 (2.6)	55 (20.8)
Decreased appetite	23 (8.6)	3 (1.1)	1 (0.4)	0	27 (10.1)	15 (5.7)	1 (0.4)	0	0	16 (6.0)
Upper respiratory tract infection	12 (4.5)	10 (3.7)	1 (0.4)	0	23 (8.6)	13 (4.9)	14 (5.3)	0	0	27 (10.2)
<i>Leukopenia</i>	4 (1.5)	8 (3.0)	2 (0.7)	1 (0.4)	15 (5.6)	11 (4.2)	10 (3.8)	8 (3.0)	0	29 (10.9)
Pain in extremity	7 (2.6)	4 (1.5)	1 (0.4)	0	12 (4.5)	25 (9.4)	8 (3.0)	0	0	33 (12.5)
Oedema peripheral	9 (3.4)	2 (0.7)	0	0	11 (4.1)	30	5 (1.9)	1 (0.4)	0	36 (13.6)
Myalgia	5 (1.9)	2 (0.7)	1 (0.4)	0	8 (3.0)	32	7 (2.6)	2 (0.8)	0	41 (15.5)
Muscle spasms	6 (2.2)	0	0	0	6 (2.2)	60	9 (3.4)	1 (0.4)	0	70 (26.4)
Periorbital oedema	4 (1.5)	0	0	0	4 (1.5)	32	5 (1.9)	0	0	37 (14.0)

Abbreviation: N=number of patients. Data snapshot date: 02 November 2016, Data cutoff date: 11 August 2016.

The TEAEs that were reported at a higher incidence (≥ 5% difference) in the bosutinib arm compared with the imatinib arm were diarrhoea, abdominal pain, ALT increased, AST increased, lipase increased, rash, pruritus, headache, and thrombocytopenia. The TEAEs that were reported at a higher incidence (≥ 5% difference) in the imatinib arm compared with the bosutinib arm were oedema peripheral, muscle spasms, myalgia, pain in extremity, neutropenia, leukopenia, periorbital oedema, eyelid oedema, lacrimation increased, and hypokalaemia.

Treatment-Related Adverse Events (TRAEs)

The most commonly reported treatment-related TEAEs (≥ 20%) were diarrhea (65.7%), thrombocytopenia (32.5%), nausea (30.6%), ALT increased (28.4%), and AST increased (21.3%) for patients receiving bosutinib compared with nausea (32.5%), diarrhea (26.4%), muscle spasms (23.8%), and neutropenia (20.4%) for patients receiving imatinib. Details on treatment-related TEAEs are shown in the following Table 30:

Table 30: Number (%) of Patients with Reports of Treatment-Related, Treatment- Emergent Adverse Events (TRAEs) by SOC (Incidence \geq 10% in Descending Order) - (Safety Population 1 and from trial 3000WW) (Study AV001)

System Organ Class ^a Preferred Term	Bosutinib 400 mg (N=268)	Imatinib 400 mg (N=265)
Any Adverse Event	250 (93.3)	235 (88.7)
Blood and lymphatic system		
Thrombocytopenia	87 (32.5)	51 (19.2)
Anaemia	39 (14.6)	39 (14.7)
Neutropenia	30 (11.2)	54 (20.4)
Eye disorders		
Periorbital oedema	4 (1.5)	36 (13.6)
Gastrointestinal disorders		
Diarrhoea	176 (65.7)	70 (26.4)
Nausea	82 (30.6)	86 (32.5)
Vomiting	37 (13.8)	33 (12.5)
Abdominal pain	33 (12.3)	11 (4.2)
General disorders and administration site conditions		
Fatigue	33 (12.3)	35 (13.2)
Oedema peripheral	4 (1.5)	31 (11.7)
Investigations		
Alanine aminotransferase	76 (28.4)	12 (4.5)
Aspartate aminotransferase	57 (21.3)	12 (4.5)
Lipase increased	30 (11.2)	14 (5.3)
Musculoskeletal and connective tissue disorders		
Myalgia	4 (1.5)	28 (10.6)
Muscle spasms	3 (1.1)	63 (23.8)
Skin and subcutaneous tissue disorders		
Rash	40 (14.9)	27 (10.2)

The treatment-related TEAEs that were reported at a higher incidence (\geq 5% difference) in the bosutinib arm compared with the imatinib arm were: thrombocytopenia, diarrhea, abdominal pain, lipase increased, pruritus, decreased appetite, ALT increased, and AST increased. The treatment-related TEAEs that were reported at a higher incidence (\geq 5% difference) in the imatinib arm compared with the bosutinib arm were neutropenia, periorbital oedema, oedema peripheral, eye oedema, myalgia, and muscle spasms.

Grade 3 or 4 Treatment-Emergent Adverse Events

Table 31 provides an overview regarding Grade 3 and 4 TEAEs as observed in trial AV001.

Table 31: Number (%) of Patients with Reports of Grade 3 or 4 Treatment-Emergent Adverse Events (Incidence \geq 5% in Descending Order) in Either Arm in Study AV001 (Safety Population 1 and from trial3000WW)

System Organ Class^a Preferred Term	Bosutinib 400 mg (N=268) n (%) AV001	Bosutinib 500 mg (N=248) n (%) 3000WW	Imatinib 400 mg (N=265) n (%) AV001
Blood and lymphatic system disorders			
Thrombocytopenia	37 (13.8)	30(12.1)	15 (5.7)
Neutropenia	18 (6.7)	18 (7.3)	32 (12.1)
Gastrointestinal disorders			
Diarrhoea	21 (7.8)	26 (10.%)	2 (0.8)
Investigations			
Alanine aminotransferase increased	51 (19.0)	43 (17.3)	4 (1.5)
Aspartate aminotransferase increased	26 (9.7)	18 (7.3)	5 (1.9)
Lipase increased	26 (9.7)	17 (6.9)	14 (5.3)

The most commonly reported Grade 3 or 4 TEAEs (\geq 5%) were ALT increased, thrombocytopenia, AST increased and lipase increased, diarrhea, and neutropenia for patients receiving bosutinib compared with neutropenia, thrombocytopenia, and lipase increased for patients receiving imatinib. The Grade 3 or 4 TEAEs that were reported at a higher incidence (\geq 5% difference) in the bosutinib arm compared with the imatinib arm were thrombocytopenia, diarrhea, ALT increased, and AST increased.

The Grade 3 or 4 TEAE that was reported at a higher incidence (\geq 5% difference) in the imatinib arm compared with the bosutinib arm was neutropenia.

Adverse Events of Special Interest (AESIs)

In Study AV001, the overall incidence of cardiac, effusion, hypersensitivity, hypertension, renal, and vascular AESIs was <8% in both treatment arms.

Myelosuppression

Overall, the incidence of myelosuppression TEAEs was similar between both treatment arms. In the bosutinib arm, myelosuppression was predominantly due to Thrombocytopenia/Platelet count decreased (35.1% vs 19.6%) which were primarily Grade 1 or 2 in severity, while in the imatinib arm, myelosuppression was predominantly due to Neutropenia/Neutrophil count decreased (11.2% with bosutinib and 20.8 % with imatinib); the incidence of Anemia/Hemoglobin decreased was essentially the same in each treatment arm (18.7 vs 18.9%).

Hemorrhage

Haemorrhage events occurred slightly rarer in the bosutinib arm (15.3% bosutinib vs 16.2% imatinib), although thrombocytopenia/Platelet count decreased were more often reported in bosutinib (B:35.1% vs I:19.6%). This is explained by the fact that most of thrombocytopenia events were Grade 1 or 2 in severity; at this grade consequences in terms of increased bleeding events are generally not expected.

Infection

Whether the higher infection rates in the imatinib arm (44.4% bosutinib vs 47.2% imatinib) are really reflecting a clinical relevant difference may be challenged, as the difference between both arms regarding infection is small.

Edema AESIs were lower in the bosutinib arm (10.1 % bosutinib vs 38.9% imatinib) and rash AESIs (33.6% vs 22.6%) were higher in the bosutinib arm.

Gastrointestinal

Diarrhoea events, occurred significantly more frequent in the bosutinib arm compared with the imatinib arm (B:70.1% vs I: 33.6%). The majority of these events were Grade 1 in severity, and few led to permanent discontinuation of study drug (2 patients in each treatment arm).

Grade 1 diarrhoea was reported in 42.9%, Grade 2 in 19.4% and Grade 3 in 7.8% of patients in the bosutinib arm compared with 26.8% , 6.0% and 0.8%, respectively, of patients in the imatinib arm. No Grade 4 or 5 Diarrhoea was reported in either arm. Diarrhoea resolved in 75.5% of patients in the bosutinib arm and 58.4% of patients in the imatinib arm. The onset of diarrhoea with bosutinib was primarily within the first month of treatment. Diarrhoea decreased in incidence and severity at Month 2. Among those patients with persistent diarrhoea, the severity was primarily Grade 1. The incidence of diarrhoea with imatinib was low but persisted throughout treatment. In the few patients who had dose escalations, there did not appear to be any dose-related increase in Diarrhoea in either treatment arm.

Liver-related and GI

The overall incidences of liver-related and GI TEAEs were higher in the bosutinib arm. Of the liver-related events, ALT increased and AST increased had notably higher incidences in the bosutinib arm than in the imatinib arm. However, most patients were successfully rechallenged with study drug. Of the 69 patients in the bosutinib treatment arm who had temporary treatment discontinuations, 76.2% (48/63 were successfully rechallenged, defined as having no subsequent AE of that type or not permanently discontinued due to that type of AE. No cases of Hy's law were identified in either arm. In the few patients who had their daily dose escalated to 500 mg or 600 mg, there did not appear to be any dose-related increases in ALT or AST in either treatment arm. Comparing bosutinib 400 mg daily (Study AV001) and bosutinib 500 mg daily (Study 1008) after a minimum of 12 months of follow-up, the overall incidence of liver-related TEAEs was lower for the bosutinib 400 mg daily dose than for the bosutinib 500 mg daily dose (39.9% vs 46.4%); however, the incidence of AST increased and ALT increased were similar between the 2 doses.

The incidence of GI TEAEs of any severity grade was similar for patients receiving bosutinib 400 mg daily and bosutinib 500 mg daily (76.1% vs 75.0% respectively). The incidences of Diarrhoea and Nausea were similar for each dosing regimen; however, the incidence of Vomiting was lower in patients receiving bosutinib 400 mg daily compared with patients receiving bosutinib 500 mg daily (17.9% vs 31.9%, respectively).

No new safety signals with regards to AESIs were identified in the newly diagnosed CP CML pool or the All Leukemia pool.

Immunological events

The overall incidence of hypersensitivity TEAEs was <2.5% in both treatment arms in AV001. In the bosutinib arm, the only hypersensitivity TEAE that occurred in more than 1 patient was hypersensitivity (0.7%; 2/268) compared with hypersensitivity, seasonal allergy, and drug hypersensitivity, which occurred in 2 patients (0.8%) each in the imatinib treatment arm.

Serious adverse event/deaths/other significant events

Serious adverse event (SAEs)

In Study AV001, the overall incidence of all-causality SAEs was slightly numerically higher for the bosutinib (20.1%) and imatinib (17.0%) arms. No SAEs were reported with an incidence $\geq 2\%$ in either treatment arm. The overall incidence of treatment-related SAEs [TR-SAEs] was 10.1% (27/268) in the bosutinib arm compared with 4.5% (12/265) in the imatinib arm. No treatment-related SAE PT was reported in more than 1.5% of patients in either arm.

Table 32: Serious adverse events in the different safety sets

Safety Set	Population included	SAE incidence	
Safety Set 1	Current Pivotal Phase 3 Study AV001 (400 mg bosutinib)	TE-SAEs B: 20.1% vs. I: 17.0%	TR-SAEs B: 10.1% vs. I: 4.5%
Safety Set 2	Comparison of Study AV001 versus Study 1008. An evaluation of the safety of bosutinib 400 mg/daily in Study AV001 with that of bosutinib 500 mg/daily in Study 1008 (12-Month Analysis)	400mg TE-SAEs: 20.1% TR-SAEs: 10.1%	500 mg TE-SAEs: 25.0% TR-SAEs: 13.3%
Safety Set 3	Newly diagnosed CP CML pool. An evaluation of the bosutinib safety profile from a pooled analysis of Studies AV001, 1008 (5 year data), and 1040 (Study 1008 first line patients only with an additional 2 years of data)	28.7%	
Safety Set 4	All Leukemia Pool	35.1%	

A comparison of safety set 2 results showed that the overall incidence of SAEs is significantly lower for the 400 mg daily dose than for the 500 mg daily dose (400 mg: 20.1 vs 500 mg 25.0%) after a minimum of 12 months of follow-up. There were no SAEs with an incidence $\geq 2\%$ in patients receiving bosutinib 400 mg daily, but the known toxicities are unmasked in the population receiving bosutinib 500 mg daily in which Diarrhoea (3.6%), ALT increased (2.8%), and Thrombocytopenia and Pneumonia (2.4% each) occurred as SAEs with an incidence $\geq 2\%$.

Deaths

In the pivotal trial, there were few deaths at the time of the data cutoff: 1 patient (0.4%) in the bosutinib arm and 6 patients (2.3%) in the imatinib arm. There were no on-treatment deaths on the bosutinib arm. A total of 4 patients died on treatment (ie, within 28 days of last dose) in the imatinib arm. Of these 4 deaths, 2 were due to AEs unrelated to study drug (Cerebrovascular accident and Pneumonia), 1 was due to a related AE of sepsis, and 1 was due to disease progression (Table 33).

Table 33: Death Summary - (Safety Population) (Study AV001)

Characteristics	Bosutinib 400 mg (N=268)	Imatinib 400 mg (N=265) n (%)
No. of patients who died		
No	267 (99.6)	259 (97.7)
Yes	1 (0.4)	6 (2.3)
Reason for death^a		
AE related to Test Article	0 (0.0)	1 (16.7)
AE unrelated to Test Article	1 (100)	2 (33.3)
Disease Progression	0	3 (50.0)
Other	0	0
No. Patients who died within 28 days of last dose		
No	268 (100.0)	261 (98.5)
Yes	0 (0.0)	4 (1.5)
Reason of death^a		
AE related to Test Article	0	1 (25.0)
AE unrelated to Test Article	0	2 (50.0)
Disease Progression	0	1 (25.0)
Other	0	0 (0.00)

An additional 3 patients (2 patients in the imatinib arm and 1 patient in the bosutinib arm) died more than 28 days after the last dose of study drug. Of the 3 deaths that occurred off treatment, the 1 death in the bosutinib arm (patient 120-10-01) was due to an AE of Spindle cell carcinoma of the lung (death occurred approximately 9 months after stopping bosutinib treatment and was unrelated to study drug), and the 2 deaths in the imatinib arm were due to disease progression.

Laboratory findings

In Study AV001, on-treatment, the overall incidence of Grade 3/4 laboratory test results was higher in the bosutinib arm compared with the imatinib arm (48.1% vs. 32.5 %) as shown in Table 34:

Table 34: Number (%) of Patients with Clinical Laboratory Results of Grade 3/4 - Study AV001 (Safety Population)

Parameter, n (%)	Bosutinib 400 mg		Imatinib 400 mg	
	All Grade n	Grade 3/4	All Grade n	Grade 3/4
NCI CTCAE Grade - Baseline				
Any abnormality	188 (70.1)	10 (3.7)	198 (74.7)	4 (1.5)
Bilirubin (high)	14 (5.2)	0	9 (3.4)	0
ALT (high)	18 (6.7)	0	24 (9.1)	0
AST (high)	26 (9.7)	0	19 (7.2)	0
HGB (low)	148 (55.2)	5 (1.9)	160 (60.4)	3 (1.1)
Platelets (low)	18 (6.7)	0	13 (4.9)	0
ANC	15 (5.6)	2 (0.7)	14 (5.3)	1 (0.4)
Creatinine (high)	16 (6.0)	0	17 (6.4)	0
Lipase (high)	13 (4.9)	1 (0.4)	8 (3.0)	0
Amylase (high)	10 (3.7)	2 (0.7)	11 (4.2)	0
WBC (low)	8 (3.0)	1 (0.4)	4 (1.5)	0
For MAX Toxicity By NCI CTCAE Grade - On-Therapy				
Any abnormality	267 (99.6)	129 (48.1)	265 (100.0)	86 (32.5)
Bilirubin (high)	44 (16.4)	3 (1.1)	40 (15.1)	2 (0.8)
ALT (high)	170 (63.4)	62 (23.1)	55 (20.8)	7 (2.6)
AST (high)	132 (49.3)	32 (11.9)	53 (20.0)	8 (3.0)
HGB (low)	234 (87.3)	19 (7.1)	235 (88.7)	15 (5.7)
Platelets (low)	179 (66.8)	38 (14.2)	156 (58.9)	17 (6.4)
ANC	106 (39.6)	24 (9.0)	163 (61.5)	49 (18.5)
Creatinine (high)	248 (92.5)	0	252 (95.1)	2 (0.8)
Lipase (high)	106 (39.6)	35 (13.1)	77 (29.1)	16 (6.0)
Amylase (high)	67 (25.0)	6 (2.2)	37 (14.0)	4 (1.5)
WBC (low)	132 (49.3)	15 (5.6)	180 (67.9)	20 (7.5)

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; HGB=hemoglobin; CML=Chronic Myeloid Leukemia; N/n=number of patients; NCI=National Cancer Institute; WBC=white blood cell count.

Data cutoff dates: AV001: 11 August 2016.

Grades are based upon the NCI CTCAE (Version 4.0).

Baseline is defined as the latest lab prior to first dose of the test article.

Note: Absolute Neutrophil Count may or may not contain Band Neutrophils depending on the site. For 'Any Abnormality', baseline maximum grade across all lab tests is summarized.

Hepatotoxicity

For ALT, 62 (23.1%) patients in the bosutinib treatment arm had a shift from baseline to Grade 3 or 4 on treatment compared with 7 (2.7%) patients in the imatinib arm.

For AST, 32 (12.0%) patients in the bosutinib treatment arm had a shift from baseline to Grade 3 or 4 on treatment and 8 (3.0%) patients in the imatinib arm had a shift from baseline to Grade 3 on treatment.

For bilirubin, 3 (1.1%) patients in the bosutinib treatment arm had a shift from baseline to Grade 3 on treatment and 2 (0.8%) patients in the imatinib arm had a shift from baseline to Grade 3 on treatment. No patients in either arm had shifts to Grade 4 on treatment.

There were no cases of Hy's law or permanent liver injury identified in the study, although three (3) patients in the bosutinib arm (400 mg daily) did report concomitant transaminase and bilirubin

increases that met the laboratory criteria of Hy's law and warranted further investigation, which excluded the occurrence of severe drug induced liver injury.

Estimated Glomerular Filtration Rate (eGFR)

In Study AV001, the MDRD equation was used to calculate eGFR at baseline and on treatment. Shifts from baseline in eGFR by maximum KDIGO grade on treatment to Grade 3 or higher were reported for 24 patients (Grade 3 a: 22 patients (8.2%) and Grade 3b: 2 patients [0.7%]) in the bosutinib arm. Of the 22 patients with Grade 3a reported at baseline in the bosutinib arm, 11 (50.0%) patients continued to have a maximum of Grade 3a on treatment; 7 (31.8%) patients were reported to have a maximum of Grade 3b, and 1 (4.5%) patient was reported to have a maximum of Grade 4 on treatment.

In the imatinib arm, 20 patients were reported to have Grade 3a at baseline; 9 (45.0%) patients continued to have a maximum of Grade 3a, 7 (35.0%) patients were reported to have a maximum of Grade 3b, and 3 (15.0%) patients were reported to have a maximum of Grade 4 on treatment.

ECG and QT prolongation

In Study AV001, on-therapy PCI changes in ECG were reported for 9 (3.5%) patients in the bosutinib arm compared with 6 (2.4%) patients in the imatinib arm who had at least 1 assessment (SCS Table 51). When the QT interval was corrected using Bazett's formula, only 1(0.4%) patient (in the imatinib arm) had an increase of >60 msec from baseline. There were no patients who had an increase of >60 msec from baseline when the QT interval was corrected using Fridericia's formula. One (1 [0.4%]) patient in the bosutinib arm and no patients in the imatinib arm had a QTcF of >500 msec.

ECHO or MUGA scans

Cardiac events were infrequent in both arms. There were no shifts to Grade 4 LVEF decline and only 1 Grade 3 shift in the bosutinib arm versus 0 Grade 3/4 in the imatinib arm.

Safety in special populations

In Study AV001, no statistical analyses were performed to compare the incidence or severity of TEAEs on the basis of age, race, or gender. However, subgroup analyses were performed to examine the incidence of all-causality TEAEs and provide descriptive comparisons of results by age (<65 years, >65 years), race (Black or African-American, Asian, White, Other), and gender (male, female). The treatment groups were balanced with respect to these characteristics. Of note, the majority of patients in the study were White and less than 65 years of age, and there were slightly more males than females in both treatment arms. In addition, subgroup analyses were performed for Grade 3/4/5 TEAEs and SAEs. Deaths were summarized by age, race, or gender.

Most patients in both treatment arms (safety population) were <65 years. In the bosutinib arm 215 (80.2%) patients were <65 years, and 53 (19.8%) patients were >65 years; in the imatinib arm 219 (82.6%) patients were <65 years and 46 (17.4%) patients were >65 years (Table 35). In the bosutinib arm, TEAEs were reported in 97.7% of patients <65 years and 100.0% of patients >65 years. Grade \geq 3 TEAEs were reported in 54.0% of patients <65 years and 66.0% of patients >65 years.

Table 35: Most Common ($\geq 20\%$) All-Causality TEAEs by Age Group by Decreasing Order of <65 and ≥ 65 Years Groups in Study AV001 (Bosutinib Treatment Arm)

Preferred Term	<65 Years (N=215)	>65 Years (N=53)
	n (%)	n (%)
Diarrhoea	152 (70.7)	36 (67.9)
Thrombocytopenia	75 (34.9)	19 (35.8)
Nausea	73 (34.0)	21 (39.6)
ALT increased	64 (29.8)	18 (34.0)
AST increased	46 (21.4)	15 (28.3)
Headache	39 (18.1)	11 (20.8)
Fatigue	38 (17.7)	14 (26.4)
Anaemia	38 (17.7)	12 (22.6)
Rash	37 (17.2)	16 (30.2)
Decreased appetite	13 (6.0)	14 (26.4)

Data cut-off date: 11 August 2016

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients.

There was a higher proportion of male than female patients in both treatment arms. In the bosutinib arm, 156 (58.2%) patients were male and 112 (48.1%) patients were female; in the imatinib arm 153 (57.7) patients were male and 112 (42.3) were female. TEAEs were reported in 96.8% of male patients and 100.0% of female patients. Grade ≥ 3 TEAEs were reported in 56.4% of male patients and 56.3% of female patients. The most commonly reported TEAEs ($\geq 20\%$ of patients) in the bosutinib arm for male and female patients are shown in Table 36.

Table 36: Most Common ($\geq 20\%$) All-Causality TEAEs by Gender Group by Decreasing Order of Male Group in Study AV001 (Bosutinib Treatment Arm)

Preferred Term	Male N=156 n (%)	Female N=112 n (%)
Diarrhoea	103 (66.0)	85 (75.9)
Thrombocytopenia	61 (39.1)	33 (29.5)
ALT increased	46 (29.5)	36 (32.1)
Nausea	46 (29.5)	48 (42.9)
AST increased	32 (20.5)	29 (25.9)
Rash	26 (16.7)	27 (24.1)
Fatigue	26 (16.7)	26 (23.2)
Abdominal pain	20 (12.8)	28 (25.0)
Anaemia	22 (14.1)	28 (25.0)
Vomiting	19 (12.2)	29 (25.9)
Headache	18 (11.5)	32 (28.6)

Data cut-off date: 11 AUG 2016

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients; TEAE=treatment-emergent adverse event.

A number of the most commonly reported TEAEs were more frequent ($\geq 5\%$ difference) among female than male patients, including diarrhoea, nausea, AST increased, rash, fatigue, abdominal pain, anaemia, vomiting, headache. of these, nausea, rash, anaemia, vomiting, and headache showed a difference of $\geq 10\%$ between the 2 groups. Thrombocytopenia was more frequent ($\geq 5\%$ difference) among male than female patients. SAEs were reported with a lower overall incidence among male than female patients (17.9% vs. 23.2%). As most individual SAE PTs were reported for 1 or 2 patients in each gender group, no conclusions can be made regarding differences in types of SAEs between male and female patients.

In the bosutinib arm, TEAEs were reported in 98.1% of White, 97.0% of Asian, 100.0% of Other, and 100.0% of Black or African-American patients. Grade ≥ 3 TEAEs were reported in 55.7% of White, 69.7% of Asian, 35.7% of Other, and 50.0% of Black or African-American patients. The most

commonly reported TEAEs ($\geq 20\%$ of patients) in each group in the bosutinib arm are shown in Table 37

Table 37.

Table 37: Most Common ($\geq 20\%$) All-Causality TEAEs by Race Group by Decreasing Order of White Group in Study AV001 (Bosutinib Treatment Arm) (Safety Analysis Population 1)

Preferred Term	White (N=210) n (%)	Asian (N=33) n (%)	Other (N=14) n (%)	Black or African American (N=10) n (%)
Diarrhoea	145 (69.0)	19 (57.6)	14 (100.0)	9 (90.0)
Nausea	81 (38.6)	5 (15.2)	5 (35.7)	3 (30.0)
Thrombocytopenia	67 (31.9)	13 (39.4)	9 (64.3)	5 (50.0)
ALT increased	64 (30.5)	13 (39.4)	1 (7.1)	4 (40.0)
AST increased	47 (22.4)	9 (27.3)	1 (7.1)	4 (40.0)
Fatigue	43 (20.5)	5 (15.2)	1 (7.1)	3 (30.0)
Anaemia	38 (18.1)	8 (24.2)	2 (14.3)	1 (10.0)
Abdominal pain	38 (18.1)	5 (15.2)	0	5 (50.0)
Headache	38 (18.1)	4 (12.1)	5 (35.7)	3 (30.0)
Rash	36 (17.1)	12 (36.4)	2 (14.3)	3 (30.0)
Vomiting	33 (15.7)	4 (12.1)	7 (50.0)	4 (40.0)
Lipase increased	25 (11.9)	8 (24.2)	2 (14.3)	1 (10.0)
Arthralgia	24 (11.4)	2 (6.1)	2 (14.3)	2 (20.0)
Neutropenia	19 (9.0)	6 (18.2)	2 (14.3)	3 (30.0)
Constipation	19 (9.0)	2 (6.1)	2 (14.3)	3 (30.0)
Decreased appetite	19 (9.0)	6 (18.2)	0	2 (20.0)
Urinary tract	12 (5.7)	1 (3.0)	2 (14.3)	2 (20.0)
Leukopenia	11 (5.2)	2 (6.1)	2 (14.3)	0
Blood creatinine	11 (5.2)	1 (3.0)	0	3 (30.0)
Dizziness	10 (4.8)	4 (12.1)	3 (21.4)	1 (10.0)
Abdominal pain	9 (4.3)	6 (18.2)	5 (35.7)	0
Blood alkaline	8 (3.8)	3 (9.1)	1 (7.1)	3 (30.0)
increased				
Dry skin	8 (3.8)	0	1 (7.1)	2 (20.0)
Amylase increased	7 (3.3)	5 (15.2)	0	2 (20.0)
Blood creatine	6 (2.9)	1 (3.0)	0	2 (20.0)
increased				
Gastroenteritis	5 (2.4)	1 (3.0)	3 (21.4)	1 (10.0)
Transaminases	4 (1.9)	0	3 (21.4)	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/n=number of patients.
Data cut-off date: 11 August 2016

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

The incidence of all-causality AEs associated with permanent treatment discontinuation in the pivotal trial AV001 was higher in the bosutinib than in the imatinib arms (14.2% vs 10.6%) The most commonly reported (incidence $\geq 1\%$) AEs leading to discontinuation of study drug in patients receiving

bosutinib were ALT increased (4.9%) and AST increased (2.2%) compared with Thrombocytopenia (1.5%) and Myalgia (1.1%) in patients who received imatinib.

Table 38 summarises AEs provides that were reported as causes for permanent discontinuation of study drug:

Table 38: Number of Subjects Experiencing Adverse Events Leading to Discontinuation of Study Drug - Safety Population Set 1

System Organ Class Preferred Term (MedDRA 19.0)	Bosutinib (N=268)			Imatinib (N=265)			Total (N=533)		
	n	%	E	n	%	E	n	%	E
Any AE	38	(14.2)	46	28	(10.6)	42	66	(12.4)	88
Investigations	19	(7.1)	24	7	(2.6)	8	26	(4.9)	32
ALT increased	13	(4.9)	13	0		0	13	(2.4)	13
AST increased	6	(2.2)	6	0		0	6	(1.1)	6
Lipase increased	2	(0.7)	2	2	(0.8)	2	4	(0.8)	4
Blood creatine phosphokinase	0		0	2	(0.8)	2	2	(0.4)	2
Platelet count decreased	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Transaminases increased	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Amylase increased	0		0	1	(0.4)	1	1	(0.2)	1
Blood creatinine	0		0	1	(0.4)	1	1	(0.2)	1
Liver function test	1	(0.4)	1	0		0	1	(0.2)	1
Gastrointestinal	4	(1.5)	4	4	(1.5)	6	8	(1.5)	10
Diarrhoea	2	(0.7)	2	2	(0.8)	2	4	(0.8)	4
Nausea	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Abdominal pain	0		0	1	(0.4)	1	1	(0.2)	1
Abdominal pain upper	0		0	1	(0.4)	1	1	(0.2)	1
Colitis	0		0	1	(0.4)	1	1	(0.2)	1
Pancreatitis acute	1	(0.4)	1	0		0	1	(0.2)	1
Skin and subcutaneous tissue disorders	2	(0.7)	2	5	(1.9)	5	7	(1.3)	7
Rash	1	(0.4)	1	2	(0.8)	2	3	(0.6)	3
Rash maculo-papular	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Night sweats	0		0	1	(0.4)	1	1	(0.2)	1
Toxic skin eruption	0		0	1	(0.4)	1	1	(0.2)	1
Blood and lymphatic system disorders	1	(0.4)	4	5	(1.9)	6	6	(1.1)	10
Thrombocytopenia	1	(0.4)	1	3	(1.1)	3	4	(0.8)	4
Neutropenia	1	(0.4)	2	2	(0.8)	2	3	(0.6)	4
Anaemia	0		0	1	(0.4)	1	1	(0.2)	1
Leukopenia	1	(0.4)	1	0		0	1	(0.2)	1
General disorders and administration site conditions	0		0	4	(1.5)	4	4	(0.8)	4
Face oedema	0		0	2	(0.8)	2	2	(0.4)	2
Asthenia	0		0	1	(0.4)	1	1	(0.2)	1
Fatigue	0		0	1	(0.4)	1	1	(0.2)	1
Hepatobiliary disorders	4	(1.5)	4	0		0	4	(0.8)	4
Hepatotoxicity	2	(0.7)	2	0		0	2	(0.4)	2
Drug-induced liver injury	1	(0.4)	1	0		0	1	(0.2)	1
Hepatitis	1	(0.4)	1	0		0	1	(0.2)	1

System Organ Class Preferred Term (MedDRA 19.0)	Bosutinib (N=268)			Imatinib (N=265)			Total (N=533)		
	n	%	E	n	%	E	n	%	E
Musculoskeletal and connective tissue	0		0	4	(1.5)	4	4	(0.8)	4
Myalgia	0		0	3	(1.1)	3	3	(0.6)	3
Muscle spasms	0		0	1	(0.4)	1	1	(0.2)	1
Infections and infestations	2	(0.7)	2	1	(0.4)	1	3	(0.6)	3
Pneumonia	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Hepatitis B	1	(0.4)	1	0		0	1	(0.2)	1
Respiratory, thoracic and	2	(0.7)	2	1	(0.4)	1	3	(0.6)	3
Dyspnoea exertional	0		0	1	(0.4)	1	1	(0.2)	1
Pleural effusion	1	(0.4)	1	0		0	1	(0.2)	1
Pulmonary hypertension	1	(0.4)	1	0		0	1	(0.2)	1
Cardiac disorders	2	(0.7)	2	0		0	2	(0.4)	2
Coronary artery disease	1	(0.4)	1	0		0	1	(0.2)	1
Coronary artery	1	(0.4)	1	0		0	1	(0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts	1	(0.4)	1	1	(0.4)	1	2	(0.4)	2
Chronic myeloid	0		0	1	(0.4)	1	1	(0.2)	1
Lung neoplasm	1	(0.4)	1	0		0	1	(0.2)	1
Nervous system disorders	0		0	2	(0.8)	2	2	(0.4)	2
Cerebrovascular	0		0	1	(0.4)	1	1	(0.2)	1
Disturbance in attention									
Eye disorders	0		0	1	(0.4)	2	1	(0.2)	2
Lacrimation increased	0		0	1	(0.4)	1	1	(0.2)	1
Periorbital oedema	0		0	1	(0.4)	1	1	(0.2)	1
Nervous system disorders	0		0	2	(0.8)	2	2	(0.4)	2
Cerebrovascular accident	0		0	1	(0.4)	1	1	(0.2)	1
Disturbance in attention	0	0	1	(0.4)	1	1	(0.2)	1	0
Eye disorders	0		0	1	(0.4)	2	1	(0.2)	2
Lacrimation increased	0		0	1	(0.4)	1	1	(0.2)	1
Periorbital oedema	0		0	1	(0.4)	1	1	(0.2)	1
Congenital, familial and genetic disorders	0		0	1	(0.4)	1	1	(0.2)	1
Cytogenetic abnormality	0		0	1	(0.4)	1	1	(0.2)	1
Psychiatric disorders	1	(0.4)	1	0		0	1	(0.2)	1
Depression	1	(0.4)	1	0		0	1	(0.2)	1
Renal and urinary disorders	0		0	1	(0.4)	1	1	(0.2)	1
Nephrotic syndrome	0		0	1	(0.4)	1	1	(0.2)	1

Note: Table presents number and percentages of subjects (n [%]) and number of events (E). Percentages were based on (N) the number of subjects treated in each arm.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; E=events; MedDRA=medical dictionary for regulatory activities

In both treatment arms, ALT increased was the most common AE leading to discontinuation of bosutinib as shown in Table 39:

Table 39: Number (%) of Patients with Reports of Adverse Events that Led to Permanent Discontinuation (Incidence \geq 1%) of Study Treatment Study AV001 (Safety Set Population 1)

Preferred Term ^a	Bosutinib 400 mg (N=268)	Imatinib 400 mg (N=265)
Any Adverse Event	38 (14.2)	28 (10.6)
Alanine aminotransferase increased	13 (4.9)	0
Aspartate aminotransferase increased	6 (2.2)	0
Thrombocytopenia	2 (0.7)	4 (1.5)
Myalgia	0	3 (1.1)

For this summary, the following clustered term for cytopenias including Thrombocytopenia (PT=Thrombocytopenia; Platelet count decreased) is used.

Note: Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.0). Descending Order of the Incidences is presented at the level of Preferred Term based on the incidences of "Bosutinib 400 mg" column.

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N/n=number of patients; PT=Preferred Term.

a. Totals of the No. of Patients at a higher level are not necessarily the sum of those at the lower levels since a patient may report 2 or more different adverse events within the higher level category.

Hepatotoxicity expressed in ALT increased (4.9%) and AST increased (2.2%) was only seen in patients receiving bosutinib while Thrombocytopenia (1.5%) and Myalgia (1.1%) were the most important reasons for discontinuation in patients receiving imatinib:

Treatment delay and Dose-reduction due to AEs

Consistently, also the incidence of AEs leading to temporary treatment delays in trial AV001 was higher in the bosutinib arm than in the imatinib arm (56.7% vs 37.0% respectively). Again most of the delays were due to ALT increased (19.0% in the bosutinib arm vs 1.5% in the imatinib arm); AST increased (11.2% vs 1.5%, respectively), and Thrombocytopenia (14.6% vs 5.7%, respectively).

And similarly also the incidence of AEs leading to dose reduction was higher in the bosutinib arm than in the imatinib arm (34.0% vs 18.1% respectively). The most commonly reported TEAEs (\geq 1%) leading to dose reduction were Thrombocytopenia (6.7%), ALT increased (6.0%), Lipase increased (4.5%), AST increased (3.4%), Neutropenia (2.6%), Diarrhoea and Nausea (2.2% each), Rash (1.9%), Anaemia (1.5%), Amylase increased, Transaminases increased, Fatigue, and Vomiting (1.1% each) in patients receiving bosutinib compared with Neutropenia (3.8%), Thrombocytopenia and Rash (1.5%), Muscle Spasm and Myalgia (1.1% each) in patients receiving imatinib.

In Set 2 Safety population (Studies AV001 and 1008; Non-Pooled Month 12 Analysis) the incidence of AEs leading to permanent discontinuation of study drug was 14.2% (38/268) for patients receiving bosutinib 400 mg daily and 21.0% (52/248) for patients receiving bosutinib 500 mg daily.

In Set 4 Safety population (Patients with Newly Diagnosed CP CML and All Leukemia Pools) the incidence of AEs leading to discontinuation of study drug was 21.9% (113/516) in patients with newly diagnosed CP CML and 22.6% (287/1272) in the All Leukemia pool.

Dose-dependence of discontinuation:

The incidence of AEs leading to permanent discontinuation was lower for patients who received bosutinib 400 mg than for those who received bosutinib 500 mg (14% vs 21%).

Also the incidence of AEs leading to treatment delay was lower for patients who received bosutinib 400 mg in Study AV001 than those who received bosutinib 500 mg in Study 1008 (56.7% vs 62.5%). A similar number of patients in both treatment arms required dose reductions (34.0% vs 37.1%).

Post marketing experience

Bosutinib is currently approved for the treatment of adult patients with CP, AP and BP Ph+ CML previously treated with one or more TKIs, and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options. A 500 mg dose is recommended and used in this indication. Due to the intensified review approach as consequence of a conditional approval, and the need for annual renewals, the MAH has submitted a number of Periodic Safety Update Report (PSUR) since the initial approval for bosutinib. As of 15 February 2017, 8626 patients worldwide had been exposed to bosutinib commercially since approval. It is estimated that 2383 patients worldwide had participated in Pfizer-sponsored clinical trials, 2046 of whom had been exposed to bosutinib either as a single agent, in combination with placebo, or in combination with other study drug.

From this data the important identified risks for bosutinib in the current RMP are hepatotoxicity, GI toxicities, hypersensitivity reactions (including anaphylaxis), fluid retention, myelosuppression, QT interval prolongation, respiratory tract infections, bleeding events, renal dysfunction, rash, and pancreatitis. The important potential risks of bosutinib are cardiac toxicity (excluding QT interval prolongation), interstitial lung disease, thyroid dysfunction, tumour lysis syndrome, bone turnover /bone mineral metabolism disorders, and immunotoxicity.

2.5.1. Discussion on clinical safety

Bosutinib was granted conditional marketing authorisation in the EU on 27 March 2013 for the treatment of adult patients with CP, AP and BP Ph+ CML previously treated with one or more TKIs, and for whom imatinib, nilotinib, and dasatinib are not considered appropriate treatment options.

For this late line indication a higher dose of 500 mg bosutinib was approved and post-marketing experience from more than 8000 patients as well as long term clinical study data (up to more than 5 years) from Study 1008-3000WW is available. This issue substantiated the view that the general safety profile of bosutinib can be seen as well characterized for an orphan disease entity.

Specific safety information supporting the newly applied treatment with a lower bosutinib dose of 400 mg in the first-line CP-CML target population is assessed from the results of the pivotal trial AV001. All treated patients were included in the safety population.

Supportive results from the previous pivotal phase III trial Study 1008-3000WW allows a better understanding of dose dependence of toxicities and adverse events observed. This trial was conducted prior to the start of Study AV001 and failed to reach the expected outcome, but provides long term safety outcome in the applied population up to 5 years of bosutinib treatment. However, it has to be considered that this data was generated with the higher 500 mg dose and the pooled analysis with AV001 reports the 12 months outcome only.

As indicated by duration of study treatment (14.1 months for bosutinib vs. 13.8 months for imatinib), exposure in the pivotal trial AV001 was sufficient to conclude on safety in this orphan disease entity. Slightly lower median dose intensity in the bosutinib arm (391.8 mg/daily for bosutinib and 400.0 mg/daily for imatinib) confirmed that bosutinib has a more pronounced toxicity than imatinib.

This assumption is further confirmed by the consistently higher rates for TEAEs (B:98.1% vs. I: 97.0%), grade 3 and 4 TEAEs (B:56.0% vs. I:41.9%) and SAEs (B:20.1% vs. I:17.0%) and also reflected by the finding that patients in trial AV001 in the bosutinib arm were more likely to experience a dose reduction (B:34.7% vs. I:17.4%) or treatment delay (56.3% vs. 35.8%) due to AEs than patients in the imatinib arm. This is in-line with the known safety profile of bosutinib and the results from the previous direct comparison with imatinib in trial 1008-3000W.

From the experience in the approved later line CML population and the reports from post-marketing bosutinib's toxicities seemed to be tolerable and manageable. This is confirmed by the similar rates of permanent discontinuations due to AEs (B:14.2% vs. I: 10.6%) and the finding that a similar number of patients treated with bosutinib versus imatinib remained on treatment (78.0% vs. 73.2% respectively) in the safety population in the current pivotal trial AV001.

In general it is acknowledged that both second generation TKI (nilotinib and dasatinib) as well as the approved third generation TKI ponatinib are known to have a more pronounced toxicity than imatinib. Insofar, a higher toxicity in comparison to imatinib can be expected also for bosutinib and was also documented in the initial trial 1008-3000WW.

The main safety risk derived from bosutinib are due to higher hepatotoxicity (AST/ALT elevations), gastrointestinal adverse events (diarrhoea, nausea vomiting) and rash, while specific concerns regarding cardiac safety or arrhythmias are rather minor according to the safety data available.

In general, types and frequencies of TEAEs in Study AV001 were fully consistent with the known safety profile of bosutinib and no new safety signal was identified from the new data. The most common TEAEs (incidence $\geq 20\%$) reported were diarrhoea (70.1%), nausea and thrombocytopenia (35.1% each), alanine aminotransferase (ALT) increased (30.6%), and aspartate aminotransferase (AST) increased (22.8%) for patients receiving bosutinib compared with nausea (38.5%), diarrhoea (33.6%), muscle spasms (26.4 %), and neutropenia (20.8%) for patients receiving imatinib.

TEAEs that were observed with a higher incidence ($>5\%$ difference) in the bosutinib arm compared with the imatinib arm were diarrhoea, abdominal pain, ALT increased, AST increased, lipase increased, rash, pruritus, headache, and thrombocytopenia. a higher incidence ($>5\%$ difference) in the imatinib arm compared with the bosutinib arm were observed for oedema peripheral, muscle spasms, myalgia, pain in extremity, neutropenia, leukopenia, periorbital oedema, eyelid oedema, lacrimation increased, and hypokalaemia.

Also similar to previous findings the rate of Grade 3 or 4 TEAEs was higher for bosutinib compared with imatinib (56.0% vs. 41.9%). The most common Grade 3 or 4 TEAEs ($\geq 5\%$) reported were ALT increased (19.0%), thrombocytopenia (13.8%), AST increased and lipase increased (9.7% each), diarrhoea (7.8%), and neutropenia (6.7%) for patients receiving bosutinib compared with neutropenia (12.1%), thrombocytopenia (5.7%), and lipase increased (5.3%) for patients receiving imatinib.

Cardiac events were infrequent in both arms. There were no shifts to Grade 4 LVEF decline and only 1 Grade 3 shift in the bosutinib arm versus 0 Grade 3/4 in the imatinib arm. There was 1 Grade 3 QT prolongation (>500 msec) in the bosutinib arm versus 0 in the imatinib arm. The overall incidence of patients with a clinically significant ECG abnormality while on treatment was 7.5% in the bosutinib arm and 6.9% in the imatinib arm and thus, similar risk for arrhythmic events is likely.

As expected from the known safety profile of bosutinib the overall incidence of gastrointestinal TEAEs was higher in the bosutinib arm (76.1%) than in the imatinib arm (53.6%). This is caused mainly by a notable difference in reported diarrhoea (B: 70.1% vs I: 33.6%), but the majority of these events were Grade 1 and only very few led to discontinuation of study drug (2 patients in each treatment arm). The lower dose of 400 mg seems to be associated with a significant reduction of vomiting in comparison to the 500 mg bosutinib dose (AV001: 400mg: 13.8% vs 3000WW: 500 mg: 24.6%) It

can be speculated that decreased vomiting in the target population may have had also an relevant impact on bosutinib's bioavailability and insofar may have contributed also to the slightly better efficacy outcome in AV001 compared with 1008-3000WW.

The overall incidence of liver-related TEAEs was again higher in the bosutinib arm (39.9%) than in the imatinib arm (13.6%), which was expected from the known safety profile. The most common liver-related TEAEs ($\geq 20\%$) were ALT increased (30.6% all toxicity grades and 19.0% Grade 3/4 for bosutinib and 5.7% and 1.5% for imatinib respectively), AST increased (22.8% all toxicity grades and 9.7% Grade 3/4 for bosutinib and 6.4% and 1.9% for imatinib, respectively). Although most of these patients were successfully re-challenged with bosutinib (of the 69 patients who had temporary treatment discontinuations, 76.2% [48/63] were successfully re-challenged), the risk for drug induced liver injuries remains open. However, Hy's law cases were again not observed in this trial.

The overall incidence of rash TEAEs was higher in the bosutinib arm than in the imatinib arm (33.6% vs. 22.6%).

Comparison of the safety profile of bosutinib 400 mg daily (Study AV001) with that of bosutinib 500 mg daily (Study 1008 12-month analysis) showed that the incidence of AEs was similar (98.1% vs. 95.6%, respectively). Of the most common TEAEs ($\geq 10\%$) the only notable differences ($\geq 5\%$ difference in frequency) in the incidence of AEs were fatigue (19.4% vs. 11.3%) and headache (18.7% vs. 11.3%), which were higher with the bosutinib 400 mg daily dose, and Vomiting, which was lower with the 400 mg daily dose (17.9% vs. 31.9%) compared with the 500 mg daily dose. The incidence of SAEs was 20.1% for the 400 mg dose and 25.0% for the 500 mg dose. No patients were reported to have treatment-emergent SAEs with an incidence $\geq 2\%$ with the bosutinib 400 mg daily dose (Study AV001).

The incidence of myelosuppression TEAEs was similar in the bosutinib (45.5%) and imatinib (43.4%) arms. In the bosutinib arm myelosuppression was predominantly due to Thrombocytopenia/Platelet count decreased (35.1% with bosutinib vs. 19.6% imatinib), which were primarily Grade 1 and 2. While in the imatinib arm myelosuppression was predominantly due to neutropenia/neutrophil count decreased (11.2% with bosutinib vs. 20.8 % with imatinib). Anemia/hemoglobin decreased rates in both arms were essentially the same (18.7% vs. 18.9 %).

On-treatment, the overall incidence of Grade 3/4 of laboratory test results was higher in the bosutinib arm compared with the imatinib arm (48.1% vs. 32.5 %). This is mainly caused due to the higher proportion of patients in the bosutinib arm than in the imatinib arm that had increased ALT and AST levels.

The eGFR shift from baseline for all grades was similar for both treatment arms with regards to degree of change over time.

No relevant signal regarding the use of bosutinib in special population was detected.

In the Phase 3 clinical study in patients with newly-diagnosed CP CML treated with bosutinib 400 mg, there were no patients in the bosutinib treatment group with an increase of > 60 ms from baseline when the QT interval was corrected using Fridericia's formula (QTcF) (SmPC, section 4.8).

2.5.2. Conclusions on clinical safety

The safety results from the submitted studies were generally consistent with the known safety profile of bosutinib. No new safety signals were identified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

In addition, the MAH should submit the following safety data within the next PSUR:

- Report any data of (1) patients with clinically significant cardiac disease (such as recent myocardial infarction, congestive heart failure or unstable angina recent or ongoing) and (2) with clinically significant gastrointestinal disorder e.g. Crohn's Disease, Ulcerative Colitis, or prior total or partial gastrectomy treated with bosutinib and the outcome, which allows to assess whether or whether not bosutinib can be safely administered in these patients.
- Report and briefly discuss on the number of cases with concomitant use of bosutinib with strong or moderate CYP3A4 inducers/ inhibitors and/or PPIs. The discussion should include an assessment of causality of the reported ADRs with potential drug interaction in the respective cases (in line with current established guidelines – e.g. WHO-UMC). Finally the need for strategies/risk minimization measures to make physicians more vigilant for the risk of drug interactions of bosutinib with CYP3A4 inducers/ inhibitors and/or PPIs should be discussed.
- Report on ongoing and planned studies, in which real-world use including concomitant use of CYP3A4 inhibitors/inducers /PPIs will be captured, and to report on available evidence for concomitant use of CYP3A4 inducers/inhibitors/PPIs with bosutinib in real-world use from these studies in the next PSUR (e.g. real-world use of bosutinib in the UK and the Netherland, Apperley et al. BSH, 2017)
- Report how many of the patients included in the supportive trial 1008-3000WW received bosutinib and CYP3A4 inducers/inhibitors and/or PPIs concomitantly, and how this potentially affected treatment (dose reduction of bosutinib, treatment interruption, no change in treatment etc.) and outcome.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 40 Summary of the Safety Concerns

Important Identified Risks	Hepatotoxicity
	Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)
	Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis
	QT Prolongation
	Renal Dysfunction
Important Potential Risk	Cardiac Toxicity (Excluding QT Prolongation)
Missing Information	Use in Paediatric ^a Patients
	Safety in Patients with Cardiac Impairment
	Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders
	Pregnancy
	Carcinogenicity

a. age: ≤17 years

Pharmacovigilance plan

Table 41 On-going and Planned Additional Pharmacovigilance Activities

Study	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Status				
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				
Phase 4 safety and efficacy (CT B1871039)	To estimate the safety and efficacy of bosutinib in subjects with Ph+ CML who have	A secondary study objective is to evaluate the overall safety profile of bosutinib in the	Final approved protocol	21 January 2014
Ongoing			Final clinical study	30 September 2018

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	been treated with 1 or more TKI(s).	study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.	report	
Category 3 – Required additional pharmacovigilance activities				
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) Ongoing	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.	To obtain additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns. Fulfilled the EMA follow-up measure for the collection and analysis of safety data focused on diarrhoea incidence and management after subject switch from the clinical formulation to the commercial formulation of bosutinib.	Final approved protocol Final clinical study report	25 February 2013 12 August 2020
Phase 1/2 to investigate safety and efficacy of bosutinib in the paediatric population (CT ITCC-054/AAML1 621) Ongoing	The Phase 1 primary objective is to determine a recommended Phase 2 dose of bosutinib in paediatric subjects with CML who are resistant or intolerant to at least 1 prior TKI	To identify a recommended dose of bosutinib administered orally once daily in paediatric subjects with CML who have received at least 1 prior TKI therapy (resistant or intolerant), and	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.	

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	therapy based on the PK, safety, and tolerability profile. The Phase 2 primary objective is to describe the clinical efficacy of bosutinib in paediatric subjects with Ph+ CML in CP who have received at least 1 prior TKI.	to preliminarily estimate the efficacy, safety, and tolerability of the selected bosutinib dose and evaluate the PKs in this patient population.	Final clinical study report	30 September 2020
Six-month transgenic rasH2 mouse carcinogenicity study (non-clinical) Planned	To determine the potential tumourigenicity of bosutinib.	Carcinogenicity.	Final approved protocol Final study report	Second or third quarter 2018 (estimated) Late 2019 or early 2020 (estimated)
Rat pre-and post-natal development study (non-clinical) Planned	To determine the developmental toxicity of bosutinib in late pregnancy through weaning stages.	Growth and development.	Final approved protocol Final study report	January 2018 (estimated) 2018 (estimated)

CT = clinical trial; Ph+ CML = Philadelphia chromosome-positive chronic myelogenous leukaemia; TKI = tyrosine kinase inhibitor; CP = chronic phase; AP = accelerated phase; EMA = European Medicines Agency; PK = pharmacokinetic; MAH = Marketing Authorisation Holder

Risk minimisation measures

Table 42 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important Identified Risks		
Hepatotoxicity	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.3, 4.4, and 4.8; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
Gastrointestinal Toxicities (Diarrhoea, Nausea, Vomiting)	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.3, 4.4, and 4.8; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u></p>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		<p>Collection of blood samples in the Japanese CT B1871048 for genetic testing for all subjects for further investigation if a severe cutaneous reaction is experienced.</p> <p>A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
QT Prolongation	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, 4.8, 5.1, and 5.3; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
Renal Dysfunction	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, 4.8, and 5.2; PL sections 2, 3, and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> Renal function will continue to be monitored in CTs AV001, B1871039, and B1871040 via measurement of serum</p>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		<p>creatinine, enabling calculation of eGFR using the Cockcroft-Gault formula.</p> <p>A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
Important Potential Risk		
Cardiac Toxicity (Excluding QT Prolongation)	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2, 4.4, and 4.8; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> A secondary study objective of CT B1871039 is to evaluate the overall safety profile of bosutinib in the study population; although no particular event is specified, the overall safety information may contribute to further descriptive characterisation of the safety concerns.</p> <p>CT B1871040 also will enable the collection of additional, long-term safety information in the target population in order to further contribute to descriptive characterisation of the safety concerns.</p>
Missing Information		
Use in Paediatric Patients ^a	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2 and 5.2; PL Section 2.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> CT ITCC-054/AAML1621 is being conducted in order to identify a recommended dose of bosutinib administered orally once daily in</p>

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
		paediatric subjects with chronic myelogenous leukaemia who have received at least 1 prior tyrosine kinase inhibitor therapy (resistant or intolerant), and to preliminarily estimate the efficacy, safety, and tolerability of the selected bosutinib dose and evaluate the pharmacokinetics in this patient population.
Safety in Patients with Cardiac Impairment	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2 and 4.4; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> This missing information topic will be assessed by reviewing the clinical course of subjects in CTs B1871039 and B1871040 who are re-challenged with bosutinib after they experience a significant cardiac event.</p>
Safety in Patients with Recent or Ongoing Clinically Significant Gastrointestinal Disorders	<p><u>Routine risk minimisation measures:</u> SmPC sections 4.2 and 4.4; PL sections 2 and 4.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> This missing information topic will be assessed by reviewing the clinical course of subjects in CTs B1871039 and B1871040 who are re-challenged with bosutinib after they experience a significant gastrointestinal event.</p>
Pregnancy	<p><u>Routine risk minimisation measures:</u> SmPC Section 4.6; PL Section 2.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p>
Carcinogenicity	<p><u>Routine risk minimisation measures:</u> SmPC Section 5.3.</p> <p><u>Additional risk minimisation measures:</u> None</p>	<p><u>Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:</u> None</p> <p><u>Additional pharmacovigilance activities:</u> A 6-month transgenic rasH2 mouse carcinogenicity study is planned in order to determine the potential tumourgenicity of bosutinib.</p>

SmPC = Summary of Product Characteristics; PL = Package Leaflet; CT = clinical trial; eGFR = estimated glomerular filtration rate

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The MAH should submit an updated RMP per separate type II variation within the next 3 months updating the following:

1. update the summary of safety concerns with “Increased toxicity due to interactions with CYP3A4 inhibitors, “Lack of efficacy due to interactions with CYP3A4 inducers or PPIs” as important identified risks and keep “long-Term Safety [>365 Days]” as a missing information. Please update the whole RMP accordingly.
2. update section III.2 and III.3 in line with “guidance on the format of the risk management plan (RMP) in the EU – in integrated format”. In particular the “PASS short name summary” should be included for all additional pharmacovigilance activities (III.2) and specific safety concerns should be listed (III.3). Safety concerns listed here need to be in line with the summary of safety concerns. In example, the rat pre- and post-natal development study addresses the safety concern “pregnancy”. Multiple safety concerns can be addressed in one study. E.g. studies CT B1871039 and Study CT B1871040 are “hepatotoxicity”, “GI toxicities”, “QT prolongation”, “renal dysfunction”, “cardiac safety”, “safety in patients with cardiac impairment” and “safety in patients with recent or ongoing clinically significant gastrointestinal disorders”. Please update in the RMP sections III.2, III.3 and other affected sections accordingly.
3. submission of a track change version of the RMP (indicating changes between the RMP v4.1 of this variation and the latest version)
4. add the column “Additional pharmacovigilance activities” for the missing information pregnancy, along with the respective non-clinical study, in section II.B (table 54).

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the SmPC is being updated with safety and efficacy data from studies B1871006 and B1871008.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Malta.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Bosulif is currently approved in EU for the treatment of adult patients with chronic phase, accelerated phase, and blast phase Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. A consultation with target patient groups (readability testing) was undertaken by an external consulting company during the initial MAA. The report from the above consultation was considered as satisfactory.

The current application is supporting the approval of a new indication for the treatment of adult

patients with accelerated phase, and blast phase Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options. The changes to the Package Leaflet due to this new application are limited to the indication wording and do not significantly alter the readability of the approved document.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Bosulif (bosutinib) is proposed for the additional therapeutic indication of treatment for adult patients with newly diagnosed Philadelphia chromosome positive chronic phase chronic myelogenous leukemia (Ph+ CP CML).

3.1.2. Available therapies and unmet medical need

Imatinib was approved for adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) CML for whom bone marrow transplantation is not considered as the first line of treatment in the EU in 2006. In 2010, dasatinib (Sprycel, orphan market exclusivity ended on 22 November 2016) was approved for the treatment of adult patients with newly diagnosed (Ph+) CML in the chronic phase and nilotinib (Tasigna, orphan market exclusivity until 21 November 2019) was approved the same year for the treatment of adult patients with newly diagnosed (Ph+) CML in the chronic phase.

3.1.3. Main clinical studies

The main evidence of efficacy is based on the AV001 study, a multicenter phase 3 randomized, open-label study of bosutinib versus imatinib in adult patients with newly diagnosed chronic phase CML.

3.2. Favourable effects

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

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

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

3.3. Uncertainties and limitations about favourable effects

N/A

3.4. Unfavourable effects

The most commonly reported Grade 3 or 4 TEAEs ($\geq 5\%$) were ALT increased, thrombocytopenia, AST increased and lipase increased, diarrhea, and neutropenia for patients receiving bosutinib compared with neutropenia, thrombocytopenia, and lipase increased for patients receiving imatinib. The Grade 3 or 4 TEAEs that were reported at a higher incidence ($\geq 5\%$ difference) in the bosutinib arm compared with the imatinib arm were thrombocytopenia, diarrhea, ALT increased, and AST increased.

The Grade 3 or 4 TEAE that was reported at a higher incidence ($\geq 5\%$ difference) in the imatinib arm compared with the bosutinib arm was neutropenia. The overall incidence of SAEs was 20.1% in the bosutinib arm vs. 17.0% in the imatinib arm. No SAEs were reported with an incidence of greater than or equal to 2% in either treatment arm.

The rate of discontinuations due to AEs was only slightly higher similar for the bosutinib arm and the imatinib arm (14.2% vs. 10.6%). The most common AEs leading to discontinuation of study drug in patients receiving bosutinib were ALT increased (4.9%) and AST increased (2.2%) compared with thrombocytopenia (1.5%) and myalgia (1.1%) in patients receiving imatinib.

3.5. Uncertainties and limitations about unfavourable effects

N/A

3.6. Effects Table

Table 43: Effects Table for Bosutinib in newly diagnosed PH+CP-CML (cut-off dates: 2 November 2016 / 30 March 2017 for MMR by 18 months)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Refer ences
			Bosutinib	Imatinib		
Favourable Effects						
Major molecular response (MMR) rate at 12 months	$\leq 0.1\%$ BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardized baseline) by RQ-PCR with at least 3,000 ABL transcripts	%	47.2 (40.9, 53.4)	36.9 (30.8, 43.0)	1-sided p-value=0.0100, (mITT)	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
			Bosutinib	Imatinib		
Complete cytogenetic response (CCyR) rate by 12 months	The absence of Ph+ metaphases in chromosome banding analysis of \geq 20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable	%	77.2 (72.0, 82.5)	36.2 (60.4, 72.4)	1-sided p-value=0.0037 (mITT)	
Unfavourable Effects						
Diarrhea	grade 3 or 4	%	7.8	0.8		
Hepato-toxicity	ALT increased	%	9.7	5.3		
	AST increased		9.7	1.9		
Thrombocytopenia	grade 3 or 4	%	9.0	4.2		
Grade 3 or 4 TEAEs	Grade 3 or 4 TEAEs	%	56.0	41.9	Significantly less events in comparison to 500mg dose in trial1008-3000WW	

Abbreviations: SAE: serious adverse event, TEAE: treatment emergent adverse events

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

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

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

3.7.2. Balance of benefits and risks

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

3.7.3. Additional considerations on the benefit-risk balance

Similar to other approved second and third generation CML-TKIs, bosutinib treatment was associated with a more rapid and deeper molecular responses compared with imatinib. This might indicate the potential for a more beneficial long-term outcome with bosutinib.

The fact that the drug has been approved since 2012 and the availability of post-marketing data in more than 8000 patients (in an orphan disease population), have contributed to the safety database and hence, the risks of bosutinib are considered well known. No new safety have been identified in the trial AV001.

In general, there is some overlap in adverse event profile and safety risk due to disease immanent and drug class effect safety events between bosutinib and the direct comparator imatinib as well as other approved second generation CML-TKIs.

In comparison to imatinib, bosutinib has a significantly higher hepatotoxicity detectable mainly in AST/ALT and bilirubin elevations. This risk seems to be the threefold higher with bosutinib; however, no Hy's law case was observed in trials AV001 and 1008-3000WW.

The gastrointestinal toxicity indicated by significantly higher incidence rates for diarrhoea, nausea and vomiting or increased lipase levels is clinical relevant and important as it may potentially impact patient's quality of life and well-being significantly. Although in this context it is reassuring that QoL data failed to show a difference between both arms and a decrease of vomiting and a trend for decreased severity of gastrointestinal TEAEs in general was observed for the applied 400 mg dose. However, no signal for an increased rate of gastrointestinal malignancies or other long term consequences of drug induced diarrhoea was detected up to now.

In conclusion, the higher general toxicity, particularly the hepatotoxicity and gastrointestinal toxicity is clinically important and long term consequences remain not fully evaluable at present. Although the slightly higher permanent discontinuation rate in bosutinib arm seems to confirm an inferiority regarding safety in comparison with imatinib, this seems to be not very pronounced.

3.8. Conclusions

The overall B/R of Bosulif is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML) for Bosulif based on study AV001. In addition, the MAH updated the SmPC with safety and efficacy information from studies B1871006 and B1871008. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 4.1 was agreed during the procedure. Furthermore, the Annex IIIA is brought in line with the latest QRD template version 10.

The group of variations leads to amendments to the Summary of Product Characteristics, Package Leaflet and Labelling and to the Risk Management Plan (RMP).

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Bosulif is not similar to Iclusig and Tasigna within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include treatment of adult patients with newly diagnosed Philadelphia Chromosome positive (Ph+) Chronic Phase (CP) Chronic Myelogenous Leukaemia (CML) for Bosulif based on study AV001. In addition, the MAH updated the SmPC with safety and efficacy information from studies B1871006 and B1871008. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated accordingly. Moreover, the updated RMP version 4.1 was agreed during the procedure. Furthermore, the Annex IIIA is brought in line with the latest QRD template version 10.

Summary

Please refer to Scientific Discussion: Bosulif H-2373-II-25-G-AR

References

1. Baccarani M, Deininger MW, Rosti G, et al. European LeukaemiaNet recommendations for the management of chronic myeloid leukaemia: 2013. *Blood* 2013; 122(6):872-84.
2. Cancer Research UK available at <http://www.cancerresearchuk.org/healthprofessional/cancer-statistics/statistics-by-cancer-type/leukaemia-cml/incidence>.
3. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 2006; 355(23):2408-17.
4. Etienne G, Dulucq S, Nicolini FE et al. Achieving deeper molecular response is associated with a better clinical outcome in chronic myeloid leukemia patients on imatinib front-line therapy. *Haematologica* 2014; 99(3):458-64.
5. Faderl S, Talpaz M, Estrov Z. The biology of chronic myeloid leukemia. *N Engl J Med* 1999; 341(3):164-72.
6. Fava C, Rege-Cambria G, Saglio G. The choice of first-line chronic myelogenous leukemia treatment. *Ann Hematol* 2015; 94 (Suppl 2): S123-31.
7. Flynn KE, Atallah E. Quality of life and long-term therapy in patients with chronic myeloid leukemia. *Curr Hematol Malig Rep* 2016; 11(2):80-5.
8. Hanfstein B, Muller MC, Hehlmann R et al. Early molecular and cytogenetic response is predictive for long-term progression-free and overall survival in chronic myeloid leukemia (CML). *Leukemia* 2012; 26(9): 2096-102.
9. Hughes TP, Saglio G, Kantarjian HM et al. Early molecular response predicts outcomes in patients with chronic myeloid leukemia in chronic phase treated with frontline nilotinib or imatinib. *Blood* 2014; 123:1353–60.
10. Jabbour E, Kantarjian H, O'Brien S, et al. The achievement of an early complete cytogenetic response is a major determinant for outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors. *Blood* 2011; 118(17):4541–6.
11. Lacroix D, Sonnier M, Moncion A, et al. Expression of CYP3A in the human liver evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. *Eur J Biochem* 1997; 247 (2):625-34.
12. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology – Chronic Myelogenous Leukemia. (Version 2.2017)
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
13. Quintas-Cardama A, Cortes JE. Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin Proc* 2006; 81(7):973-88.
14. Saglio G, Hochhaus A, Hughes TP et al. ENESTnd Update: Nilotinib (NIL) vs imatinib (IM) in patients (pts) with newly diag-nosed chronic myeloid leukemia in chronic phase (CMLCP) and the impact of early molecular response (EMR) and Sokal risk at diagnosis on longterm outcomes. *Blood* 2013; 122(21):92.
15. Saglio G, Kim DW, Issaragrisil S et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. *N Engl J Med* 2010; 362(24):2251–9.
13. SEER Chronic Myeloid Leukemia – Cancer Stat Facts available at <https://seer.cancer.gov/statfacts/html/cmyle.html>.

16. Stevens JC, Hines RN, Gu C, et al. Developmental expression of the major human hepatic CYP3A enzymes. *J Pharmacol Exp Ther* 2003;307(2):573-82.