London, 17 January 2013
EMA/70979/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bosulif

International non-proprietary name: **bosutinib**

Procedure No. **EMEA/H/C/002373**

Note

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

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Product information

Name of the medicinal product:	Bosulif
Applicant:	Pfizer Ltd. Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Active substance:	bosutinib monohydrate
International Nonproprietary Name/Common Name:	bosutinib
Pharmaco-therapeutic group (ATC Code):	Protein kinase inhibitors (L01XE14)
Therapeutic indication:	Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.
Pharmaceutical form:	Film-coated tablet
Strengths:	100 mg, 500 mg
Route of administration:	Oral use
Packaging:	Blister (PVC/ACLAR/PVC)
Package sizes:	28 tablets, 30 tablets

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List of abbreviations

AE	adverse event
ALT	aspartate aminotransferase
AP	accelerated phase
ASMT	advanced solid malignant tumours
AST	alanine aminotransferase
AUC	total area under the concentration-versus-time curve (AUC_T + CT/λz)
AUC_T	area under the concentration-time curve to the last observable concentration (C_T) at time T
BA	bioavailability
BC	blast crisis
BCR-ABL	breakpoint cluster region-abelson
BE	bioequivalence
BMI	body mass index
BP	blast phase
BSA	body surface area
CCyR	complete cytogenetic response
CHMP	Committee for Human Medicinal Products
CHR	complete haematologic response
CI	confidence interval
c-KIT	v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog
CL/F	apparent oral clearance
CL_{CR}	creatinine clearance
CL_R	renal clearance
C_{max}	peak/maximum concentration
CMH	Cochran-Mantel-Haenszel
C_{min}	minimum concentration
CML	chronic myelogenous leukaemia
CMR	complete molecular response
CNS	Central nervous system
CP	chronic phase
CrkL	v-crk sarcoma virus CT10 oncogene homolog (avian)-like
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DLT	dose limiting toxicity
DOE	Design of experiments
DSC	Differential Scanning Calorimetry
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
ER	estrogen receptor

erbB2	erythroblastic leukaemia viral oncogene homolog 2
FID	Flame Ionization Detector
FISH	fluorescence in situ hybridization
GC	Gas chromatography
GI	Gastrointestinal
GLP	Good laboratory practice
GRAS	Generally Recognised As Safe
hERG	Human ether-à-go-go related gene
HPLC	High Performance Liquid Chromatography
HRQOL	health-related quality of life
HSCT	haemopoietic stem cell transplantation
IC50	Concentration of drug required for 50% inhibition
ICH	International conference on harmonization
INN	International Non-Proprietary Name
IR	Infrared spectroscopy
IRIS	International Randomised Study of Interferon versus STI571
ITT	intent-to-treat
IV	Intravenous
K–M	Kaplan-Meier
L/h	liters per hour
Lyn	Yamaguchi sarcoma viral (v-yes-1) oncogene homolog
M2	oxydechlorinated bosutinib
M5	N-desmethyl bosutinib
MCyR	major cytogenetic response
MHR	major haematologic response
MMR	major molecular response
msec	millisecond(s)
MTD	maximum tolerated dose
NA	not applicable
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OHR	overall haematologic response
OS	overall survival
PCyR	partial cytogenetic response
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
Pgp	P-glycoprotein
PgR	progesterone receptor
Ph+	Philadelphia chromosome positive
Ph. Eur.	Pharmacopoeia Europea

PK	pharmacokinetic(s)
PRO	patient-reported outcomes
PVC	Polyvinul chloride
QD	once daily
QT interval	measure of time between the start of the Q wave and end of the T wave in the heart's electrical cycle
QTc	QT interval, corrected
QTcF interval	Fridericia's correction of QT interval
R	accumulation ratio
RH	relative humidity
RPT	report
RRT	Relative Retention Time
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SD	standard deviation
SE	standard error
SFK	Src family kinase
SR	slow release
Stat5	signal transducer and activator of transcription 5A
τ	time of the dosing interval
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
TEC	Tyrosin protein kinase
TKI	tyrosine kinase inhibitor
t_{lag}	absorption lag time
t_{max}	time to maximum or peak concentration
TR	target release
UV	ultraviolet
V_z/F	apparent volume of distribution
WBC	white blood cell
WW	worldwide

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 28 July 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bosulif, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. Eligibility for the centralised procedure was agreed by the EMA/CHMP on 29 June 2010.

Bosulif (bosutinib) 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 of chronic myeloid leukaemia.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Bosulif as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

The applicant applied for the following indication: Bosulif is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase (CP).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/170/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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 contained a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance bosutinib monohydrate contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 September 2007 and 17 December 2009. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: United States.

The product was not licensed in any country at the time of submission of the application.

Conditional marketing authorisation

The CHMP considered that bosutinib falls within the scope of Regulation (EC) No 507/2006:

Article 2(1) – medicinal product which aims at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

Article 2(3) – medicinal product designated as orphan medicinal product in accordance with Article 3 of Regulation (EC) No 141/2000.

In accordance with Article 3 (2) of Regulation EC No 507/2006, the CHMP proposed the application to be considered for a Conditional Marketing Authorisation based on the following claims:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

Based on post-hoc analyses from study 200-WW, bosutinib has demonstrated a positive risk-benefit balance in patients who had exhausted all available TKI therapies (imatinib, dasatinib and nilotinib) or for whom treatment with other available TKIs was deemed unsuitable by their physicians. This data includes patients with primary and acquired resistance as well as those with intolerance to the approved TKI.

- It is likely that the applicant will be in a position to provide comprehensive clinical data.

Additional comprehensive clinical data are likely to be provided from a clinical interventional study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Approximately 150 patients will be enrolled primarily at large medical centres in Europe and the United States, with the intent to enroll up to 75 patients in the 4th or later line setting.

The estimate probability of Major Cytogenetic Response (MCyR) (chronic phase) and Confirmed Overall Haematological Response (OHR) (accelerated and blast phase) by one year is proposed as primary endpoint. Efficacy data will be collected at regularly scheduled time-points at 3, 6, 9 and 12 months in the different CML patient populations.

It is expected that this study will further support the efficacy of bosutinib in the intended last-line treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.

The CHMP considered that this trial is feasible and that it is likely to provide comprehensive clinical data in the approved target population.

- Unmet medical needs to be fulfilled.

There is a lack of approved and standard of care pharmacological treatment for adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Beneficial effects have been reported in the proposed target population. The safety profile of bosutinib seems manageable with the proposed SmPC and RMP. In view of the unmet medical need, the benefits to public health of the immediate availability on the market of the medicinal product concerned outweigh the risk inherent in the fact that additional data are still required.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Harald Enzmann **Co-Rapporteur:Arantxa Sancho-Lopez**

- The application was received by the EMA on 28 July 2011.
- The procedure started on 17 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 November 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 08 November 2011 (Annex 2).
- During the meeting on 15 December 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 15 December 2011 (Annex 3).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 June 2012 (Annex 4).
- During the CHMP meeting on 21 June 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 12 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 November 2012 (Annex 6).
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant in which the granting of a conditional marketing authorisation was proposed (Annex 7).
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 14 December 2012.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 8 January 2013 (Annex 8).
- During the meeting on 17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Bosulif.
- The CHMP adopted a report on similarity of Bosulif with Glivec, Sprycel and Tasigna on 20 October 2011 (Appendix 1). In April 2012, Glivec was removed from the Community Register on Orphan medicinal products and is therefore no longer under market exclusivity protection. Since the CHMP concluded that Bosulif and Glivec are not similar, this has no effect on the outcome of the report on similarity adopted by the CHMP on 20 October 2011 (Appendix 1).

2. Scientific discussion

2.1. Introduction

Chronic myelogenous leukaemia (CML) is a haematopoietic stem cell disease characterised by a proliferation of granulocytes and their immature myeloid precursors including blast cells. The disease is causally linked to a characteristic cytogenetic abnormality resulting from a reciprocal translocation of the long arms of chromosomes 9 and 22. The shortened chromosome 22, known as the Philadelphia chromosome (Ph), is detected in at least 95% of patients with CML. As a result of the translocation, the terminal portion of Abelson kinase gene (c-abl) on chromosome 9 is juxtaposed to the proximal breakpoint cluster region (BCR) gene on chromosome 22, producing the breakpoint cluster region-Abelson kinase (BCR ABL) fusion gene or BCR-ABL rearrangement. The resultant oncogene encodes an enzyme, the Bcr-Abl oncoprotein, which exhibits constitutive tyrosine kinase activity. This oncoprotein phosphorylates numerous substrates, resulting in the dysregulation of intracellular signal transduction pathways for proliferation and genetic instability, apoptosis suppression, and cellular adhesion. CML is the most common phenotype of Ph+ leukaemias and is most frequently associated with a 210 kD Bcr-Abl fusion protein. The remaining 5% or fewer patients with CML do not have Ph but possess a BCR-ABL rearrangement (Ph-negative, BCR-ABL-positive), which can be detected by sensitive molecular techniques, such as RT-PCR or fluorescence in situ hybridization (FISH).

Untreated CML commonly progresses in 3 phases: chronic phase (CP), accelerated phase (AP), and blast phase (BP). The majority of patients are diagnosed during CP, which is characterised by an increased number of leukocytes and/or platelets and a bone marrow blast count less than 15%. If untreated, the initial CP lasts approximately 3 to 5 years. Progress often occurs through the AP to a terminal BP. AP may be marked by 1 or more of the following: increasing splenomegaly and leukocytosis, an increase of blasts to 15% to 29%, an increase of basophils to 20% or greater, thrombocytopenia, and clonal evolution. In BP, for which the median survival is 2-4 months, 30% or more of blood and bone marrow cells are blasts, and myeloid precursors may also form tumours in the lymph nodes, skin, and bone. Patients with BP are the most refractory to treatment and can be divided into 1 of 2 categories: those with myeloid disease and those with lymphoid disease. The rate of response to standard induction chemotherapy for patients in myeloid BP is approximately 20%, and the rate of complete remission is less than 10%. For patients in lymphoid BP, the rate of response is approximately 50%, but remissions are transient.

Haematopoietic stem cell transplantation (HSCT) is the only curative strategy for CML. Other treatments including chemotherapy, interferon alpha, and tyrosine kinase inhibitors (TKIs) are effective in controlling the disease to varying degrees in all populations. The utility of HSCT is largely limited to paediatric and younger adult patients, especially those with matched donors, and is associated with a substantial rate of morbidity and mortality. Because of this, alternate treatments

were developed, among which agents targeting the Bcr-Abl fusion protein, such as TKIs, are considered frontline therapy.

The first TKI was imatinib which was granted approval by the EC in November 2001. Between 17 and 25% of patients either fail or become intolerant to imatinib during the first 5 years of treatment, with an estimated annual rate of 3.3% after 1 year, 7.5% in 2nd year, 4.8% in 3rd year, 1.5% in 4th year, and 0.9% after 5 years of treatment. Second generation TKIs, dasatinib and nilotinib, were initially approved in 2006 and 2007, respectively, for the treatment of patients with resistance or intolerance to prior therapy including imatinib. In 2010, both substances were additionally approved for adult patients with newly diagnosed Ph+ CML in CP.

Both dasatinib and nilotinib have distinct safety profiles that may prohibit certain subjects from receiving them as treatment for CML. In patients who are resistant or intolerant to all TKIs currently available (imatinib, dasatinib and nilotinib), a high unmet medical need exists. Currently, if a stem cell transplantation cannot be performed, these patients have to be treated with interferon and cytostatic agents.

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

Additionally, cell migration and invasion via Src kinase activity were inhibited by bosutinib, with an IC50 of 3.5 nM, and a comparable inhibitory activity against other Src family kinases (SFKs). While Bcr-Abl kinase activity is the primary oncogenic driver in CML, SFK activity is believed to contribute to disease pathogenesis. SFKs associate with Bcr-Abl, resulting in activation of the SKFs, further phosphorylation of Bcr-Abl, and increased downstream signalling. Resistance to imatinib in culture has been associated with increased expression of the SFK Lyn, and dual Src/Abl inhibitors such as bosutinib retain therapeutic effectiveness in these instances.

This application was initially based on data of pivotal phase III study 3160A4-3000-WW, a randomised, open-label study in comparison with imatinib. At this time the proposed indication applied was:

> *Bosulif is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase (CP).*

Following review, the final indication for bosutinib proposed was:

> *Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.*

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as oval-shaped film-coated immediate release tablets containing bosutinib (as monohydrate) as active substance. Two strengths have been developed: 100mg and 500

mg. They are identified by different film-coat colours (yellow for the 100 mg tablets, red for the 500 mg tablets) and appropriate debossing ("100" or "500") on one side of the tablet and "Pfizer" on the other side.

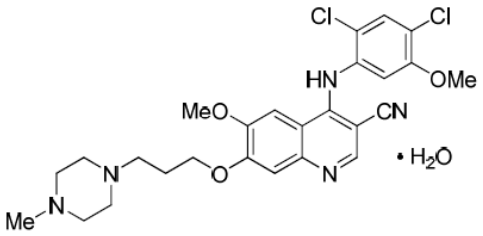
The composition of the product is described in section 6.1 of the SmPC.

The tablets are packed in white opaque 3-ply Polyvinyl chloride (PVC)/ACLAR/PVC blisters sealed with push-through foil backing.

2.2.2. Active Substance

Bosutinib monohydrate is a crystalline, non-hygroscopic white to yellowish tan powder with pH dependent aqueous solubility across the physiological pH range. At or below pH 5, it behaves as a high solubility compound; but above pH 5 its solubility reduces rapidly. It is soluble in acetone, methylethyl ketone, 2-propanol, ethyl acetate, methyl isobutyl ketone, acetonitrile, methanol; sparingly soluble in isopropyl acetate; and slightly soluble in toluene and heptanes.

The chemical name of bosutinib monohydrate is 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1). The molecular formula is $C_{26}H_{29}Cl_2N_5O_3 \cdot H_2O$ and the structural formula is as follows:



Bosutinib has a non-chiral molecular structure.

The chemical structure of the molecule has been established by spectral (FTIR, UV-VIS, mass spectrometry ESI-MS and ESI-MS/MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy) and elemental analysis.

Since bosutinib monohydrate (Form 1) is the thermodynamically favoured solid state form, this form was selected for development and commercialisation. Bosutinib monohydrate, the active substance of Bosulif, is a new active substance and is not described in any pharmacopoeia.

Manufacture

Bosutinib is supplied by one active substance manufacturer. It is synthesised in several steps using commercially available well defined starting materials. The manufacturing process conditions have been designed to robustly and reproducibly produce the monohydrate (Form 1).

The manufacturing process has been adequately described and critical in-process controls parameters have been well established and justified. Satisfactory specifications have been set for reagents, solvents and auxiliary materials used in the process.

Bosutinib monohydrate is packaged into a polyethylene bag (PE) which is inserted in a second PE and stored in in a metal drum or equivalent secondary container. Specifications and analytical reports for the packaging components have been presented and the suitability of the polyethylene bags for use with food and pharmaceuticals has been confirmed.

Specification

The active substance specification includes tests for appearance (visual), particle size (laser diffraction), identification (IR, HPLC), assay (HPLC), water content (Karl Fisher), residual solvents (GC-FID), residue ignition (Ph.Eur.), Palladium (ICP-OES), heavy metals (Ph.Eur.), and organic impurities (HPLC).

The absence of a test to confirm the solid state form in the drug substance specification has been adequately justified based on development studies, batch analysis data and stability studies which demonstrated that bosutinib monohydrate form 1 is consistently produced.

The specification proposed is suitable to control the quality of the drug substance manufactured using the current process, and has been established taking into account relevant ICH guidelines.

The non-compendial analytical methods have been adequately described and validated according to ICH Q2 (R1) guideline.

Batch analysis data on four commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Data from stability studies on three production scale batches have been provided. Samples were stored for up to 24 months under long term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH) in accordance with ICH requirements.

The following parameters were tested: appearance, assay (HPLC), water content (KF), impurities (HPLC), and crystallinity (PXRD). In all cases the batch analysis data met the predefined specification and no significant changes were observed.

In addition, a photostability study following ICH guideline Q1B was performed, revealing that bosutinib monohydrate drug substance is not light sensitive.

Stability data under stress conditions (acid, base, oxidation, heat and light) have been also provided to confirm the suitability of the assay and purity methods and to identify potential degradation products

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop immediate release tablets containing 100mg or 500 mg bosutinib monohydrate suitable for oral administration, once daily, in adult patients.

The development programme of the commercial bosutinib tablet formulation focused on the investigation physicochemical properties of the drug substance and excipients important for the manufacturability and performance of the product. The results of these studies were used to optimise the qualitative and quantitative composition of the formulation.

As mentioned above, Form 1 was selected for development and commercialization because it is the thermodynamically favoured solid form. Subsequent development studies confirmed that during

routine manufacture of the commercial drug product using the commercial manufacturing process, bosutinib monohydrate Form I was maintained through all processing steps.

Permeability studies conducted in accordance with the BCS classification guidance supported the classification of bosutinib as a low permeability drug. In addition, pharmacokinetic studies conducted showed that the in-vivo absorption of bosutinib is controlled by permeability rather than dissolution of the tablet formulation.

The excipients of this drug product were selected based upon their suitability for use and the compatibility studies performed. Based on the results, the following excipients were selected: microcrystalline cellulose as a diluent and compression aid, croscarmellose sodium as a disintegrant, poloxamer 188 as a binder and a solubilising/wetting agent, povidone as a binding agent and magnesium stearate as a lubricant. All these excipients comply with the Ph. Eur.

Suitable specifications have been set for the excipients used for film-coating. In addition statements that the colouring agents are controlled by Directive 2009/35/EC have been provided.Bosutinib tablets are packaged in PVC/Aclar/PVC blister material with aluminium foil backing. All packaging components are listed as 'Generally Recognised As Safe (GRAS)' or 'suitable for direct and/or indirect contact with food' per current EU Directives (i.e. 2002/72/EC) covering food packaging materials. All packaging components also comply, where applicable, with current European Pharmacopeia.

Adventitious agents

None of the excipients used in the manufacture of bosutinib 100 mg and 500 mg film coated tablets are of human or animal origin.

Manufacture of the product

The manufacturing process has been sufficiently described. The process is considered to be a standard manufacturing process.

Adequate in-process controls have been set up and a detailed description along with a process flow scheme have been provided.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. The in process controls are adequate for this tablets preparation.

The batch analysis data on three commercial scale batches for each of the strengths proposed (100 mg and 500 mg) shows that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

Product specification

The finished product release specifications include appropriate tests for appearance, identification (UV, HPLC), assay (HPLC), dissolution (UV), uniformity of dosage units (Ph.Eur.), degradation products (HPLC), total aerobic microbial count (Ph. Eur.), total combined yeast/mould count (Ph.Eur.), E. coli (Ph. Eur.), titanium dioxide and iron oxide identification (colorimetric).

The absence of a test for solid form in the drug product specification is justified based on batch analysis data and stability studies conducted on representative small scale 100mg and 500mg tablets manufactured using the proposed commercial formulation and by the commercial manufacturing process

The finished product specifications are considered appropriate for this dosage form, and they are in general in accordance with current guidelines and European pharmacopoeia.

Batch analysis results in three production scale batches of each strength confirm consistency and uniformity of manufacture and indicate that the process is capable and under control.

The non-compendial analytical methods have been adequately described and validated in accordance with ICH Q2 (R1).

Stability of the product

Stability data of three production scale batches of each strength of bosutinib film-coated tablets packaged in PVC/Aclar blisters stored under long term conditions (25°C/60% RH) or intermediate conditions (30°C/75% RH) for 24 months, and for 6 months under accelerated conditions (40ºC/75%RH) according to ICH guidelines were provided. Samples were tested for appearance (visual inspection), assay (HPLC), dissolution (UV), degradation products (HPLC) and microbial purity (Ph.Eur.) and water content. In all cases the batch analysis data met the predefined specification and no significant changes were observed.

Although the container used in the stability studies (PVC/Aclar blisters) was different from the proposed commercial packaging (PVC/Aclar/PVC blisters), suitable comparative permeability data showing equivalence of both systems has been presented.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the stability attributes monitored in this study confirming that bosutinib 100 mg and 500 mg tablets are not sensitive to light.

In conclusion, the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The medicinal product consists of oral immediate release film coated tablets. Relevant ICH/CHMP guidelines and Pharmacopoeial requirements have been followed in the quality documentation.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

The goal of the nonclinical studies was to support the registration of bosutinib for the treatment of CML.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Bosutinib was developed as a Src/Abl kinase inhibitor for the treatment of CML. The submitted pharmacodynamic studies confirm the antiproliferative activity of bosutinib. The drug inhibited Bcr-Abl signalling in a number of CML cell lines and in progenitor cells from patients at low nanomolar concentrations. Bosutinib also had pro-apoptotic activity as shown on CD34 positive cells from imatinib-resistant patients expressing different mutated forms of Bcr-Abl. Compared to imatinib, nilotinib and dasatinib, bosutinib showed little or no effect against the receptors c-Kit and PDGF (Platelet derived growth factor).

Besides Scr and Abl kinases, bosutinib showed inhibitory activities against a panel of other kinases, notably against the tyrosine protein kinase (TEC) family kinases, which are known to elicit immune-related side-effects. However, inhibition of TEC kinases through bosutinib had no or little influence on the observed side effects.

Various tumour xenograft models in nude mice were used to evaluate antitumour activity of bosutinib, including the K562 CML model. Bosutinib also was active in Src-transformed rat fibroblast tumours and other tumours which express Src, such as human colorectal, breast, prostate, pancreatic and lung tumours.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies showed that bosutinib inhibited alpha 1 (80%) and 2 (60%) non-selective adrenergic receptors; histamine H2 receptor (89%); non-selective muscarinic receptor (central) (64%); sodium site 2 ion channel (66%); serotonin transporter (71%); sigma non-selective receptor (76%); and neurokinin A receptor (63%).

Bosutinib demonstrated affinity toward receptors, ion channels, or transporters that have the potential for functional effects on the central nervous system (CNS) or peripheral nervous system (sodium channel, serotonin transporter, muscarinic receptor), cardiovascular system (sodium channel, alpha adrenergic receptor, muscarinic receptor, serotonin transporter), respiratory system (neurokinin A receptor, muscarinic receptor), gastrointestinal (GI) system (histamine 2 receptor, serotonin transporter), and immune system (neurokinin A receptor). Since signs of GI toxicity or irritation have been observed in both animal and human studies, it is possible that agonist activity of the H2 receptor or inhibition of the serotonin transporters may lead to increased gastric secretion or nausea, respectively, at clinically relevant concentrations of bosutinib. The potential for agonist activity at the neurokinin A receptor leading to a proinflammatory response is of low probability. While rash was observed in some patients, an inflammatory response was not observed in animal studies at concentrations exceeding those in humans.

Bosutinib M5 (*N*-desmethyl bosutinib) and M2 (oxydechlorinated bosutinib) metabolites were also profiled at concentrations up to 10 µM. For M5, less than 50% inhibition of binding or enzyme activity was observed against all targets except the A2A, adrenergic α1, D1, D2S, M1, M2, M3, NK2, 5-HT1B,

5-HT2A, and δ1 receptors, sodium (site 2) channels, and dopamine, choline transporters. The Ki/IC_{50} values of these receptors, ion channels, and transporters were ≥140 nM. For M2, less than 50% inhibition of binding or enzyme activity was observed against all targets except the A2A, adrenergic α1, D2S, H3, M1, M3, NK2, and 5-HT1B receptors, and dopamine and 5-HT transporters. The Ki/IC_{50} values of these receptors, ion channels, and transporters were ≥900 nM. These findings do not indicate a significant risk of effects from the metabolites at clinically relevant concentrations.

Safety pharmacology programme

Bosutinib did not affect respiratory or CNS parameters in female rats at doses up to 600 mg/kg. Other clinical observations were observed in both studies. Of notice is the occurrence of faecal alterations in the respiratory study, and in the CNS study a greater incidence of gait (≥ 300 mg/kg) and decreased pupil size (≥100 mg/kg) were noted. The NOEL for impaired gait occurred at exposures > 8-fold those in humans following the 500 mg dose and is therefore unlikely to be of relevance for humans.

Safety pharmacology studies with major bosutinib metabolites (M2 and M5) were restricted to hERG inhibition assays (studies PF05898965HERG and PF05312061HERG). Although neither study was conducted in compliance with GLP, the results seen for the standard comparator (terfenadine) in both studies were highly consistent with those seen in the GLP-compliant hERG inhibition studies (Chan test) with bosutinib. In addition, the hERG IC_{50} values obtained for the M5 and M2 metabolites (8.7 and 27.9 µM, respectively) were several times greater than both the maximum total human concentration of each metabolite after a 500-mg dose of bosutinib (93- and 503-fold, respectively), and the hERG IC_{50} for bosutinib (29 and 93-fold, respectively).

Bosutinib caused a concentration-dependent inhibition of the hERG current with IC_{50} values of 300 to 700 nM. These IC_{50} values are only approximately 13-fold higher than the unbound fraction C_{max} at the clinical dose of 500 mg. After single dose IV application of bosutinib in the dog, QTc prolongation was observed at all dosages tested (3 – 15 mg/kg). Since a prolonged QT interval is a biomarker for ventricular tachyarrhythmias, it can be concluded that bosutinib treatment is associated with a risk for adverse effects regarding safety pharmacology. This risk for ventricular arrhythmias such as torsade de pointes is discussed adequately in the SPC and the PL.

2.3.3. Pharmacokinetics

The pharmacokinetics of bosutinib was investigated using the intended oral route and the IV route of administration. Absorption was moderate to rapid in all species tested following oral administration of bosutinib, with t_{max} values ranging from 1.3 to 5.5 hours (absorption in humans was relatively slow with t_{max} ranging from 3 -6 hours). The half-life of bosutinib was moderate in mice and rats (2.5 to 5.4 hours) and long in dogs (13.5 to 17.7 hours). The mean half-life of bosutinib in healthy human subjects was longer still (33.8 hours). Clearance was moderate in mice and dogs (2.25 and 0.91, respectively) and high in rats (ranging from 7.68 to 4.22 in males and females, respectively). Gender differences were observed in rats. This effect could not be seen in dogs and mice since only female animals have been tested. Bosutinib concentration increased with increasing dose in rats and dogs. AUC-values on days 28 and 180 were approximately 3- to 5-fold higher in female rats than in male rats. Little or no accumulation of bosutinib or its circulating metabolite M5 (N-desmethyl bosutinib) was observed in plasma of rats given 50 mg/kg/day bosutinib for 56 consecutive days.

Bosutinib acts as a weak substrate for P-glycoprotein, BRCP and MRPs. Since the in-vivo studies showed a moderate oral bioavailability in the tested animals, it is likely that absorption of bosutinib is not limited by these efflux transporters.

Absorption of bosutinib was influenced by food: The results of a single dose study in female dogs showed that higher bosutinib exposures can be achieved in fed dogs compared with fasted dogs. However, the AUC-values under fasted and fed conditions were mostly similar, and since there was a high inter-individual variance as well as a very limited number of dogs (n=4), no conclusions can be drawn about the effect of food on the absorption of bosutinib from this study. Three different dog studies as part of the toxicokinetic evaluation showed similar results compared with the single dose study in female dogs. However, because the number of dogs was also very limited and inter-individual differences could be seen here as well, it seems likely that the bioavailability is higher under fed compared with fasted conditions but only to a minimal extent.

High radioactivity of bosutinib was observed in albino rats in the harderian gland (which is absent in adult humans, but present in the foetus and neonate), the small intestine, large intestine, liver and adrenal gland. In pigmented rats, bosutinib-derived radioactivity showed a high affinity for melanin-containing tissues, with higher exposures in the uveal tract than in the skin. The affinity for melanin-containing tissues indicated a potential for phototoxicity. However, in a follow-up photosafety study, bosutinib was found not to be phototoxic. No radioactivity was detected in the brain, indicating that bosutinib did not pass the blood-brain barrier. Toxicokinetic studies in pregnant rats showed that bosutinib can cross the placenta to reach the foetus. The drug is also excreted in the milk of lactating rats.

Bosutinib and the N-desmethyl bosutinib metabolite M5 are highly bound to plasma proteins (>93%) in mice, rats, rabbits, dogs, and humans. The blood to plasma ratio (about 1) in in-vitro and in-vivo studies showed that distribution of bosutinib into the blood cell and plasma compartment is comparable in the pre-clinical species and humans. Accumulation of bosutinib in red blood cells seems therefore unlikely.

The unchanged parent compound was found in plasma of humans and the examined animals. Although plasma metabolites could not be detected due to a dilution error in healthy humans after single dosing, the examination of plasma of humans with advanced malignant solid tumours and healthy subjects after multiple dosing showed similar results to those in animals. The primary route of excretion following oral administration was through the faeces. The bosutinib metabolites M2 (oxydechlorinated bosutinib) and M5 were the major metabolites found in humans and rats. Several other metabolites have been identified, but appear to play a minor role in metabolism. The safety of M2 was evaluated in a 6-month toxicity study in male rats, and plasma M5 concentrations were measured in the 2-year carcinogenicity study in rats.

The results of in-vitro studies indicate that CYP3A4 is the major enzyme responsible for metabolism. Drug-drug interaction studies of bosutinib in combination with ketoconazole or rifampicin confirmed the role of CYP3A4 in the metabolism of bosutinib. In human kidney microsomes the metabolite M6 was the major metabolite found and this metabolite was formed by FMO enzymes. However, FMOs contributed minimally to the formation of M6 in human liver microsomes. The metabolite M2 (as a circulating metabolite in human plasma) can be formed by both intestinal and hepatic UGTs.

2.3.4. Toxicology

Bosutinib safety was assessed in a series of nonclinical studies. These studies included single and repeat dose toxicity, genetic toxicity, reproductive and developmental toxicity, and phototoxicity evaluations. Safety studies were also performed on the prominent human metabolite M2 (PF-05898965) and the Relative Retention Time (RRT) 0.99 impurity. The oral route was used in the majority of these studies as it is the intended clinical route.

Single dose toxicity

The single-dose toxicity of bosutinib was evaluated in mice (RPT-52017; RPT-52016) and rats (RPT-52013; RPT-52015) after oral and IP administration at doses up to 2000 mg/kg (oral) and 200 mg/kg (IP). In each study, animals were observed for up to 15 days after dosing. Evaluations consisted of mortality, clinical observations, body weight, and macroscopic examination.

The maximum non-lethal doses were 2000 mg/kg in mice and 700 mg/kg in rats when given as a single oral dose. With an intraperitoneal (IP) single dose injection, the maximum non-lethal dose and the no-observed-adverse-effect level (NOAEL) were 20 mg/kg in mice and 70 mg/kg in rats.

Repeat dose toxicity

The repeat-dose toxicity of bosutinib was evaluated in rats in a 7-day oral (gavage) dose-ranging study (RPT-49310), two 1-month toxicity studies (1 with a 1-month recovery period) (RPT-52772; RPT-57924), a 6-month toxicity study (RPT-63644), and in dogs in a 10-day oral (gavage) dose-ranging study (RPT-50039), 1-month toxicity study (RPT-52074), 2-week tolerability study (RPT-60569), and a 9-month toxicity study (with a 1-month recovery period) (RPT-65542).

These studies are summarised in tables 1 and 2.

Repeat dose toxicity studies in rats

Table 1. Repeat dose toxicity studies with bosutinib in rats

Study ID	Species/ Number/ Sex/ Group	Dose (mg/kg)/ Route	Duration	NOEL/ NOAEL (mg/kg/ day)	Major findings
RPT-49310 (DRF) GLP: no	Rats (S-D) /5	0, 100, 300, 1000 / oral gavage	7 days	MTD = 100	**Died or sacrificed moribund:** **≥ 300 mg/kg:** All animals electively euthanised on day 4 (300 mg/kg) and day 3 (1000 mg/kg) **Clinical observations:** **100 mg/kg:** - faecal alterations (soft or mucoid) - clinical observations (red pigment around the nose/mouth) - food consumption↓ - postmortem observations (intestinal tract, mesenteric lymph nodes, spleen, and liver) **≥ 300 mg/kg:** faecal alterations, dehydration, ataxia, decreased motor activity BW or BWG ↓ food consumption ↓ **Organ weight:** Liver, adrenal glands ↑ (F) **Macroscopic:** **100 mg/kg:** distention of jejunum, ileum, caecum, colon (F) discoloured mesenteric lymph node (M/F) **≥ 300 mg/kg:** distention of the glandular and squamous stomach, duodenum, jejunum, ileum, caecum and colon, discoloured mesenteric lymph nodes, small spleen **Microscopic:** **100 mg/kg:** *Duodenum, jejunum, ileum, colon:* dilation of lumen; hypertrophy/hyperplasia of globet mucosa *Mesenteric lymph node:* sinusoidal erythrocytosis *Spleen:* depletion of marginal zone *Liver:* hepatocellular hypertrophy *Lung:* alveolar macrophages

RPT-52772 GLP: yes + TK	Rats (S-D) /15	0, 10, 30, 70 / oral gavage	1-months	70	**Died or sacrificed moribund:** 1M (control); 1F (70 mg/kg, TK) **Histopathology:** ***≥ 10 mg/kg:*** Mesenteric lymph nodes: Sinus erythrocytosis, hämosiderosis
RPT-57924 GLP: yes + TK	Rats (S-D) / 15	0, 100, 200 / oral gavage	1-months / 1 months recovery	<100	**Died or sacrificed moribund:** 1M, 1F (100 mg/kg); all animals (200 mg/kg) **Clinical observations:** **200 mg/kg:** - Faecal alterations - Dehydration - Red pigment, nose/mouth - Yellow discoloration, perineal pelage - High carriage - Thin, hunched appearance **Body weight:** **≥ 100 mg/kg:** ↓ **Food consumption** **≥ 100 mg/kg:** ↓ **Haematology:** **≥ 100 mg/kg:** RBC, HBG, HCT, NEU, FBGN ↑ **Organ weight:** **100 mg/kg:** adrenal, heart, liver, spleen ↑ **Macroscopic Pathology:** **100 mg/kg:** *Thymus:* small (1F) *Mesenteric lymph node:* discoloration (9M/9F) *Spleen:* discoloration (2F) *Uterus:* agenesis **Histopathology:** ***100 mg/kg (final necropsy):*** *Squamous Stomach:* Ulceration, hyperkeratosis *Caecum:* mucosal hypertrophy *Colon:* mucosal hypertrophy *Jejunum:* Globet cell hypertrophy/hyperplasia (1F) *Ileum:* Globet cell hypertrophy/hyperplasia (1F) *Liver:* hepatocellular hypertrophy *Mesenteric lymph node:* Sinus erythrocytosis (1M/1F), lymphoid atrophy (1F), pigment (1F) *Spleen:* lymphoid atrophy, capsular fibrosis (F) *Thymus:* lymphoid atrophy (F) ***200 mg/kg (unscheduled necropsy):*** *Caecum:* Haemorrhage, Mucosal hyperplasia, Oedema, Lumenal dilatation *Colon:* Haemorrhage, Mucosal hyperplasia, Oedema, Lumenal dilatation *Duodenum:* Villus atrophy, Haemorrhage, Lumenal dilatation, Mucinous glandular hyperplasia *Jejunum:* Villus atrophy, Haemorrhage, Lumenal dilatation, Mucinous glandular hyperplasia *Ileum:* Villus atrophy, Haemorrhage, Lumenal dilatation, Mucinous glandular hyperplasia *Liver:* necrosis, hepatocellular hypertrophy *Mesenteric Lymph Nodes:* Sinus erythrocytosis lymphoid atrophy, pigment *Mandibular Lymph Nodes:* Lymphoid atrophy *Spleen:* Lymphoid atrophy *Thymus:* Lymphoid atrophy *Pancreas:* zymogen depletion *Bone marrow:* hypocellularity *Prostate:* atrophy *Seminal vesicle:* atrophy *Mammary gland:* atrophy *Adrenal Cortex:* hypertrophy, lipidosis *Lung:* alveolar macrophages **Recovery:** **100 mg/kg:** BW ↓ Food consumption ↓ (F)

					Organ weight: spleen, thymus ↑ ***Histopathology:*** mesenteric lymph node: sinus erythrocytosis (1F)
RPT-63644 GLP: yes + TK	Rats (S-D) / 15	0, 10, 30, 100/70 / oral gavage	6-months	30 (M) 10 (F)	**Died or sacrificed moribund:** 3M (control); 2M (10 mg/kg); 2M, 1F (30 mg/kg); 3M, 7F (100/70mg/kg) **Clinical observations:** 100/70 mg/kg: - soft/liquid faeces - salivation - red pigment, nose/mouth - rough hair coat - faeces adherent to fur (F) - yellow discoloration, perineal pelage (F) - alopecia, neck/thorax (F) - decreased motor activity (F) - pale and/or hunched appearance (F) **Body weight:** 30 mg/kg ↓ (F) 100/70 mg/kg ↓ **Haematology:** ≥ 10 mg/kg: EOSIN (F) ↑ ≥ 30 mg/kg: NEU, FBGN, EOSIN (M), MONO (F), PLT ↑ 100/70 mg/kg: WBC, RDW ↑; RBC, HGB, HCT ↓ **Clinical chemistry:** ≥ 10 mg/kg: GLOB (F) ↑ ≥ 30 mg/kg: ALB (F) ↓, GLOB (M) ↑ 100 mg/KG: ALB; INPH, CHOL, TP ↓ **Organ weights:** ≥ 10 mg/kg: heart, liver (F), ovaries, pituitary, testes ↑, thyroid ↓ ≥ 30 mg/kg: liver (M) ↑ 100/70 mg/kg: adrenals, brain (relative to body weight) ↑ **Macroscopic pathology:** ***≥ 10 mg/kg:*** *Mesenteric lymph node:* discoloration *Thyroid:* enlarged (2M) ***≥ 30 mg/kg:*** *Mesenteric lymph node:* enlarged (M) ***100/70 mg/kg:*** *Duodenum:* distended, thickened wall *Jejunum:* distended, thickened wall *Ileum:* distended, thickened wall *Thyroid:* enlarged (3F) **Histopathology:** ***≥ 10 mg/kg:*** *Ileum:* globet cell hypertrophy/hyperplasia *Mesenteric lymph node:* sinus erythrocytosis, pigment (haemosiderin) ***≥ 30 mg/kg:*** *Duodenum:* mucosal hyperplasia *Ileum:* haemorrhage (M) ***100/70 mg/kg:*** *Duodenum:* lumenal dilatation, haemorrhage *Jejunum:* mucosal hyperplasia, luminal dilatation (1M), Haemorrhage (1M) *Ileum:* luminal dilatation *Adrenal Cortex:* vacuolation, hypertrophy (F) *Thyroid:* increased colloid (F) *Mammary Gland:* atrophy (F) *Spleen:* lymphoid atrophy (F) *Thymus:* lymphoid atrophy

In a 7 day dose ranging study in rats, bosutinib was administered by oral gavage at dosages of 0, 100, 300, or 1000 mg/kg/day. Mortality occurred at ≥ 300 mg/kg/day as a result of poor clinical condition (including faecal alterations, dehydration, ataxia, decreased motor activity) and decreased body weight or body-weight gain and food consumption. At 100 mg/kg/day, bosutinib-related faecal alterations (soft or mucoid), clinical observations (red pigment around the nose/mouth), decreased food

consumption, and postmortem observations (intestinal tract, mesenteric lymph nodes, spleen, and liver) were not considered dose-limiting because they did not affect the overall health of the animals.

In a 1 month oral toxicity study in rats, bosutinib was administered by oral gavage at dosages of 0, 10, 30, or 70 mg/kg/day. Compound-related erythrocytosis and haemosiderosis were found in the mesenteric lymph node at ≥ 10 mg/kg/day. However, these effects were not considered adverse because there was no macroscopic or microscopic evidence of haemorrhage in the GI tract and there was no compound-related decrease in parameters of red cell mass. Therefore, in this study, the NOAEL of bosutinib was 70 mg/kg/day, the highest dosage administered.

In a second 1 month toxicity study in rats with a 1-month recovery period, bosutinib was administered by oral gavage at dosages of 0, 100, or 200 mg/kg/day. Mortality due to poor clinical condition occurred at 200 mg/kg/day; clinical observations in these animals were consistent with bosutinib-induced gastrointestinal (GI) toxicity. At 100 mg/kg/day, decreased body weight was associated with GI toxicity (sinus erythrocytosis and haemosiderosis of the mesenteric lymph nodes; goblet cell hypertrophy/hyperplasia of the small intestine; and mucosal hyperplasia of the caecum or colon). Based on the presence of decreased body weight and evidence of GI toxicity, the NOAEL was determined to be < 100 mg/kg/day.

In a 6 month toxicity study in rats, bosutinib was administered orally (gavage) at dosages of 10, 30, or 100/70 mg/kg/day. The high dosage of 100 mg/kg/day was lowered to 70 mg/kg/day in week 7 because of mortality, the severity of clinical observations and the magnitude of decrease in body weight in this group. The cause of death was bosutinib induced GI toxicity, which was manifested as faecal alterations, debilitation, and body-weight loss in males (18%) and females (12%), as well as macroscopic (red mucosal foci, diffuse mucosal discoloration, abnormal contents, and/or distension of stomach and intestine) and microscopic (haemorrhage, erosion and oedema of the caecum and colon; haemorrhage, erosion, mixed cell inflammation and mucosal hyperplasia of the duodenum, jejunum, and ileum; and sinus erythrocytosis; and haemosiderin pigment in the mesenteric lymph nodes) findings in the GI tract in females. At dosages of 10 and 30 mg/kg/day, there were no effects of bosutinib administration on body weight or food consumption. There was 1 death in a female at 30 mg/kg/day on day 168. Although there was no macroscopic or microscopic evidence of GI toxicity, this death was considered possibly bosutinib related based on clinical signs. Intestinal lesions were observed at 10, 30, and/or 100/70 mg/kg/day (surviving animals), but were not adverse because of their slight to mild severity. Based on mortality and decreases (18% in males and 12% in females) in mean body weights observed at 100/70 mg/kg/day, the NOAEL was 30 mg/kg/day in males. Based on the bosutinib related death in 1 female administered 30 mg/kg/day, the NOAEL in females was 10 mg/kg/day.

Repeat dose toxicity studies in dogs

Table 2. Repeat dose toxicity studies with bosutinib in dogs

Study ID	Species/ Number/Sex/ Group	Dose (mg/kg)/ Route	Duration	NOEL/ NOAEL (mg/kg/ day)	Major findings
RPT-50039 (DRF) GLP: no	Dogs (Beagle)/2 or 3 F	0, 5 (fed), 37.5 (fed), 37.5 (fasted), 75 (fasted), 150 (fasted)/ oral gavage	10 days	MTD = 5	**5 mg/kg:** bosutinib related faecal alterations (soft, mucoid, liquid, and/or containing red pigment) occurred but were not considered dose-limiting. **≥ 37.5 mg/kg:** - dose-limiting emesis - faecal alterations **150 mg/kg:** - cessation of dosing or elective euthanasia after 1 to 3 days - BW ↓ - food consumption ↓ - red or brown discolorations of the mucosa in the GI tract and discoloration of the mesenteric and mediastinal lymph nodes
RPT-52074 GLP: yes + TK	Dogs (Beagle)/ 3	0, 0.5, 1.5, 5/ oral gavage	1 month	5	**Died or sacrificed moribund:** 1M (5 mg/kg) **Clinical observations:** **≥ 1.5 mg/kg:** faecal alterations
RPT-60569 (DRF) GLP: no	Dogs (Beagle)/ 2M	10, 20/ oral gavage/ fed	14 days	MTD: 10	**≥ 10 mg/kg:** emesis, faecal alterations, decreased motor activity, thin appearance, BW ↓, food consumption ↓ clinical pathology parameters: increases in red cell mass, BUN, decreases in glucose, increases in WBC, NEU, Mono, FBGN, PLT
RPT-65542 GLP: yes +TK	Dogs (Beagle)/ 7	0, 1, 3, 10/ oral gavage	9-months/ 1 month recovery	10	**Clinical observations:** **≥1 mg/kg:** faecal alterations **10 mg/kg:** emesis **Clinical chemistry:** **10 mg/kg:** TP, ALB, CHOL, Ca ↓ **Histopathology:** **10 mg/kg:** *Duodenum:* crypt abscess

In a 10 day dose-ranging study in dogs, 5 mg/kg/day was tolerated. At this dosage, bosutinib related faecal alterations (soft, mucoid, liquid, and/or containing red pigment) occurred but were not considered dose-limiting. At ≥ 37.5 mg/kg/day, dose-limiting emesis, faecal alterations, and/or body-weight loss (0.5 to 1.1 kg) were observed and at 150 mg/kg/day resulted in cessation of dosing or elective euthanasia after 1 to 3 doses. In addition, red or brown discolorations of the mucosa in the GI tract and discoloration of the mesenteric and mediastinal lymph nodes were observed at 150 mg/kg/day.

In a 1 month oral toxicity study in fed dogs, bosutinib was administered by oral gavage at dosages of 0, 0.5, 1.5, or 5 mg/kg/day. An increase in incidence and/or frequency of faecal alterations (mucoid, liquid, containing red pigment) occurred in males and females at ≥ 1.5 mg/kg/day. These clinical observations were not considered adverse because they were sporadic, transient, and infrequent; they were not associated with toxicologically meaningful decreases in body weight or food consumption, or with toxicologically meaningful alterations in clinical pathology, macroscopic, or microscopic parameters; and they did not affect the overall health of the animals; therefore, the NOAEL was 5 mg/kg/day.

In a 2 week tolerability study in dogs, bosutinib was administered at dosages of 10 and 20 mg/kg/day to further characterise bosutinib-induced toxicity and select dosages for future toxicity studies in dogs. Dose-limiting emesis, faecal alterations, decreased motor activity, and body-weight loss (up to 2 kg

compared with pretest) occurred at 20 mg/kg/day. The dosage of 10 mg/kg/day was tolerated with no dose-limiting effects.

In a 9 month toxicity study in dogs, bosutinib was administered orally (gavage) at dosages of 0, 1, 3, or 10 mg/kg/day. Faecal alterations and/or emesis were observed at ≥ 1 mg/kg/day and 10 mg/kg/day, respectively. The faecal alterations correlated with slight reductions in albumin (5% to 28%) and total protein (2% to 20%) and, microscopically, with slight crypt abscesses in the duodenum. These findings were not considered adverse because they were sporadic, transient, and did not affect the overall health of the animals. Based on the absence of adverse effects at any dosage in this study, the NOAEL was 10 mg/kg/day, the highest dosage administered.

Genotoxicity

Table 3. Overview of genotoxicity studies with bosutinib

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria / RPT-46058 / yes screening assay	Salmonella strains TA98, 100	+/- S9: 0, 10 – 5000 µg/plate	negative
Gene mutations in bacteria / RPT-49003 / yes	Salmonella strains TA98, 100, 1535, 1537 E. coli WP2 uvrA	+/- S9: 0, 1 – 1000 µg/plate	negative for genotoxicty for significant bacteriotoxicity MTD was chosen at 1000 µg/plate (moderate to extreme reduction of background lawn at 333 or 667 µg/plate and above)
Chromosomal aberration in mammalian cells / RPT-50322 / yes	human peripheral blood lymphocytes	- S9 4 and 20h treatment: 0, 0.25 – 2.5 µg/ml + S9 4h treatment: 0, 0.25 – 2.5 µg/ml	negative for chromosomal aberration mitotic index decreased ≥ 50% at 2.5 µg/ml and above
Chromosomal aberrations in vivo / RPT-52501 / yes	CD-1 mouse males only, 6 or 7/dose and time point micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg single dose, oral (gavage) sampling 24h and 48h post dose	negative for micronuclei
supporting toxicokinetic study / PRT-52338 / yes	24 CD-1 mouse males only	2000 mg/kg, single dose, oral gavage, sampling 0, 0.5, 1, 2, 4, 8, 12, 24 h post dose	Tk results: mean C_{max} 9811 ± 3998 ng/ml, mean AUC_{0-24h} 172495 ± 26050 ng*h/ml, t_{max} 2h

Table 4. Overview of genotoxicity studies with oxydechlorinated bosutinib (M2)

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria / RPT-73086 / yes	Salmonella strains TA98, 100, 1535, 1537 E. coli WP2 uvrA	+/- S9: 0, 50 – 5000 µg/plate	negative for genotoxicty
Chromosomal aberration in mammalian cells / RPT-73087 / yes	human peripheral blood lymphocytes	- S9 4h treatment: 0, 10 – 25 µg/ml - S9 20h treatment: 0. 5 – 15 µg/ml + S9 4h treatment: 0, 5 – 15 µg/ml	negative for chromosomal aberration reduction of mitotic index ≥ 50% at and above 25 or 15 µg/ml

Bosutinib and its human metabolite oxydechlorinated bosutinib (M2) were tested in standard test for genotoxicity with no evidence for any relevant genotoxic potential.

Carcinogenicity

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.

Neoplastic findings in treated groups were thyroid follicular cell tumours in males, pituitary tumours in males, skin fibromas in males and females, schwannoma in males, lipoma/liposarcoma combined in females and squamous cell papilloma/keratoacanthoma/ squamous cell carcinoma combined in females. These tumours although showing statistical significance compared to combined vehicle controls by trend analysis or pairwise comparison with Peto were however not considered treatment-related.

Overall, no relevant treatment related increase in neoplastic lesion was shown.

Reproduction Toxicity

The reproductive and developmental toxicity of bosutinib was evaluated in rats and rabbits. These included studies on male and female fertility in rats and embryofoetal developmental studies in female rats and rabbits. A summary of the studies is given in the table below.

Table 5. Reproductive and developmental toxicity studies with bosutinib in rats and rabbits

Study type / Study ID / GLP	**Species; Number / group**	**Dose (mg/kg/day) / Route**	**Dosing period**	**Major findings**	**NOAEL (mg/kg &AUC)**
Fertility and developmental DRF/ RPT-61450/ GLP: no	Rats (S-D); 10/sex/group	0, 10, 30, 100/ oral (gavage)	M: 7.5 weeks F: 5 to 6 weeks	**Paternal effects:** Clinical observations: ≥ 10 mg/kg: salivation, BW ↓, food consumption↓ 30 mg/kg: discoloration of mesenteric lymph node **Maternal effects:** ≥ *10 mg/kg:* gravid uterine weight ↓ *30 mg/kg:* faecal changes, salivation Body weight ↓ Macroscopic: enlargement of mesenteric lymph node *100 mg/kg:* all animals electively euthanised after 3 dosages (loose/decreased faeces, yellow fur discoloration, red pigment around eyes/nose/mouth, body weight loss, decreased food consumption); macroscopic: discoloration of mesenteric lymph node, GI-toxicity (fluid in small and large intestine) distended stomach), enlarged adrenal (increased corticosteroid release) **Caesarean section and foetal data:** ≥ 10 mg/kg - number pregnant dams ↓ - number viable foetuses ↓ - number of implantations ↓ - early resorptions ↑ - number of corpora lutea ↑	
Male fertility/ Female	Rats (S-D) M: 25	M: 0, 10, 30, 70 F: 0, 3, 10, 30/	M: 7 weeks	**F_0 Males:** *Died or sacrificed moribund:* 1M (70	F_0 Males:

Study type / Study ID / GLP	Species; Number / group	Dose (mg/kg/day) / Route	Dosing period	Major findings	NOAEL (mg/kg &AUC)
fertility/ RPT-63257/ GLP: yes	F: 25	oral gavage	(4 week PM to GD 7) F: 3-6 weeks (2 weeks PM to GD 7)	mg/kg) *Clinical observations:* ≥ 30 mg/kg: salivation, red pigment around nose/mouth, faecal alterations, positive skin tend 70 mg/kg: red pigment around eyes, yellow discoloration, perineal pelage, thin appearance, faeces adhered to fur *Body weight:* 70 mg/kg: ↓ *Body weight gain:* 70 mg/kg: ↓ *Premating food consumption:* 70 mg/kg: ↓ *Fertility index (%):* 70 mg/kg: ↓ (-16%) **F_0 Females:** *Clinical observations:* ≥ 3 mg/kg: yellow discoloration, perineal pelage ≥ 10 mg/kg: salivation *Premating body weight gain:* ≥ 10 mg/kg ↑ *Premating food consumption:* ≥ 10 mg/kg ↑ *Gestation weight gain:* 30 mg/kg ↓ *Gestation food consumption:* 30 mg/kg ↓ *Gravid uterus weight:* 30 mg/kg ↓ Total resorption: ≥ 10 mg/kg ↑ *% Preimplatation loss:* 30 mg/kg ↑ **Hysterectomy findings:** ≥ 10 mg/kg: total resorptions ↑; % resorptions ↑, % resorbed or dead ↑ 30 mg/kg: live embryos ↓, viable embryos ↓	30 F_0 Females: 3
Embryo-fœtal development/ RPT-63107/ GLP: yes + TK	Rats (S-D) 25 F/group	0, 1, 3, 10/ oral (gavage)	GD 6 through GD 17	**F_0 females:** none **Litters from F_0 treated females:** *Fetal anomalies:* *≥ 3 mg/kg:* Visceral: dilated renal pelvis *10 mg/kg:* Skeletal: reduced ossification frontal, parietal and interparietal bones	F_0: 10 F_1: 10
Embryo-fœtal development - DRF/ RPT-62710/ +TK (RPT-64285)	Rabbits (NZW)/ 8 F	0, 10, 30, 60/ oral (gavage)	GD 6 through GD 19	**≥ 10 mg/kg:** BW ↓ Food consumption ↓, Gravid uterus weight ↓ **≥ 30 mg/kg:** faeces ↓ foetal body weight ↓ **60 mg/kg:** 2F euthanised on GD 15 or GD 16 (clinical signs, BW ↓, food consumption ↓, distended caecum with abnormal content, large intestine) number of pregnant animals ↓ number of viable foetuses ↓ early resorption ↑, early interruption of pregnancy (3F) granular placentas ↑	
Embryo-fœtal development/ RPT-65533/ +TK	Rabbits (NZW)/ 20 F	0, 3, 10, 30/ oral gavage	GD 6 through GD 19	**F_0 females:** *Died or sacrificed moribund:* 1 (3 mg/kg) gavage trauma *30 mg/kg:* faecal alterations (none. loose, decreased, red pigment in faeces, faeces adhered to fur)	F_0: 10 F_1: 10

Study type / Study ID / GLP	Species; Number / group	Dose (mg/kg/day) / Route	Dosing period	Major findings	NOAEL (mg/kg &AUC)
				BW ↓ Food consumption ↓ Gravid uterus weight ↓ **Litters from treated F_0 females:** *≥ 3 mg/kg:* Fetal anomalies: Skeletal: Fused sternebrae *10 mg/kg:* early resorption ↑ % postimplantation loss ↑ *30 mg/kg:* Fetal anomalies: Visceral: - gallbladder absent (4 foetus of 2 litters) - cardiomegaly (1 foetus) - enlarged liver (1 foetus) - hydrocephaly (1 foetus)	

In a rat fertility study, fertility was slightly decreased in males. In females increased embryonic resorptions and decreases in implantations and viable embryos were observed. The dose at which no adverse reproductive effects were observed in males (30 mg/kg/day) and females (3 mg/kg/day) resulted in exposures equal to 0.6 and 0.3-fold, respectively, the human exposure resulting from the clinical dose of 500 mg.

There was no evidence of adverse developmental toxicity in rats at exposures equal to 0.5-fold the human exposure at the 500 mg dose (based on unbound AUC in the respective species). In a rabbit developmental toxicity study there were fetal anomalies observed (fused sternebrae, and two fetuses had various visceral observations), and a slight decrease in fetal body weight. The exposure at the highest dose tested in rabbits (10 mg/kg) that did not result in adverse fetal effects was 0.7-fold that in humans at the 500 mg.

Studies on pre- and postnatal development have not been conducted with bosutinib. Those studies are not warranted for the proposed indication in the treatment of an advanced cancer, in line with ICH guideline S9.

Toxicokinetic data

The toxicokinetics of bosutinib were evaluated as part of oral repeat-dose dose-ranging and pivotal toxicity studies in rats and dogs, developmental and reproductive toxicity studies in rats and rabbits, and in support of a mouse micronucleus assay and in a 2-week toxicity study with M2.

Bosutinib exposure in rats and dogs, as defined by C_{max} and AUC (0-24), increased with increasing dose over the dose ranges tested. In studies with repeated daily administration, there were no gender differences in dogs. For rats, systemic exposure of bosutinib in the 1-month and 6-month oral toxicity study was higher in females compared to males at all dose groups. Exposure was generally increased at the end of the study compared to Day 1 exposure, although the accumulation was low to moderate in rat and dog plasma.

Local Tolerance

Specific local tolerance studies with bosutinib were not conducted. The oral local tolerance was evaluated in toxicological studies.

Other toxicity studies

Bosutinib was not found to be phototoxic in rats exposed to ultraviolet radiation. No toxicities were identified for the M2 metabolite and RRT 0.99 impurity. The Applicant appropriately justified that impurity RRT 0.99 does not have genotoxic potential and clarified that the level of this impurity in the current lots of bosutinib was below the qualification threshold for non-genotoxic impurities

2.3.5. Ecotoxicity / environmental risk assessment

The applicant submitted an environmental risk assessment on the active ingredient bosutinib. The ERA included a Phase I and Phase II assessment, Tier B terrestrial environmental fate and effects analysis. In result of the risk characterisation it can be concluded that bosutinib is unlikely to represent a risk to the environment.

Table 6. Summary of main study results

Substance Bosutinib			
CAS-number :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:open	no
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}		
	BCF	60	no
Persistence	DT50 or ready biodegradability	**OECD 308:** $DT_{50\ whole\ system}$ (20°C) 1260 d (FOMC recalculated) **OECD 307:** $DT_{50\ geomean}$ (20°C) 231d (SFO)	vP vP
Toxicity	NOEC or CMR	NOEC (fish)=0.034 mg/l	Not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	$PEC_{surfacewater\ refined}$ 0.015	µg/L	> 0.01 threshold Y
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 …	Activated sludge: 10 233 L/kg Silty clay loam sediment: 97 724 L/kg Sand sediment: 275 423 L/kg	List all values
Ready Biodegradability Test	OECD 301	not provided	not necessary since OECD 308

					provided
Biodegradation in activated sludge	OECD 314 B	Mineralisation: 0,24 %/ 28 d Primary degradation: 6,1 %/ 28 d Not extractable residues: 44,9 %/ 28 d			not relevant for risk assessment
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 Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	30	µg/L	*Pseudokirch-neriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	145	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	34	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	$>10^6$	µg/L	

2.3.6. Discussion on non-clinical aspects

Bosutinib was shown to inhibit the Src and Abl tyrosine kinase families with low nanomolar antiproliferative and pro-apoptotic activity in chronic myelogenous leukaemia cell lines. Bosutinib also exhibited antitumour activity in the subcutaneous K562 CML model. Besides Src and Abl, bosutinib inhibits certain other receptor and non-receptor tyrosine kinases and certain serine/threonine kinases which could have the potential to mediate other/additional adverse effects as already known from the approved inhibitors imatinib, dasatinib, and nilotinib. Safety pharmacology studies exhibited a potential for ventricular arrhythmias since QT prolongation was observed in in-vivo and in-vitro studies.

The non-clinical safety program of bosutinib included single and repeated dose toxicity studies, genetic toxicity, reproductive and developmental toxicity, and phototoxicity evaluations. Safety studies were also performed on the major human metabolite M2 and the RRT 0.99 impurity.

The primary target organ of bosutinib-related toxicity was the gastrointestinal tract and this demonstrated a steep dose-response relationship. Toxicity was characterised by luminal dilation, goblet cell hyperplasia of the intestinal tract, sinus erythrocytosis, haemorrhage, and erosion and oedema of the intestinal tract, with clinical observations of faecal alterations, loss of body weight and reduced food consumption. A further target organ was the liver, with hepatocellular hypertrophy accompanied by increase in liver weights. The exposures at the NOAEL were equal to the human exposure at the recommended human daily dose of 500 mg. Gastrointestinal toxicity and hepatotoxicity are also common adverse effects in patients receiving bosutinib therapy.

Lymphoid atrophy in spleen lymph nodes and thymus occurred in rats. Although these effects were regarded as secondary to GI toxicity, a direct effect of bosutinib on immune function cannot be excluded due to the pharmacodynamic action of bosutinib on Src, Abl, and Tec kinase inhibition.

Reproduction and developmental toxicity studies showed impairment of male and female fertility in rats and foetotoxicity (reduced foetal weight, skeletal and visceral anomalies) in rabbits at exposures lower than the human exposure at the recommended human dose of 500 mg. In gravid rats, bosutinib-derived radioactivity crosses the placenta and foetuses were exposed to bosutinib and/or its metabolites.

Consequently, the SmPC indicates that Bosulif is not recommended for use during pregnancy, or in women of childbearing potential not using contraception. Women of childbearing potential should be advised to use effective contraception and avoid becoming pregnant while receiving Bosulif. The SmPC also highlights that based on non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans.

In lactating rats, transfer of bosutinib-derived radioactivity through the milk to nursing litters was demonstrated, with a milk-to-plasma ratio of 8. The SmPC therefore indicates that a potential risk to the breast-feeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with bosutinib.

Specific local tolerance studies with bosutinib were not conducted. The oral local tolerance was evaluated in toxicological studies. The tolerance was appropriately evaluated in several studies further to IV and intraperitoneal administration of bosutinib which examined clinical, macroscopic and microscopic signs in the application site.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies conducted were adequate to support the marketing authorisation of bosutinib in the treatment of CML.

2.4. Clinical aspects

2.4.1. 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

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
Pharmacokinetics and Initial Tolerability Studies in Healthy Subjects and Subjects with solid tumours					
3160A4-1112-US	Phase 1, open-label, single-dose, inpatient study of [^{14}C]bosutinib 1/ to characterise the mass balance and metabolic disposition and to identify the metabolites and general metabolic pathways after administration of a single oral dose of [^{14}C]-labeled bosutinib to healthy male subjects. 2/ to provide the PK profile of [^{14}C]-labeled oral bosutinib.	Each subject received a single oral dose of 500-mg [14C]bosutinib with 240 mL of distilled water on study day 1	Randomised: 6 Treated: 6 Completed: 6	Sex: 6 M Mean Age (min/max): 25 (22/29) years Race, % W/B/O: 50/17/33	Single dose
3160A1-100-US	Phase 1, open-label, dose-escalation study. 1/ to determine the MTD of oral bosutinib administered daily to fed subjects with advanced malignant solid tumours. 2/ to obtain preliminary information on the PK, PD, and antitumour activity.	Part 1 (dose-escalation): bosutinib 50 to 600 mg QD (50- and 100-mg capsules) Part 2: bosutinib Recommended Part 2 dose: 400 mg QD	Randomised and treated: 151 - 51 in part 1 - 100 in part 2	Sex: 83F/68M Mean Age (min/max): 59 (19/83) years Race, % W/B/A/O: 84.8/9.9/0.7/4.7	QD (1 cycle = 21 days); until disease progression, unacceptable toxicity, or withdrawal of consent.
3160A1-102-JA	Phase 1, open-label, dose-escalation study. 1/ to determine the safety, tolerability, and MTD of oral bosutinib administered daily to subjects with advanced malignant solid tumours. 2/ to obtain preliminary information on the PK and antitumour activity.	Bosutinib 100 to 400 mg QD.	Randomised: 25 Treated: 25 100 mg: 6 200 mg: 3 300 mg: 6 400 mg: 10	Sex: 9F/16 M Mean Age (min/max): 59 (35/72) years	QD (1 cycle = 21 days); until disease progression, unacceptable toxicity, or withdrawal of consent.
Bioavailability and Bioequivalence Studies					
3160A4-1109-US	Phase 1, open-label, single-dose, 5-treatment, 3-period crossover, balanced incomplete block design in healthy fed subjects. 1/ to compare the BA of 3 new formulation tablets (500 mg bosutinib) with a reference capsule and an oral solution. 2/ to obtain in vitro/in vivo correlations for the absorption of bosutinib.	5 bosutinib 500 mg groups; 3 new formulation tablets: - slow, target and fast release (SR, TR, FR) - reference capsule - reference oral solution. Subjects randomly assigned to 1 of 10 treatment sequences (to receive 3 of the 5 different formulations).	Randomised: 40 Treated: 40 Completed: 32 SR: 22 TR : 21 FR : 22 Capsule : 22 Oral solution: 21	Sex: 40 M Mean Age (min/max): 29 (18/46) years Race,% W/B/A/O: 67.5/20.0/0/12.5	Single doses: 3 periods Minimum 14-day washout
3160A4-1115-US	Phase 1, randomised, open-label, inpatient/outpatient, 2-period crossover study 1/ to assess the BE of the proposed commercial bosutinib tablet formulation to the reference Phase 3 tablet formulation in healthy fasting subjects. 2/ to provide additional safety and tolerability data.	Bosutinib 3×100-mg commercial tablet and 3×100-mg reference Phase 3 tablet	Randomised: 30 Treated: 30 Completed: 25	Sex: 30 M Mean Age (min/max): 29 (19/50) years Race,% W/B/A/O: 67/23/3/7	Single doses: 2 periods Minimum 14-day washout
3160A4-1120-US	Phase 1, randomised, open-label, inpatient/outpatient, 2-period crossover study. 1/ to assess the BE of the proposed commercial bosutinib tablet formulation (500-mg tablet) to the reference tablet formulation for the Phase 3 study (5x100-mg tablets) in healthy fed subjects 2/ to obtain safety and tolerability data.	Test product: Bosutinib 1 x 500-mg (Excella-produced) commercial tablet Reference product: Bosutinib 5 x 100-mg (Montreal-produced) current Phase 3 tablet	Randomised: 31 Treated: 31 Completed: 30	Sex: 31M Mean Age (min/max): 29 (19/50) years Race, %: W/B/A/O: 55/32/13/0	Single doses: 2 periods Minimum 14-day washout

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
Food-effect Studies					
3160A1-103-EU	Phase 1 randomised, double-blind, placebo-controlled, inpatient, sequential-group study of ascending single oral doses. 1/ to assess the safety and tolerability of ascending single oral doses of bosutinib in healthy subjects. 2/ to provide the initial PK and PD profiles and to evaluate the effect of a high-fat meal on the PK of bosutinib administered to healthy subjects.	Bosutinib single oral doses (capsules) of 200 and 400 mg after an overnight fast of at least 10 hours. Bosutinib single doses from 200 to maximum of 1200 mg (actual 800 mg) after a high-fat breakfast.	Randomised: 55 Treated: 55 Completed: 55	Sex: 8F/47 M Mean Age (min/max): 31 (18/50) years Race, % W/B/A/O: 87/5/4/4	Single dose
3160A4-1110-US	Phase 1, single-dose, randomised, open-label, 2-period, 2-sequence crossover, inpatient/outpatient study. 1/ to assess the effect of a high-fat meal (breakfast) on the relative BA and PK of a single oral bosutinib dose in healthy subjects. 2/ to obtain additional safety and tolerability data.	Bosutinib 100-mg tablets; 2 single doses of 400 mg (4 x 100 mg tablet) under fed and fasting conditions.	Randomised: 24 Treated: 24 Completed: 22	Sex: 24 M Mean Age (min/max): 25 (18/40) years Race, % W/B/A/O: 63/21/8/8	Single doses: 2 periods Minimum 10-day washout
Hepatic Metabolism and Drug-Interaction Studies					
3160A4-104-US	Phase 1, open-label, randomised, 2-period, 2-sequence crossover, inpatient/outpatient study in healthy subjects. 1/ effect of a CYP3A inhibitor (multiple doses of ketoconazole) on bosutinib PK and safety. 2/ safety and tolerability of bosutinib and ketoconazole when coadministered.	Bosutinib 100-mg capsule; 2 single doses: 1 alone after an overnight fast of at least 10 hours and 1 dose coadministered with ketoconazole 400 mg (2 x 200-mg tablet) from days -1 to 4.	Randomised: 24 Treated: 24 Completed: 24	Sex: 24 M Mean Age (min/max): 35 (24/49) years Race,% W/B/A: 33/63/4	2 periods Minimum 13-day washout
3160A4-1106-US	Phase 1, open-label, nonrandomised, inpatient/outpatient study to be performed. 1/ effect of a CYP3A inducer (multiple doses of rifampin/rifampicin) on the PK profile of a single oral dose of bosutinib in healthy subjects. 2/ safety and tolerability of bosutinib and rifampin when coadministered.	Bosutinib 500 mg (5 x 100-mg tablet); 2 single doses of 500 mg each with a standard meal: 1 dose alone and 1 dose coadministered with rifampin 600 mg (2 x 300-mg capsule), which is given for 10 days (6 days before day of coadministration, and 3 days after).	Randomised: 24 Treated: 24 Completed: 22	Sex: 24 M Mean Age (min/max): 31 (19/49) years Race,% W/B/A/O: 71/17/4/8	2 periods: Period 1: single dose Period 2: 10 days Minimum 14-day washout
3160A4-1108-US	Phase 1, open-label, non-randomised, inpatient/outpatient study. 1/ to assess the effect of multiple oral doses of H2-receptor antagonists or proton pump inhibitors (lansoprazole) on the PK profile of a single oral dose of bosutinib in healthy subjects. 2/ to assess the safety and tolerability of the coadministration of bosutinib and antacids.	On Day 1, 400 mg bosutinib alone on day 14, 60 mg lansoprazole on day 15, 400 mg bosutinib coadministered with multiple oral doses of 60-mg lansoprazole	Randomised: 24 Treated: 24 Completed: 23	Sex: 24 M Mean Age (min/max): 41 (18/49) years Race,% W/B: 83/17	2 periods; Period 1: single dose Period 2: 2 days Minimum 14-day washout
3160A4-1111-EU	Phase 1, open-label, single-dose, parallel-group, inpatient, nonrandomised study. 1/ to assess the PK of bosutinib in subjects with chronic hepatic impairment (Child-Pugh classes A, B, and C) and in matched healthy adults by age, sex, BMI,	Single 200-mg oral dose (2 x 100-mg oral tablets) of bosutinib in the morning of study day 1	Randomised: 27 Treated: 27 Completed: 27 18 subjects with chronic hepatic impairment (6 per Child-	Sex: 9F / 18 M Mean Age (min/max): 53 (37/65) years Race, % W: 100	Single dose

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
	and smoking habit. 2/ to assess the safety and tolerability of bosutinib.		Pugh class) 9 healthy subjects.		
3160A4-1114-EU	Phase 1, randomised, double-blind, sponsor-unblinded, placebo-controlled, inpatient, sequential-group study. To assess the safety, tolerability, and PK of ascending single oral doses of bosutinib administered with multiple doses of ketoconazole in healthy subjects.	Ketoconazole 400 mg QD (2 x 200-mg tablets) administered from days -1 through 4. On day 1, single oral doses of bosutinib (100-mg capsule) ranging from 100 to 600 mg (100, 200, 300, 400, 500, and 600 mg) or matching-placebo capsule.	Randomised: 48 Treated: 48 Completed: 48	Sex: 48 M Mean Age (min/max): 32 (18/50) years Race, % W/B/O: 92/4/4	4 days
QTc Study					
3160A4-105-US	Randomised, single-dose, double-blind with respect to bosutinib, crossover, placebo- and open-label moxifloxacin-controlled study in healthy subjects. 1/ to assess the effect on corrected QT interval after the administration of bosutinib. 2/ to characterise the PK/PD relationship and provide additional safety information.	Part A: 3 periods to receive single dose of bosutinib 500 mg as capsules, bosutinib matching placebo, and moxifloxacin (400-mg) tablets. Part B: 2 periods to receive ketoconazole 200-mg as tablets alone on days -1 and coadministered with bosutinib 500 mg or placebo on day 1.	Randomised: 60 Treated: 60 Completed: 49	Sex: 60 M Mean Age (min/max): 31 (18/50) years Race, % W/B/O: 77/20/3	Part A: 3 periods (single dose); 5-day washout. 8-day washout between parts A and B. Part B: 2 periods; 2 days of treatment, 4-day washout.
Efficacy and Safety Studies					
Clinical Studies in the Claimed Indication					
3160A4-200-WW	Phase 1/2 open-label 2-part study in subjects with Ph+ leukemia. Part 1: dose escalation. Part 2: efficacy study at the selected Phase 2 dose. To determine safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukaemias. To explore pharmacogenomic effects.	Parts 1 and 2: bosutinib 100-mg capsules or 100-mg tablets Part 1: Dose levels studied were 400, 500, and 600 mg Part 2: selected dose=500 mg.	Randomised: 571 Treated: 570 - 18 in Part 1 - 553 in Part 2		QD until disease progression, unacceptable toxicity, or withdrawal of consent.
		CP CML Second line	288	Sex: 135F/153M Mean Age (min/max): 52 (18/91) years Race, % W/B/A/O: 64/5/19/12	
		CP CML Third line	118	Sex: 65F/53M Mean Age (min/max): 54 (20/79) years Race, % W/B/A/O: 72/3/11/14	
		Advanced phase Ph+ leukaemias (AP and BP CML; Ph+ ALL)	164	Sex: 69F/95M Mean Age (min/max): 50 (18/84) years Race, % W/B/A/O: 63/11/13/13	
3160A4-2203-JA	Phase 1/2 open-label, continuous daily dose administration, 2-part study in subjects with Ph+ leukaemia. To determine safety, tolerability, MTD, PK, PD, and efficacy of bosutinib in Japanese subjects with Ph+ leukaemias.	Part 1: bosutinib capsules (100 mg). Part 2: bosutinib tablet (100 mg). Part 1: Starting dose of 400 mg (up to max. 600 mg). Part 2: MTD=500 mg. Contin	Part 1 Treated: 17 Part 2 Treated: 35	Sex: 20F /32M Mean Age (min/max): 54 (78/20) years Race, %: A: 100	QD until disease progression, unacceptable toxicity, or withdrawal of consent.

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
		uous oral dose administration from Day 1 onwards.			
3160A4-3000-WW	Phase 3 randomised open-label trial. 1/ to compare the efficacy (rate of CCyR at 1 year) of bosutinib vs imatinib in subjects with chronic phase (CP) CML. 2/ to compare MMR at 1 year, duration of CCyR, CHR, and MMR, time to transformation to AP and BP; to assess the population PK; to assess the comparative safety of bosutinib vs imatinib.	Bosutinib 500 mg QD (100-mg tablets).	Randomised: 250 Treated: 248	Sex: 101F/149M Mean Age (min/max): 47 (19/91) years Race, % W/B/A/O: 64.5/1.0/24.15/ 10.4	QD until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, o withdrawal of consent
		Imatinib 400 mg QD (100-mg and/or 400-mg tablets).	Randomised: 252 Treated: 251	Sex: 117F/135M Mean Age (min/max): 46 (18/89) years Race, % W/B/A/O: 65/1/23/11	
			Total: Randomised: 502 Treated: 499	Sex: 218F/284M Mean Age (min/max): 47 (18/91) years Race, % W/B/A/O: 65/1/24/10	
Other Efficacy and Safety Studies (not pertinent to the claimed indication)					
3160A2-201-WW	Phase 2, open-label, safety and efficacy study in women with relapsed or refractory advanced or metastatic breast cancer. 1/ to determine the rate of PFS at 16 weeks after administration of bosutinib 400 mg daily. 2/ to determine the safety profile, the ORR within 1 year and the survival rate at 2 years.	Bosutinib single 400-mg dose QD; capsules (100 mg).	Randomised: 75 Treated: 73	Sex: 75F Mean Age (min/max): 54 (33/71) years Race, % W/A/O: 81/16/2	QD until disease progression, unacceptable toxicity, or withdrawal of consent
3160A6-2206-WW	Phase 2 open-label, randomised study. 1/ to compare the efficacy (PFS) of bosutinib in combination with exemestane vs exemestane alone as second line treatment for postmenopausal women with locally advanced or metastatic ER+/PgR+/ erbB2- breast cancer. 2/ to evaluate the safety, evaluate the PK, the HRQoL, and additional efficacy parameters (ORR, OS at 2 years, duration of response).	Part 1 (safety lead-in phase): bosutinib 400 mg + exemestane 25 mg; QD.	Randomised: 42 Treated: 42		QD until disease progression, unacceptable toxicity, or withdrawal of consent
			14 subjects received bosutinib 400 mg + exemestane 25 mg	Sex: 14F Mean Age (min/max): 64 (49/76) years %W/B/A/O: 71/7/14/8	
			28 subjects received bosutinib 300 mg + exemestane 25 mg	Sex: 28F Mean Age (min/max): 58 (40/79) years %W/B/A/O: 75/0/21/4	
		Part 2: bosutinib 400 mg + exemestane 25 mg vs exemestane 25 mg ; QD.	Randomised: 0		
3160A6-2207-WW	Phase 2 open-label, randomised study. 1/ to compare the efficacy (PFS) of bosutinib in combination with letrozole vs letrozole alone as 1st line treatment for postmenopausal women with locally advanced or metastatic ER+/ PgR+ / erbB2- breast cancer. 2/ to evaluate the safety, the PK, the HRQoL, and additional efficacy parameters (ORR, OS at 3 years, duration of response).	Part 1 (safety lead-in phase): 400 mg bosutinib and 2.5 mg letrozole; QD	Randomised: 16 Treated: 16	Sex: 16F Mean Age (min/max): 60 (45/81) years Race, % W/A: 81/19	QD until disease progression, unacceptable toxicity, or withdrawal of consent
		Part 2: bosutinib 400 mg + 2.5 mg letrozole vs 2.5 mg letrozole QD.	Randomised: 0		

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
3160A6-2 208-WW	Phase 1/2, open-label randomised study. Part 1: 1/ to assess the safety and tolerability and determine the MTD combination(s) of bosutinib + capecitabine in subjects with solid tumours. 2/ to assess preliminary antitumour activity for bosutinib plus capecitabine.	Part 1: 12 cohorts to assess several combinations ("up and down" rule). Bosutinib 200 to 400 mg QD in combination with capecitabine 625 to 1000 mg/m^2 BID	Randomised: 32 (25 subjects in 12 cohorts)	Sex: 18F/14M Mean Age (min/max): 61 (53/67) years Race, % W/B/A: 75/3/22	Bosutinib is given QD. Capecitabine is given for 14 days followed by 7 days off. Subjects are treated until disease progression, unacceptable toxicity, or withdrawal of consent.
		MTD Extension MTD=300mg Bosutinib QD + 1000 mg/m^2 Capecitabine BID	7 subjects in MTD extension cohort		
	Part 2: 1/ to determine the ORR in women with: - ER+ and/or PgR+ / erbB2- - ER-/PgR-/ erbB2- locally advanced or MBC. 2/ to confirm the MTD by collecting further data on the safety and tolerability of the combination; to evaluate PK; and to evaluate additional efficacy parameters, ORR, duration of response, and clinical benefit rate.	Part 2: MTD of the combination	Randomised: 0		

a. For ongoing studies, study status is as of 15 Nov 2010; all studies were closed to enrollment as of 15 November 2010, except study 2208-WW, which was closed to enrollment on 02 December 2010.

Abbreviations: A=Asian; AP=Accelerated phase; B = Black; BA =Bioavailability; BE = Bioequivalence; BID = Twice daily; BMI=Body mass index; BP = Blast phase; CCyR=Complete cytogenetic response; CHR=Complete haematologic response; CML=Chronic myelogenous leukaemia; CP=chronic phase; CYP3A=Cytochrome P450 isoenzyme 3A; DB = Double-blind; ER=estrogen receptor; erbB2=epidermal growth factor receptor 2; F = Female; FR=fast release; HRQoL=health-related quality of life; M = Male; MBC=metastatic breast cancer; MMR=Major molecular response; MTD = Maximum tolerated dose; No = Number; O=other; ORR= objective response rate; OS= overall survival; PC = Placebo-controlled; PD = Pharmacodynamic; PG = Parallel-group; PgR=progesterone receptor; Ph+ = Philadelphia chromosome positive; PK = Pharmacokinetic; PFS=progression-free survival; QD=once a day; SR=low-release; TR=target release; vs = versus; "+" = Positive (for receptors);"-" = Negative (for receptors); W = White.

2.4.2. Pharmacokinetics

Within the phase I and II clinical development program for oral bosutinib 11 phase 1 studies were carried out with healthy subjects, and 1 phase 1 study was conducted in subjects with hepatic impairment; 8 studies were conducted in subjects with cancer. The biopharmaceutical clinical development program comprised 5 Phase 1 single-dose studies in healthy subjects under fasting and fed conditions.

Absorption

Bioavailability

Absolute bioavailability has not yet been studied.

Bosutinib showed an absorption lag time of ~1 hour with the capsule formulation which was confirmed in population PK analyses regardless of formulation. Median t_{max} was reached between 3-6 hours, indicative of slow absorption. There was no difference in t_{max} between healthy subjects and cancer patients, nor between single and multiple dosing or fasted and fed state.

Exposures between C_{max} of 88 142ng/mL and AUC of ~2190-2970 ng*h/mL were observed after administration of 400-600mg in fed healthy subjects. For cancer patients the relative bioavailability was lower for low doses but being linear in higher doses, at least between 300-600mg. Between 200 to 600 mg, bioavailability was within ±20% of the reference dose of 400 mg.

Bioequivalence

Several formulations of bosutinib capsules and film-coated tablets have been used during the clinical pharmacology development. Bioequivalence (BE) was shown for the capsule formulation, an oral solution and 3 potential commercial film-coated-tablet formulations at a 500-mg dose in the fed state. From comparison with in-vitro dissolution data it was concluded that the dissolution of the tablet/capsule would not be a rate limiting step in terms of bioavailability.

A study in fasted state showed BE for AUC and C_{max} for 3*100mg film-coated tablets ("clinical formulation") versus the 3*100mg commercial formulation. However, due to the proposed therapeutic dose of 500 mg bosutinib in combination with food, a BE study in fed state comparing the 500mg commercial tablets with 5*100mg clinical tablet formulation was requested in SA. In this study BE for AUC was shown, but the CI for C_{max} was outside the acceptable regulatory ranges. As it was not pre-specified in the study protocol whether bosutinib might be regarded as a highly variable drug (intrasubject CV 30.7% for C_{max}) and no replicate sampling design was used, a widening of the acceptance limits for bioequivalence was not foreseen. Two additional BE analyses were provided:

1. Including 2 patients who had to be excluded according to protocol due to vomiting; with this, bioequivalence was calculated for AUC and C_{max}.

2. Without a subject with carry-over effect, AUC was still calculated within the BE limits and C_{max} was further outside with ~128%.

These results can be seen as supportive information.

Dissolution profiles together with satisfactory results have been submitted with the response comparing the different (500 mg and 100 mg) commercial formulations and showing their similarity. It is now considered that BE between the 100-mg clinical tablet and commercial formulations has been unequivocally demonstrated in terms of both C_{max} and AUC by means of study 3160A4-1120-US although the upper limit for BE was slightly outside regulatory ranges. The claim of a biowaiver for the lowest dosage of the commercial tablet was accepted.

Influence of food

Food has a significant effect on the pharmacokinetics of bosutinib. In healthy volunteers, AUC and C_{max} increased 1.57-fold (95% CI: 1.42, 1.73) and 1.68-fold (95% CI: 1.47, 1.90), respectively, relative to fasting. The food effect was more pronounced with the lower dose of 200mg, where both parameters increased 2.3-2.5-fold. Volume of distribution and clearance were decreased in the presence of food by approximately 2-2.4-fold. Food also caused an increase in bosutinib tolerability.

Distribution

Volume of distribution in fed healthy subjects for a 500mg dose was large and varied between ~4300 L and ~14300 L, suggesting extensive tissue distribution and/or low oral bioavailability. Apparent oral clearance ranged from 119 to 246 L/h after single ascending oral doses of bosutinib 200mg-800mg under fed conditions.

Plasma protein binding of bosutinib was high with 94% in vitro and 96% ex vivo from healthy subjects from study 3160A4-1111-EU, with no difference between degrees of liver impairment.

Elimination

Metabolism

In-vitro assessment in human liver microsomes and cryopreserved hepatocytes indicated that the predominant enzyme capable of metabolizing bosutinib was CYP3A4. The predominant in-vitro human metabolites by oxydechlorination (M2), N-demethylation (M5), and N-oxidation (M6) were compared to bosutinib in the nonclinical pharmacology Src enzyme assay and anchorage-independent Src fibroblast proliferation assay. All 3 metabolites had comparable activity in the Src enzyme assay, but cellular activity was approximately ≤5% of bosutinib activity. The two major metabolites (M2 and M5) were not pharmacologically and toxicologically active in non-clinical studies on rats.

No metabolism of bosutinib was observed with cyclooxygenases CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A5. Flavin-containing monooxygenase enzymes (FMO1, FMO3, and FMO5) are capable of metabolizing bosutinib to its N-oxide metabolite but it was acceptably justified that a clinical DDI study with FMOs is not essential.

The 2 main identified metabolites (M5 and M2) are formed in ratios of about 19% for M2 and 20-25% for M5 of bosutinib AUC_T. Mean $t_{½}$ of M5 was observed by 37 hours, for M2 $t_{½}$ was 39 hours. Metabolite ratios were increased in fasting state as well as under CYP3A4 induction by rifampin. CYP3A4 inhibition by ketoconazole and increasing hepatic impairment reduced the formation of the metabolites markedly.

Elimination

Elimination was fast, with a mean recovery of almost 76% within 4 days and 95% within 9 days. Mean $t_{1/2}$ was about 32 hours for the 500mg dose, with longer observed $t_{1/2}$ after lower doses (39 hours with 200mg) or in the fasting state (41 hours with 200mg).

In a mass-balance study with an oral 500-mg dose, radioactivity was mainly excreted in the faeces (91.3%) and to a minor extent in the urine (3.29%) within 10 days. The major components in faeces were unchanged bosutinib (40% of dose) and N-desmethyl-bosutinib=M5 (22%) while in urine bosutinib (72%) and oxydechlorinated-bosutinib=M2 (7.5%) were the major components. It remains as yet unresolved whether the >90% portion is excreted to a significant extent in bile i.e. whether bosutinib is subject to a high hepatic first-pass effect or is absorbed from the gut to a yet unknown extent, because the metabolites M2 and M5 are also formed by the cytochrome CYP3A4 in the gut luminal wall. The applicant acknowledged the possibility of bosutinib showing a high extraction ratio.

Dose proportionality and time dependencies

Dose linearity for AUC and C_{max} was shown in healthy volunteers between 200 and 800 mg, and in cancer patients between 300-600mg, after single dose administration; it was less pronounced after multiple-dosing with higher variability.

The recommended phase II and III doses were derived from 2 ascending-dose studies in cancer and 2nd line CML patients and were dependent on the observation of DLTs. Most common DLTs were diarrhoea, and grade 3 rash and other grade 3 gastrointestinal toxicities in both studies. Due to these, the starting dose for part 2 of study 200-WW was 400mg, and the recommended phase III dose was 500mg.

Special populations

Intra- and inter-individual variability

In the population PK analysis over 8 studies in healthy subjects, inter-subject variability (ω) and intra-subject variability (σ) were calculated with 30.3 CV% and 19.3 CV% for AUC, and 31.6 CV% and 26.3 CV% for C_{max}, respectively.

Pharmacokinetics in target population

In general, bosutinib exposures in patients with AMST and CML were within the range of values observed in healthy volunteers suggesting that there are no inherent differences in the PK of bosutinib between healthy subjects and cancer patients.

From population PK analysis in cancer patients from 3 studies, pharmacokinetics can be described by a 2-compartmental model with first-order absorption ($t_{1/2}$ 1.14 hours) with an absorption lag (0.87 h). Simulations for the 500mg dose revealed the following calculations, however, the final model was characterised by high inter-individual variability(mean±SD): AUC 5216±3316 ng/ml*h, C_{max} 255±152 ng/ml, C_{min} 180±126 ng/ml; CV of 64, 59, and 70%, respectively.

For a 400mg-dose, the volume of the central compartment was about 4900 L (CV 48%) with an alpha-$t_{1/2}$ of 19 hours, the volume of the peripheral compartment was large (>380,000 L; CV of 211%) with a slow turnover (beta-$t_{1/2}$ 290 days). CL/F was calculated with 120 L/h (CV 60%).

Mean accumulation ratio (R) at steady-state ranged from to 1.9 to 3.1, which is consistent with a half-life that is longer than the 24-hour dosage interval (Table 7).

Table 7. Summary of Multiple-Dose PK of Bosutinib From Individual Studies (Mean±SD) in Cancer Patients on Day 15

			Bosutinib in Plasma					
Study Number	**Dose (mg)**	**N**	**C_{max} (ng/mL)**	**t_{max}[a] (hr)**	**$t_{1/2}$ hr)**	**AUC_{ss} (ng*h/mL)**	**CL/F (L/h)**	**Accumulation Ratio**
3160A1-100-US	50	3	6.9 ± 3.1	4 (3-6)	25.8 ± 12.3	114 ± 33	467 ±148	3.0 ± 1.1
	100	4	19.6 ± 3.3	3.5 (2-4)	64.7 ± 67.3	329 ± 58	310 ±49	2.2 ± 0.8
	200	5	95.4 ± 60.0	4 (3-6)	30.0 ± 20.1	1670 ± 1130	162 ±93	3.0 ± 1.0
	300	5	76.6 ± 37.0	4 (3-6)	19.4 ± 7.5[b]	1170 ± 699[b]	361 ±264[b]	2.4 ± 0.7[b]
	400	69	190 ± 116	4 (1-8)	19.9 ± 16.7[c]	2900 ± 1700[d]	180 ±103[d]	2.6 ± 1.5[e]
	500	10	273 ± 197	5 (1-8)	23.3 ± 15.0[f]	3580 ± 1820[f]	186 ±113[f]	2.6 ± 1.0[g]
	600	2[h]	182, 425	3.5 (3-4)	21.4, 11.2	3160, 5280	190, 114	1.9, 1.9
3160A1-102-JA	100	5	55.5 ± 27.7	6 (3-6)	20.8 ± 5.8	904 ± 589	138 ± 55	2.9 ± 1.4
	200	3	145 ± 30.1	3 (2-24)	NC	NC	NC	NC
	300	6	213 ± 90.2	6 (4-6)	16.6 ± 6.9[i]	3880 ± 1860[j]	99 ± 61[j]	3.1 ± 1.4
	400	7	242 ± 86	3 (2-8)	18.8 ± 2.6	3840 ± 1880	129 ± 67	2.5 ± 0.5
3160A4-200-WW, Part 1	400	3	146 ± 20	4 (3-6)	46.0 ± 32.3	2720 ± 442	150 ± 23	3.1 ± 1.4
	500	3	200 ± 12	6 (4-8)	21.7 ± 4.6	3650 ± 425	138 ± 17	2.8 ± 0.8

600	10	208 ± 73	6 (3-11)	25.9 ± 24.9[k]	3630 ± 1270[l]	185 ± 66[l]	2.5 ± 0.9

N = number of subjects with evaluable PK, NC = not calculated.

a. Median (min - max)
b. N=4
c. N=53
d. N=58
e. N=35
f. N=9
g. N=8
h. Actual data presented because n=2
i. N=4
j. N=5
k. N=7
l. N=9

Sources: CSR-77176; CSR-74686, CSR-79850.

Covariate analysis of bosutinib clearance and volume of distribution indicated that none of the covariates (age, weight, BSA, BMI, sex, race, protocol, ECOG, creatinine clearance, total bilirubin, ALT, AST, and albumin) exerted an effect on the PK of bosutinib. However, it was not excluded by the applicant in the response that older age or higher body weight may have contributed to longer elimination half-life, as was seen in a hepatic impairment study. Bilirubin level had small effect on clearance that was not considered clinically relevant. In addition, the results indicated that PK of bosutinib was not affected by tumour type or prior anticancer treatment.

Special populations

Hepatic impairment

The effect of hepatic impairment on the PK of bosutinib was examined in 18 subjects without cancer with mild, moderate or severe hepatic impairment (Child-Pugh class A, B and C, respectively) and in 9 matched healthy control subjects. Liver impairment showed a significant effect on the pharmacokinetics of bosutinib. Oral clearance was reduced by 45-50% and AUC was similarly increased about twice for all Child-Pugh stages. C_{max} was 2.5-fold for Child-Pugh class A, 2-fold for CP B and 1.5-fold for CP C. T_{max} decreased from 4 to 1.5 hours. With declining liver function $t_{1/2}$ increased up to 2-fold, half-life was longest in the C-P class B and C cohorts (113 and 111 hours, respectively), followed by the C-P class A cohort (86 hours) and then healthy subjects (55 hours). The observations were consistent with the finding that the concentrations of the metabolites M2 and M5 were decreased.

Renal impairment

The effect of renal impairment on bosutinib PK has not been explicitly evaluated.
The applicant argued that based on the low (3%) excretion of bosutinib and its metabolites in urine observed in healthy subjects, it was unlikely that renal impairment would have significant effects on the pharmacokinetics of bosutinib.

Reduced renal function (creatinine clearance ≥1.5 ULN) was an exclusion criterion in the phase II/III efficacy studies in cancer patients. As some patients had shown declining renal function and a trend of increasing AUC with moderate renal impairment compared to none or mild during study was seen, an evaluation of renal function was requested. This revealed that neither creatinine clearance nor hepatic parameters like ALT, AST, and bilirubin declined in relation to exposure or time of exposure of bosutinib. The SmPC was revised accordingly.

Demographics

Population PK analysis of 3 clinical studies in patients with cancer indicated that age, body weight, gender and race do not affect the PK of bosutinib. These results are consistent with results from population in healthy volunteers. However, in a Japanese population especially the low doses between 100-300mg bosutinib led to exposures (C_{max} and AUC) of up to >2-fold of those measured in a respective US study. Furthermore, the exposure *vs* dose-curves showed a steeper increase with the lower doses. The applicant confirmed they will discuss these observations when the final study report of the Japanese study 2203-JA is submitted.

No studies in population below the age of 18 have been performed.

Pharmacokinetic interaction studies

In-vitro data showed no effect of bosutinib as an inducer or inhibitor of the metabolic liver enzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

The applicant explained that genetic polymorphism of CYP3A4 is quite rare and that therefore a contribution to a different bosutinib/metabolite pattern affecting efficacy and/or safety can be regarded as minor. On the other hand, and in view of bosutinib possibly being a high-extraction drug, differences in expression levels of CYP3A4 might have a greater impact on the plasma exposures, safety and efficacy.

CYP3A4 inhibitors

Addition of the CYP3A4 inhibitor ketoconazole increased exposure 5.2-fold, 7.6- to 8.6-fold for C_{max} AUC_T and AUC, respectively, at a 100mg dose. Similarly, mean CL/F decreased approximately 9-fold to 42L/h and mean V_z/F decreased about 5-fold. Mean $t_{1/2}$ increased 1.5-fold to 69.0 hours.

CYP3A4 inducers

The CYP3A4 inducer rifampicin suppressed bosutinib exposure 7-fold for C_{max} and 13-fold for AUC. Inversely, distribution volume and clearance were increased by the same ranges, respectively, resulting in shorter elimination half-life. The applicant stated that it is likely that the more profound relative effects on the parent drug as compared with metabolites are due to enhanced susceptibility of bosutinib to metabolism during first-pass absorption. The gastrointestinal tolerability of bosutinib was improved by concomitant administration of rifampicin (diarrhoea 18.2% combined *vs* 45.8% alone) and this was considered to result from reduced local and systemic bosutinib concentrations.

Proton-pump inhibitors

Bosutinib displays pH-dependent aqueous solubility *in vitro*. An effect of gastric pH-dependence was also seen with the concomitant proton-pump inhibitor lansoprazole, when bosutinib exposures (C_{max} and AUC) decreased to 54% and 74%.

P-glycoprotein

Due to expected therapeutic plasma levels being below the IC_{50} values for enzyme inhibition, a P-glycoprotein (P-gp) interaction or a possible effect of bosutinib on the pharmacokinetics of other drugs have not been studied. However, the presumed bosutinib concentration in the intestine is higher than the *in vitro* calculated IC_{50} and thus inhibition of intestinal P-gp by bosutinib may occur.

2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

Primary pharmacology

The underlying clinically relevant mutation in Ph+ CML is the t(9;22) chromosomal translocation that forms the BCR-ABL fusion gene, leading to expression of the oncogenic Bcr-Abl protein tyrosine kinase.

Bosutinib is a potent Src and Abl kinase inhibitor. Bosutinib treatment inhibits Bcr-Abl activity, including Bcr-Abl phosphorylation, phosphorylation of the Src family kinase Lyn, along with phosphorylation of downstream effector proteins such as CrkL and Stat5 at concentrations comparable to those necessary to inhibit CML cell line proliferation.

Bosutinib also inhibits most of the clinically relevant mutants of Bcr-Abl that lead to imatinib-resistance, however it is ineffective against the T315I mutant. Unlike other Abl kinase inhibitors now in the clinic, bosutinib has minimal activity against the receptor tyrosine kinases c-Kit and PDGF receptor.

Data from early studies in healthy subjects and cancer patients, however, did not show a trend of bosutinib to inhibit Src phosphorylation.

Secondary pharmacology

Positive pre-clinical investigations on hERG channels and in-vivo animal models provided evidence for a proarrhythmic potential of bosutinib. Additionally, bosutinib belongs to a class of drugs where a potential pharmacological concern has been evaluated. In the CML studies patients with QTc >450ms, intake of QT prolonging medication or relevant cardiac diseases were excluded.

From a thorough QT/QTc study a proarrhythmic potential of bosutinib as specified in ICH E14 note for guidance was not established. Liver impaired subjects had shown TEAEs with prolonged QTc intervals in 37%, the incidence increased with declining hepatic function, but single patient data did not establish a correlation to bosutinib plasma concentrations. An observation in study 200 was that 19.4% of the CML patients with blast phase had QT interval changes >60ms and 4.8% had QTcB intervals >500ms. In accelerated phase, changes >60ms were seen in only 1.4% and in chronic phase in up to 3.7%. Unfortunately, none of the blast phase patients experiencing QT prolongations had concurrent plasma levels drawn to evaluate a PKPD-relationship, but the cardiac observations might have also been due to the underlying disease. Adequate information on the proarrhythmic potential was added in the SmPC.

Relationship between plasma concentration and effect

As could have been expected, the more advanced CML stages have a lower probability of MCyR or cumulative CHR response than observed in second-line CML patients.

Differences in exposure metrics were similarly seen between responders and non-responders in $3^{rd}/4^{th}$ line advanced CML as in 1^{st} line patients. While the mean±SD and the maximal levels for AUC, C_{max} and C_{min} were comparable between the subgroups, minimal exposure levels in responding patients were 4.7-fold higher for AUC, 4.4-fold higher for C_{max} and 5.7-fold higher for C_{min}. Several patients had dose escalations to 600 mg bosutinib and experienced improved response after the dose escalation but it is not known whether the increased minimal exposures only represent such patients or whether the high PK variability of bosutinib had also resulted in such plasma levels in some responders taking 500 mg.

From the 1^{st} line data it had already been suggested that a certain minimal exposure to bosutinib could be an important prerequisite for efficacy. This has been confirmed in the advanced CML patient population. The dose escalation to 600 mg in case of insufficient response should therefore become an important standard in clinical practice. And monitoring of bosutinib plasma levels might be useful in case of (even early) unsatisfactory or failure of therapeutic response

Genetic differences in PD response

Pharmacogenomic analyses had been optional only and were not performed.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics of bosutinib have been reasonably well studied in the phase I/II development program in adult healthy volunteers and cancer patients.

The pharmaceutical formulation of bosutinib was changed several times during the clinical development program. Bioequivalence was established between the capsule and 3 film-coated tablet formulations, and was also demonstrated between the clinical film-coated tablet and the commercial tablet formulation by means of study 1120-US, together with the claim of a biowaiver for the lowest dosage of the commercial tablet. Up to now, the proposed commercial tablet formulation was administered as single-doses only in 3 bioequivalence studies with a very low number of subjects, and it was of concern that a higher diarrhoea incidence was reported compared to the clinical formulation. In a recently performed study with 24 Asian subjects an even higher incidence of diarrhoea (63%) with the commercial formulation and 53% with the clinical formulation was reported. From the current data no final conclusion can be drawn whether this observation was formulation dependent or might also be due to racial differences in susceptibility. The applicant indicated that the ongoing CML studies will have to change study drug from the clinical to the commercial formulation during 2013. Additional post-hoc analyses with regard to safety information for diarrhoea frequency will be provided to be able to better characterise the to-be-marketed formulation.

The interaction with food has been satisfactorily studied and a significant increase in bosutinib exposure for C_{max} and AUC by 1.6-1.7-fold with food was established, the effect being more pronounced at lower doses. However, tolerability was improved by food. The SmPC correctly describes the intake with food.

The gastric-pH increase by proton-pump inhibitors was shown to reduce bioavailability up to one half. The interaction is correctly described in the SmPC.

The absorption of bosutinib is slow and is linear between 300-600 mg. In cancer patients exposure was about 2-fold higher and V_z/F about 2-fold lower than in healthy subjects. Generally, the volume of distribution was large, thus suggesting extensive tissue distribution and/or low bioavailability.

Elimination occurs via faeces to > 91% with a $t_{1/2}$ of 19 hours in cancer patients (34 hours in healthy subjects) after extensive metabolism by liver and/or GI CYP3A4, and only about 3% via urine. Hence it is suspected that bosutinib is subject to extensive first-pass-metabolism. This makes bosutinib susceptible to interactions with CYP3A inducers and inhibitors, and substantial changes in parent and metabolite pharmacokinetics were established. Consequently, sections 4.4 and 4.5 of the SmPC include warnings with respect to concomitant use of bosutinib with potent or moderate CYP3A inhibitors and inducers.

Patients with hepatic impairment showed about 2-fold increases of bosutinib exposure and elimination half-life. Hepatic impairment is included as a contraindication in the SmPC (see Discussion on Clinical Safety).

In the absence of more convincing data so as to rule-out the possible inhibition of P-gp by bosutinib, a clinical drug-drug interaction (DDI) study using known P-gp substrates should be performed post-authorisation.

Absolute bioavailability has not been studied. The applicant will conduct a study as post-authorisation measure to address this issue.

The effect of renal impairment on elimination had not been formally assessed. Though the renal excretion of bosutinib was low (around 3%) in the oral mass balance study, kidney impaired patients were excluded from the CML studies. Based on a population pharmacokinetic analysis in CML patients a trend to increasing exposure (AUC) in patients with moderate impairment during studies was observed. This information has been reflected in section 4.4 of the SmPC. A study in patients with renal impairment is ongoing and results will be submitted as a post-authorisation measure.

A proarrhythmic potential of bosutinib cannot be ruled out, although the thorough QT study was negative, because in other studies QTc prolongations > 450 ms or > 60 ms from baseline were observed. A warning in this respect is included in the SmPC.

From a pharmacodynamic point of view, no firm conclusions can be drawn regarding the inhibition of pSRC expression.

For incidence and severity of diarrhoea a strong exposure-effect relationship was shown, a minor relationship was calculated for incidence of rash, nausea and vomiting. In the last line CML population a dose-dependent increased probability for rash was observed for responders but a lower probability of ATL/AST elevations compared to non-responders.

From population PK analyses on exposure-efficacy relationships in both CML studies no clear pattern was identified. However, exposure-efficacy data separated into responders and non-responders revealed higher minimal plasma levels in responding patients in all treatment lines which might thus be regarded a certain prerequisite for efficacy of bosutinib. Final conclusions on the necessary and sufficient minimal levels cannot be drawn from the current data.

2.4.5. Conclusions on clinical pharmacology

Clinical pharmacology data were adequately presented to support the application for a CML CP indication at a dose of 500 mg of bosutinib administered once daily with food.

2.5. Clinical efficacy

This application was initially submitted with Study 3160A4-3000-WW (hereafter named 3000 WW) as pivotal to support the authorisation of bosutinib in adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase (CP). The phase I/II trial, 3160A4-200-WW (hereafter named 200 WW) was submitted as supportive study.

Further to review of the data (see results and discussion below), Study 200-WW became the main study to support of a last-line indication, with additional data from compassionate use programmes as well as from Study 3000-WW being supportive.

Details of the two studies are given in the table below.

Table 8. Clinical Studies in the Claimed Indication

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
3160A4-200-WW	Phase 1/2 open-label 2-part study in subjects with Ph+ leukaemia. Part 1: dose escalation. Part 2: efficacy study at the selected Phase 2 dose. To determine safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukaemias. To explore pharmacogenomic effects.	Parts 1 and 2: bosutinib 100-mg capsules or 100-mg tablets Part 1: Dose levels studied were 400, 500, and 600 mg Part 2: selected dose=500 mg.	Randomised: 571 Treated: 570 - 18 in Part 1 - 553 in Part 2		QD until disease progression, unacceptable toxicity, or withdrawal of consent. database snapshot of 28 March 2011
		CP CML Second line	288	Sex: 135F/153M Mean Age (min/max): 52 (18/91) years Race, % W/B/A/O: 64/5/19/12	
		CP CML Third line	118	Sex: 65F/53M Mean Age (min/max): 54 (20/79) years Race, % W/B/A/O:	

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics	Duration of Treatment
				72/3/11/14	
		Advanced phase Ph+ leukaemias (AP and BP CML; Ph+ ALL)	164	Sex: 69F/95M Mean Age (min/max): 50 (18/84) years Race, % W/B/A/O: 63/11/13/13	
3160A4-3000-WW	Phase 3 randomised open-label trial. 1/ to compare the efficacy (rate of CCyR at 1 year) of bosutinib vs imatinib in subjects with chronic phase (CP) CML. 2/ to compare MMR at 1 year, duration of CCyR, CHR, and MMR, time to transformation to AP and BP; to assess the population PK; to assess the comparative safety of bosutinib vs imatinib.	Bosutinib 500 mg QD (100-mg tablets).	Randomised: 250 Treated: 248	Sex: 101F/149M Mean Age (min/max): 47 (19/91) years Race, % W/B/A/O: 64.5/1.0/24.15/10.4	QD until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, or withdrawal of consent data cutoff: 31 August 2010
		Imatinib 400 mg QD (100-mg and/or 400-mg tablets).	Randomised: 252 Treated: 251	Sex: 117F/135M Mean Age (min/max): 46 (18/89) years Race, % W/B/A/O: 65/1/23/11	
			Total: Randomised: 502 Treated: 499	Sex: 218F/284M Mean Age (min/max): 47 (18/91) years Race, % W/B/A/O: 65/1/24/10	

2.5.1. Dose response studies

Evidence for bosutinib doses and dosing regimen used in Phase 2 and 3 studies was obtained in studies 100-US in subjects with advanced solid malignant tumours (ASMT), study 200-WW in subjects with Ph+ leukaemias, and in Study 103-EU in healthy subjects.

In Study 100-US, ASMT patients received bosutinib at doses of 50 to 600 mg. However, due to the number of Grade 2 gastrointestinal toxicities observed in the 500-mg lead-in cohort, 400 mg was selected as the recommended daily dose for Part 2 of Study 100-US. Based on this experience the 400 mg dose was selected also as the starting dose in Part 1 of Study 200-WW.

In the part I of this completed trial, 18 subjects total were enrolled, at dose levels of 400 mg, 500 mg and 600 mg. The applicant stated that sample size for Part 1 of the study was determined by clinical rather than statistical considerations, without further explanations.

There were 1 dose-limiting toxicity (DLT; grade 3 rash) and 2 “near” DLTs (grade 2 rash and grade 2 diarrhoea) observed at the 600-mg dose level. As a result of this finding the 500-mg daily dose was selected to be taken with food as the recommended starting dose for patients enrolled in Part 2. As clinical efficacy was seen at doses of 500 mg in 200 WW and dose escalation to 600 mg resulted in distinctly more toxicity no more dose response studies were performed

In conclusion, dose finding was obviously dominated by the toxicity observed and no formal dose finding was performed. This might be justified for a drug where exposure was limited due to very high rate of diarrhoea events and other adverse events observed above a dose of 400mg or 500 mg, respectively.

2.5.2. Main studies

Study 200-WW

Methods

This pivotal study was an open-label, multicentre, 2-part, safety and efficacy study of bosutinib in subjects with Philadelphia chromosome positive (Ph+) leukaemia. Part 1 was a dose-escalation study in subjects with CP CML who were resistant/refractory to imatinib to establish the MTD in this subject population and determine a dose for part 2. Part 2 studied the efficacy and safety of bosutinib in this partially heavily pretreated population with more advanced disease stages.

The post-hoc defined subpopulation of patients with a “high medical need” of this trial was pivotal for the applied last-line indication.

Study Participants

Part 1 of the study included patients with CP CML who were resistant/refractory to imatinib. Part 2 studied the efficacy of bosutinib 500 mg daily in subjects with CP, imatinib-resistant/refractory CML, who had no prior Src, Abl, or Src-Abl inhibitor exposure other than imatinib. Part 2 also included exploratory cohorts of the following subjects:

- CP CML imatinib intolerant
- CP CML imatinib resistant/intolerant followed by dasatinib resistance
- CP CML imatinib resistant/intolerant followed by dasatinib intolerance
- CP CML imatinib resistant/intolerant followed by nilotinib resistance
- CP CML imatinib resistant/intolerant followed by nilotinib resistant/intolerant and dasatinib (Imatinib + NI +/or D) (In this cohort, there was 1 subject who only received previous imatinib and nilotinib and no prior therapy with dasatinib; the subject was nilotinib intolerant).
- Advanced Ph+ leukaemia (AP CML, BP CML, Ph+ ALL)

Treatments

In Part 1, bosutinib once daily dosing was studied at 3 dose levels (400 mg, 500 mg, and 600 mg).

Further to completion of Part 1, the 500-mg daily was the recommended starting dose for patients enrolled in Part 2. Dose escalations to 600 mg were permitted for subjects who had a suboptimal response to 500 mg provided they were not exhibiting toxicity. Dose reductions in 100-mg increments to a minimum dose of 300 mg daily were permitted for toxicity.

Objectives

The primary objectives of Part 2 of the study were to:

- Determine the rate of attaining major cytogenetic response (MCyR) in subjects with imatinib-resistant CP CML, who had no prior Src, Abl, or Src-Abl kinase inhibitor exposure other than imatinib
- Determine the population pharmacokinetic (PK) parameters of this population (includes all subjects in Part 2)

The secondary objectives of Part 2 of the study were to:

- Estimate the time to and duration of MCyR in subjects with imatinib-resistant CP CML, who had no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
- Estimate the MCyR rate in CP CML subjects intolerant of imatinib, who had no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
- Estimate the time to and duration of MCyR in CP CML subjects intolerant of imatinib, who had no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
- Estimate the time to and duration of complete haematologic response (CHR) in the imatinib-resistant and imatinib-intolerant groups
- Estimate MCyR rate in CP CML subjects who failed imatinib and were resistant to other tyrosine kinase inhibitors (TKIs; dasatinib or nilotinib)
- Estimate MCyR rate in CP CML subjects who failed imatinib and were intolerant to dasatinib
- Estimate overall survival (OS) and progression-free survival (PFS) rates at 1 and 2 years
- Estimate CHR rate in advanced leukaemia (AP CML, BP CML, Ph+ ALL) subjects
- Estimate overall haematologic response (OHR) rate in imatinib-resistant AP and BP CML subjects
- Assess the safety of bosutinib during prolonged oral exposure in a leukaemic population.

Outcomes / endpoints

a.) Clinical evaluation of efficacy **CP CML** patients who were **resistant to imatinib:**

- MCyR (PCyR or CCyR) at 24 weeks

(This primary endpoint was met, lending support to evaluation of secondary endpoints.)

b.) Clinical evaluation of efficacy in **CP CML** patients who had **received prior imatinib only**:

- cumulative MCyR and MMR.

c.) Clinical evaluation of efficacy in the **CP CML** patients **who had received imatinib and either dasatinib and / or nilotinib:**

- efficacy endpoints of cytogenetic and haematologic responses,
- time to and durations of these responses
- transformation to AP/BP, PFS, OS (with 13 months minimum follow-up [time from last patient's first dose to database snapshot]) and
- efficacy by baseline BCR-ABL kinase mutational status, as reported in the previously submitted

Mature data from updated analyses from the database snapshot of 15 February 2012, which corresponds to a minimum follow-up of 25 months for all treated CP CML patients who had received prior imatinib and dasatinib and/or nilotinib is available.

d.) Clinical evaluation of efficacy in **advanced phase (AP and BP) CML patients**:

- cytogenetic and haematologic responses,
- time to and duration of these responses,
- transformation to BP for AP patients,
- PFS, and OS.

Cytogenetic and haematologic efficacy analyses in Study 200-WW utilised the evaluable population, which included all treated patients with an adequate baseline assessment for the respective response. All treated patients were included in the analyses of PFS and OS, and patients with at least one post-baseline haematologic assessment were included in the analyses of AP/BP transformation.

Sample size

Not applicable.

Randomisation

Not applicable.

Blinding (masking)

Not applicable.

Statistical methods

The analysis of the primary and key secondary efficacy endpoints was performed for the evaluable population. PFS and OS were also analyzed based on the all-treated population. Populations for exploratory endpoints were defined mostly on a post-hoc basis.

- -Evaluable Population: The evaluable population is defined as all enrolled subjects who received at least 1 dose of bosutinib and had an adequate baseline efficacy assessment.
- -All-treated Population: The all-treated population is defined as all enrolled subjects who received at least 1 dose of bosutinib. Note: Based on this definition, the all-treated population is also the population used in the safety analysis, which is referred to as the safety population.

Results

Participant flow

A total of 571 subjects were enrolled in the study; 570 subjects received at least 1 dose of study drug (all-treated population or safety population). Of these 570 subjects, 18 subjects (400 mg: 3 subjects, 500 mg: 3 subjects, and 600 mg: 12 subjects) participated in Part 1 of the study and continued into Part 2. The remaining subjects were enrolled in Part 2 of the study and initiated treatment at the recommended starting dose for Part 2, as determined at the end of Part 1 (500 mg). In China, 3 subjects with CP CML who met eligibility criteria for Part 1 were enrolled in Part 2 of the study. These subjects were to receive 400 mg of bosutinib, with safety and PK assessments performed as described per protocol for Part 2.

Following a 28-day period for safety assessment of the Chinese subjects, dosing at 500 mg of bosutinib could begin. Chinese subjects receiving an initial dose of 400 mg were eligible for dose escalations based on the conditions described above.

An overview of the number of subjects enrolled who received at least 1 dose of study drug and the key efficacy endpoints are summarised in the table below.

Table 9. Number of Planned and Enrolled Subjects by Cohort and Disease Group Including Key Efficacy Endpoints in study 200-WW

Disease Status	Key Efficacy Endpoint	Number of Subjects	
		Planned	Enrolled
CP CML 2nd line (prior imatinib only)			
CP CML imatinib resistant	MCyR at Week 24	186	200
CP CML imatinib intolerant	MCyR at Week 24	61	88
CP CML 3rd line (prior imatinib and at least 1 additional TKI)			
Nilotinib intolerant or nilotinib and dasatinib intolerant/resistant[a]	MCyR by Week 24	NA	4
Dasatinib resistant	MCyR by Week 24	32	37
Dasatinib intolerant	MCyR by Week 24	39	50
Nilotinib resistant	MCyR by Week 24	32	27
Advanced phase CML 2nd line (prior imatinib only)[b]			
AP CML	OHR by Week 48	55	45
BP CML	OHR by Week 48	50	35
Advanced phase CML Multiple TKI exposure (prior imatinib and at least 1 additional TKI)[a]			
AP CML	OHR by Week 48	NA	31
BP CML	OHR by Week 48	NA	29
Ph+ ALL (prior imatinib only or multiple TKI exposure)[a,c]	OHR by Week 48	NA	24

Abbreviations: AP=accelerated phase, BP=blast phase, CHR=complete hematologic response, CP=chronic phase, CML=chronic myelogenous leukemia, MCyR=major cytogenetic response, NA=not applicable, OHR=overall hematologic response, Ph+ ALL=Philadelphia chromosome-positive acute lymphoblastic leukemia, TKI=tyrosine kinase inhibitor

a. Results were to be summarized descriptively.

b. The key endpoint for the advanced phase second-line cohort was CHR by Week 24; however, based on the interim results, the Ph+ ALL cohort was discontinued and the endpoint for AP and BP CML in the second-line setting was changed to the OHR rate at Week 48.

c. Based on the interim results, the Ph+ ALL cohort was discontinued and the results in the second- and third-line setting were combined.

Among the 118 CP CML patients in the all-treated population who had received prior imatinib and dasatinib and/or nilotinib and who took at least 1 dose of bosutinib, all patients had received prior therapy with imatinib (resistant or intolerant) as first-line treatment, and 37 patients were dasatinib-resistant, 50 were dasatinib-intolerant, 27 were nilotinib-resistant and 1 patient was nilotinib intolerant. Additionally, 3 patients received bosutinib after treatment with all 3 currently approved TKIs: 2 patients were resistant to all 3 prior TKI therapies (imatinib, dasatinib, nilotinib) and 1 was intolerant of all 3 prior TKI therapies.

In the CP CML all-treated population of patients treated with 2 or more TKIs (imatinib and 1 or both second-generation TKIs [third-line treatment group]), the median duration of treatment was 8.3 months (range 0.23 to 51.78) and the minimum follow-up (i.e., duration from the last patient's first dose to database snapshot) was 13.4 months as of the 28 March 2011 database snapshot and median duration of treatment was 8.6 months (range 0.23 to 60.82) and the minimum follow-up was approximately 25 months as of the 15 February 2012 database snapshot.

In the advanced phase CML reference population of patients treated with 1 or more TKIs (imatinib only or imatinib and 1 or both second-generation TKIs) 76 patients were in accelerated phase (AP) and 64 in blast phase (BP). Median duration of treatment in the advanced phase CML population was 10.1 months (range 0.1 to 51.64) for AP CML patients and 2.8 months (range 0.03 to 44.24) for BP

CML patients. The minimum follow-up was 12.3 months for AP CML and 18 months for BP CML patients as of the 28 March 2011 database snapshot.

After a first line CP-CML indication for bosutinib based on study 3000-WW was assessed to be not approvable (for details please refer to "supportive studies") also the second-line indication was precluded. According the relevant CHMP guideline-document a comparative study for bosutinib against the EU-approved second line TKIs (dasatinib and nilotinib) is necessary for approval.

Insofar, only a last line indication for patients with CML and "Unmet Medical Need" could be discussed for an approval of bosutinib. In order to demonstrate efficacy and safety in this setting a post-hoc defined subpopulation of study 200-WW was selected for further assessment.

Tthe following approach was used to identify patients with "Unmet Medical Need" in Chronic Phase and Advanced Phase (AP and BP) CML:

Following imatinib failure, clinical practice guidelines (ELN) recommend treatment with a second-generation TKI (dasatinib or nilotinib). There are, however, patients for whom either dasatinib or nilotinib may not be considered suitable treatment after failure of the other second generation agent due to a pre-existing medical condition, TKI intolerance, or mutation which would be expected to confer resistance to that therapy. In addition, there are patients who had received prior imatinib only for whom neither second-generation TKI agent may be considered a suitable treatment for the above referenced reasons. These patients represent a population with a significant medical need.

To identify these subpopulations, the Applicant conducted a review of the Study 200-WW CP CML and advanced phase CML reference populations, using the post-hoc selection algorithm as displayed in the table below. It includes the presence of a BCR-ABL kinase domain mutation that would be reasonably expected to confer resistance to dasatinib (F317, E255) or nilotinib (E255, Y253, F359) and expected to have sensitivity to bosutinib, or the presence of medical conditions or prior toxicities that may predispose the patient to unacceptable risk in the setting of nilotinib or dasatinib therapy (Table 10). These prior toxicities were selected based on adverse drug reactions associated with treatment with other TKIs.

Table 10. Criteria Used to Identify the "Unmet Medical Need" Subpopulation in Study 200-WW

	Nilotinib Risk Factors	**Dasatinib Risk Factors**
Mutation	Y253, E255, F359	F317, E255
Medical History or evidence of prior TKI intolerance	Coronary artery occlusion, coronary arterial stent insertion, arterial occlusive disease, coronary artery disease, arteriosclerosis, glucose tolerance impaired, coronary angioplasty, coronary artery bypass, hyperglycaemia, hypertriglyceridaemia, diabetes, pancreatitis	Pleural effusion, blood pressure increased, interstitial lung disease, chronic obstructive pulmonary disease, bronchitis chronic, pulmonary hypertension, pulmonary fibrosis, pulmonary oedema, emphysema, hypertension (Grade 3 or 4), cardiomyopathy, cardiac failure, ventricular failure, ventricular dysfunction, myocardial infarction, myocardial ischemia, respiratory disorder

Based on these selection criteria, 4 subpopulations (n=52 patients) with "unmet medical need" were identified as displayed in the figure below.

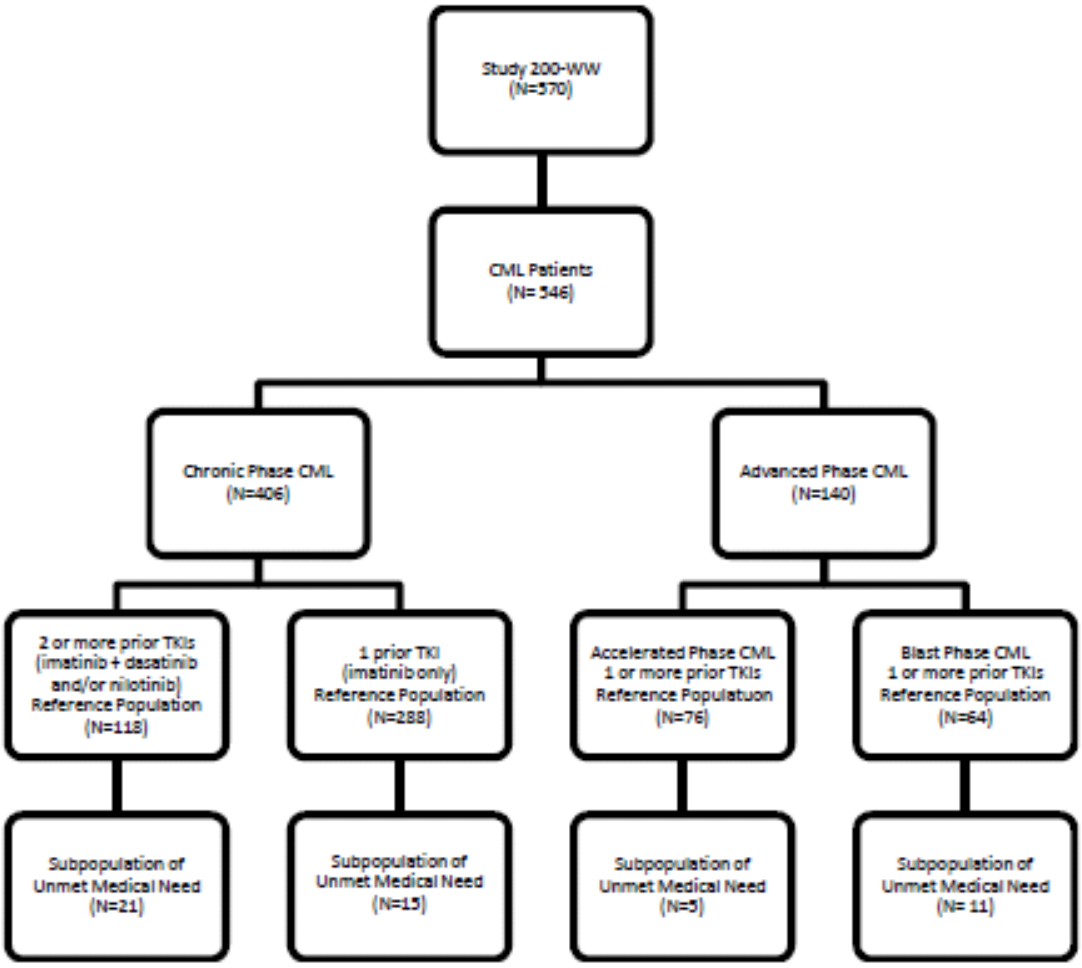


Figure 1 - Subpopulations of patients with an unmet medical need identified and reference populations of patients in Study 200-WW

In conclusion, of the 52 patients identified, 36 patients were in the CP CML subpopulation (21 who had previously received 2 prior TKIs and 15 who had received 1 prior TKI). And there was also a subpopulation of 16 advanced phase patients (5 AP CML and 11 BP CML patients) that failed treatment with either imatinib alone or imatinib in addition to one or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) were not considered appropriate treatment options.

Recruitment

The study is ongoing. The study started on 18 January 2006 and was conducted in 26 countries (including 9 European countries). Interim data for the reference populations are based on the 28 March 2011 database snapshot. Updated data as of the 15 February 2012 database snapshot were added for the major endpoints in the third-line CP CML reference population, including an analysis of efficacy by baseline mutation status.

Conduct of the study

There were 5 protocol amendments.

Baseline data

Demographics and baseline characteristics of the subpopulation identified with “unmet medical need” are presented in the table below.

Table 11. Demographic and Baseline Characteristics of “Unmet Medical Need” Subpopulation in Study 200-WW

	Cohort				
	Chronic Phase Second Line (n = 15) [n(%)]	**Chronic Phase Third Line (n = 21) [n(%)]**	**AP Total (n = 5) [n(%)]**	**BP Total (n = 11) [n(%)]**	**TOTAL (n = 52) [n(%)]**
Characteristic					
SEX					
Female	5 (33)	10 (48)	2 (40)	4 (36)	21 (40)
Male	10 (67)	11 (52)	3 (60)	7 (64)	31 (60)
RACE					
Asian	0	2 (10)	0	2 (18)	4 (8)
Black	1 (7)	2 (10)	0	4 (36)	7 (13)
Other[b]	2 (13)	3 (14)	0	0	5 (10)
White	12 (80)	14 (67)	5 (100)	5 (45)	36 (69)
WEIGHT (kg)					
N	15	21	5	11	52
Mean	88.60	76.62	77.20	74.12	79.60
Standard Deviation	22.34	15.62	19.64	14.96	18.48
Minimum	58.00	50.00	52.50	54.50	50.00
Maximum	141.90	117.40	98.30	94.30	141.90
Median	88.80	72.20	78.50	72.60	78.00
HEIGHT (cm)					
N	15	20	4	11	50
Mean	171.51	168.93	167.75	172.05	170.30
Standard Deviation	9.89	8.95	9.95	5.74	8.62
Minimum	156.00	156.00	156.00	162.00	156.00
Maximum	194.00	191.00	179.00	180.00	194.00
Median	170.00	166.50	168.00	172.70	170.00
Missing	0	1	1	0	2
AGE (yrs)					
N	15	21	5	11	52
Mean	61.47	58.71	62.40	46.55	57.29
Standard Deviation	14.65	11.25	11.76	21.39	15.57
Minimum	24.00	30.00	48.00	19.00	19.00
Maximum	81.00	79.00	73.00	80.00	81.00
Median	65.00	58.00	66.00	51.00	58.00
AGE CATEGORY					
AGE<65	6 (40)	14 (67)	2 (40)	9 (82)	31 (60)
Age>=65	9 (60)	7 (33)	3 (60)	2 (18)	21 (40)
ECOG PERFORMANCE STATUS					
0	6 (40)	13 (62)	1 (20)	2 (18)	22 (42)
1	9 (60)	8 (38)	4 (80)	6 (55)	27 (52)
2	0	0	0	3 (27)	3 (6)
NUMBER OF PRIOR THERAPIES [a]					
1	10 (67)	0	0	6 (55)	16 (31)
2	5 (33)	9 (43)	3 (60)	1 (9)	18 (35)
3	0	12 (57)	2 (40)	4 (36)	18 (35)
PRIOR INTERFERON THERAPY?					
No	10 (67)	9 (43)	1 (20)	7 (64)	27 (52)
Yes	5 (33)	12 (57)	4 (80)	4 (36)	25 (48)
PRIOR IMATINIB/GLEEVEC THERAPY?					

	Cohort				
	Chronic Phase Second Line (n = 15) [n(%)]	Chronic Phase Third Line (n = 21) [n(%)]	AP Total (n = 5) [n(%)]	BP Total (n = 11) [n(%)]	TOTAL (n = 52) [n(%)]
Characteristic					
Intolerant	3 (20)	6 (29)	1 (20)	2 (18)	12 (23)
Resistant	12 (80)	15 (71)	4 (80)	9 (82)	40 (77)
PRIOR DASATINIB/SPRYCEL THERAPY?					
No	15 (100)	5 (24)	2 (40)	9 (82)	31 (60)
Yes	0	16 (76)	3 (60)	2 (18)	21 (40)
PRIOR NILOTINIB THERAPY?					
No	15 (100)	16 (76)	5 (100)	8 (73)	44 (85)
Yes	0	5 (24)	0	3 (27)	8 (15)
PRIOR STEM CELL TRANSPLANT?					
No	14 (93)	20 (95)	3 (60)	10 (91)	47 (90)
Yes	1 (7)	1 (5)	2 (40)	1 (9)	5 (10)

Date of Snapshot: 28MAR11
Abbreviations: AP- Accelerated phase subjects, BP- Blast phase subjects
(a) If a subject received more than 1 treatment regimen with imatinib, dasatinib, nilotinib or interferon the subject is only counted once for the respective treatment

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Numbers analysed

A total of 571 subjects with Ph+ Leukemia were enrolled in the study 200-WW; 570 subjects (including 24 with Ph+ALL) received at least 1 dose of study drug (all-treated population or safety population). Of these 570 subjects, 18 subjects (400 mg: 3 subjects, 500 mg: 3 subjects, and 600 mg: 12 subjects) participated in Part 1 of the study and continued into Part 2. The remaining subjects were enrolled in Part 2 of the study and initiated treatment at the recommended starting dose for Part 2, as determined at the end of Part 1 (500 mg).

The reference population with CML patients enrolled 546 subjects (24 subjects with Ph+ALL excluded).

Among these patients, the applicant has identified in the included CP, AP, or BP CML patient a subpopulation with “unmet medical need” (n=52). To support the data in these subpopulations, results are summarised in the table below for the reference populations of CP and advanced phase CML from which the patients in these “unmet medical need” subpopulations were identified.

Table 12. “Unmet Medical Need” Subpopulations and Reference Populations in Study 200-WW

Disease Stage	Reference Population (N=546)[a]	Unmet Medical Need Subpopulation (N=52)
Chronic Phase CML	406	36
1 prior TKI (imatinib only)	***288***	***15***
2 prior TKIs (imatinib + dasatinib or nilotinib)	***118[b]***	***21***
Advanced Phase CML (1 or 2 prior TKIs)	***140***	***16***
Accelerated phase	76[c]	5
Blast phase	64[d]	11

Abbreviations: CML=chronic myelogenous leukaemia; TKI=tyrosine kinase inhibitor.
a. N=546 does not include the 24 Ph+ALL patients in the study.
b. Includes 3 patients who received imatinib, dasatinib, and nilotinib.
c. Includes 10 patients who received imatinib, dasatinib, and nilotinib.
d. Includes 6 patients who received imatinib, dasatinib, and nilotinib.
Source: Study 200-WW CSR, Table 7-3, Table 7-4, Section 9.1.1, and Section 10.2.1.13; Module 5, Table 1; Module 5, Table 2; Module 5, Table 3; Module 5, Table 4; Module 5, Table 5

Outcomes and estimation

Efficacy for patients identified within the Phase 1/2 study population who failed either imatinib alone or imatinib in addition to one or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) are not considered appropriate treatment options was reviewed. Of the 52 patients identified, 36 patients were in the CP CML subpopulation (21 who had previously received 2 prior TKIs and 15 who had received 1 prior TKI).

Of the 21 CP CML patients treated with Bosulif following failure of imatinib and 1 additional second-generation TKI identified, 9 of these patients had MCyR or better including 2 patients with complete molecular response (CMR), 1 patient with major molecular response (MMR), 4 patients with CCyR, and 2 patients with partial cytogenetic response (PCyR) and had a treatment duration exceeding 24 weeks. In addition, 7 other patients had a response of CHR on Bosulif treatment. Among the 9 patients with a response of MCyR or better, duration of MCyR ranged from 8 to 204 weeks with a treatment duration ranging from 35 to 215+ weeks.

There were 15 patients who received imatinib and no other second-generation TKI who met these criteria. Of these 15 patients with "unmet medical need" who had received prior imatinib only, 9 patients had a response on Bosulif treatment of MCyR or better, including 3 patients with CMR, 1 patient with MMR, 4 patients with CCyR, and 1 patients with PCyR with a duration of MCyR ranging from 12 to 155 weeks and a treatment duration ranging from 24 to 197+ weeks.

There was also a subpopulation of 16 advanced phase patients (5 AP CML and 11 BP CML patients) that failed treatment with either imatinib alone or imatinib in addition to one or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) were not considered appropriate treatment options. Of these, 4 of the 5 AP patients had notable treatment duration with a range from 46 to 114 weeks with responses including CMR (1 patient), CCyR (2 patients) and major haematologic response (MaHR) (1 patient) with 1 patient still on treatment. Among the 11 BP CML patients, 3 patients remained on treatment for more than 24 weeks with notable responses (2 patients with a CCyR and 1 patient with a MaHR) and a treatment duration ranging from 46 to 118 weeks with one patient still on treatment.

Efficacy in the reference population of Study 200-WW are also presented in the table below. Number of patients (N) in this table differs for the different endpoints due to different evaluable populations for the different endpoints.

Table 13. Study 200-WW Efficacy results in previously treated patients with chronic and advanced phase CML

	Ph+ CP CML with prior imatinib treatment only	**Ph+ CP CML With prior treatment with Imatinib and Dasatinib or Nilotinib**	**Accelerated Phase With prior treatment of at least Imatinib**	**Blast Phase With prior treatment of at least Imatinib**
Cumulative Cytogenetic Response[a]	N=266	N=110	N=69	N=54
MCyR, % (95% CI)	59.0 (52.9,65.0)	40.9 (31.6,50.7)	34.8 (23.7,47.2)	29.6 (18.0,43.6)
CCyR, % (95% CI)	48.1 (42.0,54.3)	31.8 (23.3,41.4)	24.6 (15.1,36.5)	20.4 (10.6,33.5)

Time to MCyR for responders only[b], wks (95% CI)	12.3 (12.1, 12.9)	12.3 (12.0, 22.3)	12 (8.1, 12.3)	8.2 (4.3, 12.1)
Duration of MCyR[b] **K-M at Year 1 % (95% CI)** **K-M at Year 2 % (95% CI)** **Median , wks (95% CI)**	N=157 76.5 (68.5, 82.7) 76.5 (68.5, 82.7) N/R	N=45 74.0 (56.9, 85.1) 70.9 (53.5,82.8) N/R	N=24 62.4 (38.6, 79.1) N/A[c] 73.0 (36.1, N/E)	N=16 7.9 (0.5, 29.8) N/A[c] 28.9 (11.9, 29.6)
Cumulative Hematologic Response[d] **Overall, % (95% CI)** **Major, % (95% CI)** **Complete, % (95% CI)**	N=287 N/A N/A 85.0 (80.4, 88.9)	N=115 N/A N/A 73.0 (64.0, 80.9)	N=69 55.1 (42.6,67.1) 46.4 (34.3,58.8) 34.8 (23.7,47.2)	N=60 28.3 (17.5,41.4) 18.3 (9.5,30.4) 15.0 (7.1,26.6)
Time to OHR for responders only, wks (95% CI)	N/A	N/A	12 (11.1, 12.1)	8.9 (4.1, 12.0)
Duration of CHR/OHR[e] **K-M at Year 1 % (95% CI)** **K-M at Year 2, % (95% CI)** **Median, wks (95% CI)**	N=244 84.6 (79.0, 88.8) 72.1 (65.2, 77.8) N/R	N=84 72.6 (60.7, 81.5) 67.4 (54.9, 77.2) N/R	N=38 80.0 (60.5,90.5) N/A[c] N/R	N=17 25.0 (7.8,47.2) N/A[c] 31.5 (28.9, 48.0)
Transformation to AP/BP[f] **On-treatment transformation, n**	N=288 11	N=118 5	N=63 4	N/A
Progression Free Survival[g] **K-M at Year 1, % (95% CI)** **K-M at Year 2, % (95% CI)** **Median, months (95% CI)**	N=288 91.3 (86.8, 94.3) 80.6 (74.3,85.4) N/R	N=119 78.3 (67.9, 85.6) 75.1 (64.2,83.1) N/R	N=76 64.9 (51.8,75.3) N/A[c] 22.1 (14.6, N/E)	N=64 14.4 (6.0,26.4) N/A[c] 5.5 (3.2, 8.3)
Overall Survival[g] **K-M at Year 1, % (95% CI)** **K-M at Year 2, % (95% CI)** **Median, months (95% CI)**	N=288 96.8 (94.0, 98.3) 90.6 (86.5,93.5) N/R	N=119 91.4 (84.6, 95.3) 84.0 (75.8,89.6) N/R	N=76 76.0 (64.7,84.2) N/A[c] N/R	N=64 43.8 (31.3,55.6) N/A[c] 11.1 (8.9, 19.8)

Snapshot date: 15Feb12 for CP treated with imatinib and at least one other TKI and 28Mar11 for AP and BP and CP treated with imatinib only.

Abbreviations: K-M=Kaplan-Meier, N/A=Not applicable, N/R = Not reached, N/E=Not estimable, CI=confidence interval, MCyR=major cytogenetic response, CCyR=complete cytogenetic response, OHR= Overall haematologic response, CHR = Complete haematologic response.

Cytogenetic Response criteria: Major Cytogenetic response included Complete (0% Ph+ metaphases from bone marrow or <1% positive cells from fluorescent in situ hybridization [FISH]) or partial (1%-35%) cytogenetic responses. Cytogenetic responses were based on the percentage of Ph+ metaphases among >/= 20 metaphase cells in each bone marrow sample. FISH analysis (>/= 200 cells) could be used for post-baseline cytogenetic assessments if >/= 20 metaphases were not available.

Overall haematologic response (OHR) = major haematologic response (complete haematologic response + no evidence of leukaemia) or return to chronic phase (RCP). All responses were confirmed after 4 weeks. Complete haematologic response (CHR) for AP and BP CML: WBC less than or equal to institutional ULN, platelets greater than or equal to 100,000/mm^3 and less than 450,000/mm^3, absolute neutrophil count (ANC) greater than or equal to 1.0 x 10^9/L, no blasts or promyelocytes in peripheral blood, less than 5% myelocytes + metamyelocytes in bone marrow, less than 20% basophils in peripheral blood, and no extramedullary involvement. No evidence of leukaemia (NEL): Meets all other criteria for CHR except may have thrombocytopenia (platelets greater than or equal to 20,000/mm^3 and less than 100,000/mm^3) and/or neutropenia (ANC greater than or equal to 0.5 x 10^9/L and less than 1.0 x 10^9/L). Return to chronic phase (RCP) =disappearance of features defining accelerated or blast phases but still in chronic phase.

[a] Includes patients (N) with a valid baseline assessment. For CP patients, the analyses allow baseline responders who maintained response post-baseline to be responders. Minimum follow-up time (time from last patient first dose to data snapshot date) of 24 months for CP treated with imatinib only, 25 months for CP treated with imatinib and at least one other TKI, 12 months for AP and 18 months for BP.

[b] For CP patients, includes patients (N) who attained or maintained MCyR.
[c] For AP and BP patients, 2-year data is not provided as minimum follow-up time is 12 and 18 months respectively.
[d] Sample size (N) includes patients with a valid baseline haematologic assessment. These analyses allow baseline responders who maintained response post-baseline to be responders.
[e] Includes patients (N) who attained or maintained CHR for CP patients and OHR for AP and BP patients.
[f] Including patients (N) with at least 1 post-baseline haematologic assessment.
[g] Including patients (N) who received at least one dose of Bosulif.

Summary of main study

The following table summarise 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 14. Summary of Efficacy for the subpopulation of patients with "Unmet Medical Need" from study 3160A4-200-WW

Title: A Phase 1/2 Study of SKI-606 in Philadelphia Chromosome Positive Leukaemia				
Study identifier	Study 3160A4-200-WW (EUDRACT 2005-004230-40)			
Design	Open-label, continuous daily dosing, two-part safety and efficacy study.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable not applicable	
Hypothesis	Exploratory: Non-Randomized Safety/Efficacy Study			
Treatments groups	Part 1		starting dose 400 mg oral, daily dosing in the dose-escalation component	
	Part 2		500 mg oral, continuous, daily dosing	
Endpoints and definitions	Primary endpoint	MCyR	for chronic phase CML patients Time Frame: Every 3 months until Year 2, every 6 months thereafter, until treatment failure]	
Database lock	28 March 2011			
Results and Analysis				
Analysis description	**Subgroup Analysis**			
Analysis population and time point description	"Unmet medical need" subgroup (see definition in the text) in the evaluable (all enrolled subjects who received at least 1 dose of bosutinib and had an adequate baseline efficacy assessment) population			
Descriptive statistics and estimate variability	Treatment group	Bosutinib - Chronic Phase CML	Bosutinib – Accelerated Phase CML	Bosutinib – Blast Phase CML
	Number of subjects	36	5	11
	MCyR (n)	9	3	2
	Multiple efficacy endpoints (see text) (n)	2 CMR 1 MMR 4 CCyR 2 PCyR	1 CMR 2 CCyR 1 MaHR	2 CCyR 1 MaHR

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

Not applicable.

Clinical studies in special populations

No clinical studies in special populations were performed in this explorative setting with a very heterogenous population.

Supportive studies

Compassionate use data

Additional supportive data was provided regarding 16 CML patients treated with bosutinib in the "compassionate use" setting, in which bosutinib was provided to patients with no alternative TKI treatment options. Bosutinib treatment led to clinical relevant benefit and appeared to be well tolerated in these patients with an "unmet medical need".

At least 10 of these 16 patients with no other TKI treatment option had a clinically relevant response to bosutinib. All patients had a diagnosis of Ph+ CML in CP, AP, or BP and patients were considered by their treating physicians to have no other available or suitable TKI option.

The following reasons for resistance and/or intolerance to previous TKI therapies are summarised for the 16 patients identified from the compassionate use program. All 16 patients received prior imatinib therapy, and 15 of the 16 also received both dasatinib and nilotinib.

Imatinib

Nine (9) patients discontinued imatinib due to resistance (IM-R), while 7 patients discontinued imatinib due to drug intolerance.

Of the 10 IM-R patients, 1 patient received imatinib only, which was discontinued due to the presence of a new mutation, F359V. This mutation ruled out both imatinib and nilotinib as therapy options, while the presence of recurrent pleural effusions contraindicated treatment with dasatinib. For the other 8 IM-R patients, specific reasons for resistance provided by the treating physicians included:

- Primary resistance in 3 patients
- Progressive disease – loss of response in 4 patients
- Progressive disease – presence of new mutations (F359V, Y253H/E459K and "Various mutations" not specified, in 1 patient each)

Drug intolerance associated with imatinib discontinuation in 6 patients included the following toxicities: rash/dermal toxicity (4 patients); hepatic and renal toxicity, diarrhoea, cytopenia, stomatitis, and severe diarrhoea with weight loss (1 patient each). Notably, 5 of the 6 patients also discontinued dasatinib and nilotinib due to intolerance.

Dasatinib

As noted, fifteen compassionate use patients received dasatinib as a prior therapy from which the majority discontinued due to drug intolerance (13 patients). Resistance was reported as the reason for

dasatinib discontinuation in only 2 patients with the following additional information provided by the treating physician:

- Progressive disease -- loss of response in 1 patient
- Progressive disease – "various mutations" in 1 patient

Drug intolerance reported for dasatinib in 13 patients included the following toxicities: pleural effusion (5 patients); fever, pain, neuropathic disorders, skin lesions, allergic reaction, arthralgia, throat tightness, interstitial pulmonary oedema and unspecified (1 patient each.)

Nilotinib

Fifteen compassionate use patients also received nilotinib as a prior therapy and resistance was reported as the reason for nilotinib discontinuation in 7 patients with the following additional information provided by the treating physician:

- Primary resistance in 2 patients (due to lack of molecular response, drug was no longer reimbursable by payor, thus discontinued for 1 pt)
- Progressive disease -- loss of response in 3 patients
- Progressive disease – mutations in 2 patients (G250E and F359C)

Drug intolerance was reported as the reason for nilotinib discontinuation in the remaining 8 patients and included the following toxicities: cardiotoxicity, myocardial infarction, LFT elevations, headache, rash and abdominal/back pain (1 patient each) and unspecified (2 patients).

In conclusion, bosutinib treatment led to clinical relevant benefit and appeared to be well tolerated in at least 10 these patients with an "unmet medical need".

Study 3000-WW

Study 3000-WW was a multinational, multicentre, randomised, open-label, parallel-arm phase 3 study to compare the efficacy and safety of bosutinib alone to that of imatinib alone in subjects with newly diagnosed chronic phase CML.

Methods

Study design and treatment

After screening, eligible subjects were randomised to receive either bosutinib 500 mg per day or imatinib 400 mg per day. Randomisation of subjects into each arm was stratified based on Sokal score (low, intermediate, high) and geographical region.

In both treatment arms, subjects were allowed to dose escalate to 600 mg as long as there were no grade 3/4 or persistent grade 2 adverse drug reactions, and if at least 1 of the following conditions was met: CHR was not attained after 12 weeks of treatment, or MCyR was not attained after 24 weeks of treatment, or CCyR was not attained after 48 weeks of treatment, or the subject had loss of CHR or loss of CCyR.

The trial enrolled adult subjects ≥18 years with newly diagnosed CP CML, defined as having a cytogenetic diagnosis of Ph+ CP CML for ≤ 6 months. A total of 250 subjects randomised to receive

bosutinib and 252 subjects randomised to receive imatinib comprised the ITT population. Three subjects did not receive study drug and therefore, the safety population consisted of 248 subjects treated with bosutinib and 251 treated with imatinib.

Treatment

In study 3000 WW, subjects were randomly assigned in a 1:1 ratio to receive either bosutinib 500 mg once daily by mouth or imatinib 400 mg once daily by mouth. In both treatment arms, subjects were allowed to dose escalate to a daily dose of 600 mg, as long as there were no grade 3/4 or persistent grade 2 adverse events, and achievement of predefined efficacy endpoints was delayed.

The study consisted of a treatment phase and a follow-up phase. In the treatment phase, subjects were required to visit the clinic on weeks 1 (first day of treatment), 4, 8, 12, 16, 20, and 24, and then every 12 weeks while the subject was on treatment. Subjects will remain on treatment until completion of 8 years or early discontinuation due to treatment failure, unexpected toxicity, death, or consent withdrawal. Subjects who prematurely discontinue treatment for any reason prior to completion of 8 years may be entered into the follow-up phase. In the follow-up phase, subjects are contacted approximately every 3 months.

Dose-escalation up to 600 mg was only performed in 10 patients in the pivotal trial (compared with 32 patients in trial 200 WW). This might reflect the both the product's efficacy and its high level of toxicity.

Objective and efficacy endpoints

Study 3000-WW was designed as a superiority trial against imatinib regarding the following primary and secondary respectively exploratory endpoints:

Primary endpoint: CCyR rate at 1 year based on ITT population.

Short-term secondary endpoint: MMR rate at 1 year based on ITT population.

Long-term secondary endpoints: Duration of CCyR based on ITT population (responders only), duration of MMR based on ITT population (responders only), time to AP/BP based on ITT population, EFS based on ITT population, Duration of CHR based on ITT population (responders only).

Exploratory endpoints: time to response (CCyR, MMR, CHR), overall survival (OS).

Data baseline and demographics

With the exception of some imbalances regarding gender and race, the baseline characteristics of the study population (age, height, bodyweight, ECOG and Sokal risk) were balanced between the two study arms. The same is true with respect to the characteristics of the prior cancer therapy.

Efficacy populations

There were 3 populations analysed for this study: the intent-to-treat (ITT), safety, and evaluable populations.

The evaluable population included all subjects who were randomised, received at least 1 dose of test article, had no major violations and had an adequate baseline cytogenetic disease assessment (defined as having at least 1 Ph+ chromosome present at screening) and at least 1 adequate post baseline cytogenetic disease assessment (defined as having at least 20 metaphases by conventional cytogenetics or at least 200 cells by FISH). Subjects who experienced disease progression or death prior to week 12 (before the first post baseline cytogenetic assessment) were included in the evaluable population. In the course of the study, due to different causes, a number of patients were not analysed.

Results

A total of 460 subjects (219 bosutinib vs 241 imatinib) comprised the evaluable population, which included all randomised subjects who received at least 1 dose of study drug, had no major protocol violations determined to impact efficacy (e.g., concomitant other anti-cancer therapy), and had an adequate baseline and at least 1 adequate post baseline cytogenetic assessment. More subjects in the bosutinib arm (31 subjects) than in the imatinib arm (11 subjects) were excluded from the evaluable population. The most frequent reason for exclusion from the evaluable population in the bosutinib arm was no post baseline assessment (21 subjects).

Outcome for the primary efficacy endpoint

In the ITT population, the CCyR rate at 1 year was numerically higher on the bosutinib arm (70.0%, 95% CI: 64.3, 75.7) compared to the imatinib arm (67.9%, 95% CI: 62.1, 73.6), however, the difference did not reach statistical significance (2-sided p-value = 0.601 (CMH test, adjusted for Sokal score and geographic region). The adjusted odds ratio estimate was 1.10 (with the associated 95% CI of 0.74, 1.63).

Superiority with regard to the relevant primary endpoint of CCyR in the bosutinib arm in the ITT population was not established.

Furthermore, in the ITT population, the CCyR rate at 24 months was 57.6% (95% CI: 51.5%, 63.7%) in the bosutinib arm and 65.1% (95% CI: 59.2%, 71.0%) in the imatinib arm. The cumulative CCyR rate by 24 months in this population was 78.8% for the bosutinib arm (95% CI: 73.7%, 83.9%) compared to 79.8% with the imatinib arm (95% CI: 74.8%, 84.7%).

Outcome of Short-term secondary endpoint MMR rate at 1 year

Results of MMR by 1 Year in ITT Population are presented in the table below.

Table 15. Major Molecular Response (MMR) by 1 Year in ITT Population

	Bosutinib (n=250)	**Imatinib** (n=252)	Total (n=502)	p-value[a]
COMPLETE OR MAJOR MOLECULAR RESPONSE				
N (%) of subjects with MMR	98 (39.2)	66 (26.2)	164 (32.7)	0.002
N (%) of subjects with CMR	25 (10.0)	6 (2.4)	31 (6.2)	<0.001
Date of snapshot: 31AUG2010.				

Table 16. Derived Major Molecular Response at 24 Months: ITT Population

	Bosutinib (n=250)	Imatinib (n=252)	Total (n=502)
N (%) of subjects with MMR (or better)	**117 (46.8)**	**104 (41.3)**	**221 (44.0)**
95% CI for Rate	(40.6%, 53.0%)	(35.2%, 47.3%)	(39.7%, 48.4%)
N (%) of subjects with derived CMR (4.5 Log Sensitivity Analysis)[a]	2 (0.8)	6 (2.4)	8 (1.6)
95% CI for Rate	(0.0%, 1.9%)	(0.5%, 4.3%)	(0.5%, 2.7%)
N (%) of subjects with derived CMR (4.0 Log Sensitivity Analysis)[b]	40 (16.0)	31 (12.3)	71 (14.1)
95% CI for Rate	(11.5%, 20.5%)	(8.2%, 16.4%)	(11.1%, 17.2%)

Note: MMR (or better) is defined as any subject with [(BCR copies/ABL copies)^{IS}] ≤0.001 and ABL copies ≥3,000
a. CMR (4.5 log sensitivity) is defined as [(BCR Copies/ABL Copies)^{IS}] ≤0.000032 and ABL copies ≥25,614.
b. CMR (4.0 log sensitivity) is defined as any subject with [(BCR Copies/ABL copies)^{IS}] ≤0.0001 and ABL copies ≥8,100
Abbreviations: CMR=complete molecular response; ITT=intent to treat; MMR=major molecular response; n/N=number of subjects.
Source: MMR5SEN_M24 28FEB2012 9:33; CMR5SEN1B_M24 06DEC2011 10:54; CMR5SEN2B_M24 06DEC2011 10:54; and RESPRT_M24 28FEB2012 9:34.
Date of snapshot: 26SEP2011

Long-term secondary endpoints: Estimate the duration of CCyR, MMR and complete haematologic response (CHR)

In the bosutinib arm, 97.5% of subjects compared to 95.9% of subjects in the imatinib arm did not experience a loss of CCyR or treatment failure up to and including 1 year from the first response. In the bosutinib arm, 96.9% of subjects compared to 96.0% of subjects in the imatinib arm did not experience a loss of MMR or treatment failure up to including 1 year from the first response. Duration of MMR rate at 1 year was 97.1% in the bosutinib arm compared to 93.8% in the imatinib arm. In the bosutinib arm, 98.5% of subjects compared to 91.4% of subjects in the imatinib arm did not experience a loss of CHR or treatment failure up to including 1 year from the first response.

Analyses at 24 months were also provided: The Kaplan-Meier estimate of the probability of maintaining derived MMR at 24 months was 95.2% (95% CI: 89.5%, 97.8%) for bosutinib compared with 96.6% (95% CI: 91.1%, 98.7%) for imatinib.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The phase III Study 3000-WW was initially submitted as pivotal to support the authorisation of bosutinib in adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) in chronic phase (CP).

The primary endpoint selected was in accordance with the recommendations given in the relevant regulatory guideline document (Appendix 2 to the Guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 rev. 3) on haematological malignancies; EMEA/CHMP/EWP/520088/2008). Herein it is stated that complete cytogenetic response rate at 1 year is an acceptable primary objective only for superiority trials, whereas for non-inferiority trials, prolonged follow-up is needed prior to licensure and PFS is the preferred primary endpoint.

The pivotal study 3160A4-200-WW, which was a well-designed, open-label, uncontrolled efficacy and safety phase I/II study of bosutinib in Philadelphia chromosome-positive (Ph+) leukaemia, was performed to explore whether bosutinib has some efficacy in second and third line CP-CML-patients as well as in some of those with more advanced CML stages (AP-CML and BP-CML). This study, initially submitted as supportive to the claimed indication, became pivotal to the application.

Efficacy data and additional analyses

With respect to the posology, the effects of dose escalation to 600 mg bosutinib regarding efficacy and safety cannot be assessed from the information submitted. This has been reflected in the SmPC.

Although bosutinib has demonstrated efficacy in the intended target population in terms of attaining relevant surrogate endpoints as CCyR and MMR, Study 3000-WW failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib.

Results for the short term secondary endpoints MMR in the ITT demonstrate significant superiority against imatinib only at 12 months, while at 24 months this superiority disappeared. As the primary endpoint was missed the relevance of this finding remains questionable. Due to the gate-keeping procedure defined and the lack of adequate control of the type I error level of 5% in the amended statistical analysis plan, any conclusion of robust superiority for the short-term secondary endpoint MMR, and in particular for the important long-term secondary endpoints, is deemed questionable, as it can be expected that many subjects will be censored until end of follow-up.

Therefore, bosutinib could not be considered approvable for a 1st line indication in CML, although these data support that bosutinib is an active drug in CML and might also be efficacious in pre-treated patients at advanced disease stages.

Instead, results of study 200-WW were considered as pivotal to support an indication of Bosulif in a last-line CML indication. In this study, efficacy was seen in the subpopulation of CP, AP, and BP CML patients who, based on clearly defined criteria, may not be candidates for treatment with at least 1 of the currently approved TKI due to intolerance, mutations, or comorbidities. Although these subpopulations were small, the efficacy is further supported by the results seen in the larger reference populations within Study 200-WW.

In the CP CML subpopulations with “unmet medical need”, 9 of the 21 patients treated with bosutinib, following imatinib plus one additional TKI and for whom the remaining TKI was not suitable, saw notable responses (CMR, MMR, CCyR, or PCyR) associated with a treatment duration exceeding 24 weeks. For these 9 patients, the duration of MCyR ranged from 8 to 204+ weeks and treatment duration ranged from 35 to 215+ weeks as of the 28 March 2011 database snapshot. In addition, 9 of the 15 patients with unmet need treated with bosutinib following imatinib failure only also experienced notable responses (CMR, MMR, CCyR or PCyR). As of the 28 March 2011 database snapshot, the duration of MCyR ranged from 12 to 155+ weeks and a treatment duration ranging from 24 to 197+ weeks for these 9 patients.

For the reference population of CP CML patients previously treated with both imatinib and either one of the second generation TKIs (dasatinib or nilotinib), bosutinib was associated with MCyR and CCyR being attained or maintained by 40.9% and 31.8% of patients, with a minimum 25 months follow-up. Clinical benefit is furthermore supported by the durability of these cytogenetic responses with 1-year and 2-year K-M estimates of maintaining MCyR of 74.0% and 70.9%, respectively. The durability of these cytogenetic responses is critical as the maintenance of response will necessarily minimise the risk of transformation to AP or BP with their attendant poorer prognosis. Accordingly, only 5 of the 117 patients with a valid post-baseline haematologic assessment in the reference population experienced disease transformation to AP or BP CML while on bosutinib treatment. K-M estimates of PFS and OS at 2 years were 75.1% and 84%, respectively, underscoring the clinically meaningful, long-term benefit obtained with bosutinib in this setting. These efficacy results were consistent with those seen previously in patients after a minimum of 12 months follow-up.

Moreover, bosutinib efficacy (MCyR rates, PFS and OS) was comparable in patients who had a mutation detected at baseline versus those without a mutation in the reference population and, of particular note, cytogenetic responses were noted in patients who had mutations which would be expected to impart clinical resistance to dasatinib and/or nilotinib (with the exception of T315I).

Given that there are no TKIs currently approved for third-line therapy, comparative published data regarding the efficacy of nilotinib or dasatinib in this population are limited.

Of the 5 AP CML patients in the "unmet medical need" subpopulation, 4 patients experienced notable responses (CMR, CCyR, MaHR) associated with a treatment duration ranging from 46 to 114 weeks. In the AP CML reference population, analyses of confirmed OHR and MaHR were attained or maintained by 55.1% and 46.4% of patients, respectively, with a 1-year K-M estimate of maintaining an OHR of 80.0%. Furthermore, the 1-year K-M estimates of PFS and OS in AP patients were 64.9% and 76.0%, respectively.

Blast phase CML presents a significant treatment challenge with short median survival even with imatinib treatment (6.5 months). Of the 11 BP CML patients in the "unmet medical need" subpopulation who received more than 24 weeks of treatment, 3 showed notable responses (CCyR and MaHR) associated with a treatment duration ranging from 46 to 118 weeks. In the BP CML reference population, which also includes patients following failure with 1, 2 or even 3 prior TKIs, 28.3% and 18.3% of patients attained or maintained OHR and MaHR, respectively, after bosutinib therapy. These haematologic response rates are clinically meaningful considering the highly refractory nature of BP CML. Among responders, the median duration of OHR was 31.5 weeks, thereby highlighting a subset of patients who exhibited a benefit with bosutinib, with some patients maintaining a response years beyond the expected survival of BP CML patients.

In patients with BP CML treated with bosutinib, K-M estimates of median PFS and OS were 5.5 months and 11 months, respectively. Similar to the AP CML data, it is notable that these rates are comparable to PFS and OS data published for myeloid BP CML patients (6.7 months and 11.8 months, respectively) and lymphoid BP patients (3 months and 5.3 months, respectively), treated with dasatinib, the only second generation TKI approved for BP CML after imatinib failure, given that these latter patients had received imatinib as the only prior TKI therapy, as opposed to the bosutinib BP CML cohort which included more heavily treated patients (>1 TKI). The K-M estimates of PFS and OS at 1 year were 14.4% and 43.8%, respectively.

There was one patient, intolerant against all approved TKIs (imatinib, nilotinib and dasatinib), who achieved CCyR and MMR by Week 24 during bosutinib therapy and is still on treatment in study 200-WW.

Additionally, bosutinib has shown also similar clinical benefit in 10 patients in the "compassionate-use" setting, which included patients who had exhausted all available TKI therapies or for whom treatment with other available TKI(s) was deemed unsuitable by their physicians.

Furthermore, in patients who discontinued a prior TKI due to pleural effusion, or who had a prior history of cardiovascular, diabetes, or hyperglycaemia events, bosutinib appeared to have an acceptable safety profile.

However, it is acknowledged that due to the high degree of cross-resistance between bosutinib and dasatinib or nilotinib, efficacy is mainly seen in patients with intolerance to the approved TKIs. From the information submitted it can be concluded that patients with CP CML who have F317L and E255V mutation (both reported to confer resistance to dasatinib therapy), may respond to bosutinib. But from 10 evaluable patients with dasatinib resistance, only 1 patient (11.1%) with CML harbouring a F317L *BCR-ABL* mutation attained / maintained a MCyR until last analysis dated 15 February 2012. A better efficacy was observed in patients with some mutations which have been previously reported to confer

nilotinib resistance (Y253H, F359C/V). From 12 patients with these mutations, seven patients (58.3%) attained/maintained a MCyR with bosutinib. However, for the *E255K/V* mutation neither bosutinib nor nilotinib or dasatinib seemed to be efficacious.

Additionally, it is noted that in the subpopulation with "unmet medical need", 2 patients with mutations that would reasonably be expected to confer resistance to subsequent dasatinib therapy experienced at least some disease response on bosutinib.

In conclusion, bosutinib has demonstrated to have benefits in some patients treated in the last line, who had exhausted all available TKI therapies or for whom treatment with other available TKI(s) was deemed unsuitable by their physicians. It is noted that patient with pre-existing resistance against imatinib or dasatinib or nilotinib, respectively, had a significantly worse outcome than those with intolerance to these TKIs. However, this finding can be expected due to the differences in the clinical course of the disease, the high degree of cross-resistance between these second generation TKIs and the general prognostic impact of resistance in CML.

Additional efficacy data needed in the context of a conditional MA

As indicated above, there is a lack of approved and standard of care pharmacological treatment for adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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. Insofar, there is an unmet medical need in this patient population that could be fulfilled with the proposed medicinal product.

Information is currently only available from a post-hoc defined population of 52 patients and some additional patients from the compassionate use programme. Therefore, additional efficacy data is needed in the context of a conditional MA in order to confirm the benefit of bosutinib in the intended indication.

Additional comprehensive clinical data can be provided from a clinical study in the approved target population. The applicant should conduct a single-arm open-label, international, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options as a specific obligation for approval.

Approximately 150 patients should be enrolled primarily at large medical centres in Europe and the United States, up to 75 patients are expected to be treated in the 4th or later line setting.

The estimate probability of Major Cytogenetic Response (MCyR) (chronic phase) and Confirmed Overall Haematological Response (OHR) (accelerated and blast phase) by one year is proposed as primary endpoint. Efficacy data will be collected at regularly scheduled time-points at 3, 6, 9 and 12 months in the different CML patient populations. The use of a centralized efficacy endpoint and mutation assessment was recommended.

It is expected that this study will further support the efficacy of bosutinib in the intended last-line treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.

2.5.4. Conclusions on the clinical efficacy

Bosutinib is a second generation TKI that binds the kinase domain of Bcr-Abl, which is characteristic for Ph+ CML, in an intermediate conformation thereby inhibiting Abl kinase activity in vitro with an IC50 of 1 nM. In cell lines transfected with both wild type and imatinib-resistant mutant BCR-ABL it suppresses proliferation. In imatinib-sensitive CML cell lines, the in-vitro inhibitory activity of bosutinib is up to 100 fold that of imatinib, with IC_{50} values ranging from 1 to 20 nM. In imatinib-resistant cell lines (with or without mutations) bosutinib inhibited proliferation up to 114 fold that of imatinib. Bosutinib has been shown to inhibit phosphorylation of various signalling proteins and downstream substrates of Bcr-Abl, most notably the transcription factor Stat5 and the docking protein CrkL.

Although bosutinib has demonstrated some efficacy in the initially intended first line CP-CML population in terms of attaining relevant surrogate endpoints as CCyR and MMR, the initially pivotal study 3000-WW failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib.

As according the relevant CHMP guideline a second-line treatment can only be approved with comparative data using one of the two approved product for this indication (dasatinib and nilotinib), efficacy of bosutinib was then assessed to approve a last-line indication "*for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) previously treated with one or more tyrosine kinase inhibitor(s) (TKIs) and for whom imatinib, nilotinib or dasatinib are not considered appropriate treatment options".*

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

In this study, efficacy was seen in the 52 patient unmet need cohort [36 were in chronic phase CML (21 who had previously received 2 prior TKIs, and 15 who had received 1 prior TKI) and 16 were in advanced phases of CML (AP and BP)] and the overall reference population of Study 200-WW. Although the subpopulations identified were small, the efficacy is further supported by the results seen in the larger reference populations within Study 200-WW. Data from patients in compassionate use programmes also support the evidence of efficacy of bosutinib in this last-line indication.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
    - Submission of protocol: 30 May 2013
    - Final clinical study report: 30 September 2018

The benefit to public health of the immediate availability on the market of Bosutinib outweighs the risk in the fact that additional data are still required.

2.6. Clinical safety

Patient exposure

Safety data in previously treated subjects with Ph+ leukaemia is available from Study 200-WW (bosutinib n=570). Relevant clinical safety data, including long-term safety, are also available from the Phase III Study 3000-WW in subjects with newly diagnosed CP CML (bosutinib n=248/ imatinib N=251).

Other safety data was presented from phase I/II studies conducted in patients with solid tumours (mainly breast cancer). In total, 1572 subjects were exposed with bosutinib in clinical studies from phase I to III and 1209 patients received at least 1 dose of oral bosutinib alone or in combination with another anticancer agent.

In study 3000-WW median duration of exposure was 16.5 months in the up-dated analysis for bosutinib and 16.75 months for imatinib, respectively. A further updated analysis after 24 months has been provided to assess long-term safety during the study. The dose intensity was lower for bosutinib compared to imatinib (87.3% versus 97.5%). Dose escalation up to 600 mg (foreseen in both arms if tolerated) was rare in the bosutinib group (3.6% versus 12.0% for bosutinib and imatinib, respectively).

Adverse events

In *Study 200-WW* all 118 patients treated in third line had at least 1 TEAE as of the 28 March 2011 as presented in the table below. As of the 15 February 2012 database snapshot, there was 1 new TEAE with a ≥20.0% incidence: abdominal pain was reported in 24 (20.2%) patients compared with 23 (19.5%) patients reported in the Study 200-WW CSR. There were no new Grade 3 or 4 TEAEs with a ≥10.0% incidence.

Table 17. Treatment-Emergent Adverse Events (≥10% Incidence) and Grades 3 or 4 Treatment-Emergent Adverse Events Chronic Phase CML Safety Population: Prior Imatinib and Dasatinib and/or Nilotinib (Third-Line)

System Organ Class Preferred Term	Total n=118	
	All Grades	Grade 3/4
Any Adverse Event	118 (100)	74 (62.7)
Blood and lymphatic system disorders	58 (49.2)	35 (29.7)
Thrombocytopenia	41 (34.7)	30 (25.4)
Neutropenia	21 (17.8)	17 (14.4)
Anaemia	18 (15.3)	6 (5.1)
Gastrointestinal disorders	111 (94.1)	16 (13.6)
Diarrhoea	98 (83.1)	10 (8.5)
Nausea	56 (47.5)	1 (0.8)
Vomiting	46 (39)	1 (0.8)
Abdominal pain	23 (19.5)	1 (0.8)
Abdominal pain upper	20 (16.9)	0
Constipation	15 (12.7)	0
General disorders and administration site conditions	59 (50)	2 (1.7)
Fatigue	28 (23.7)	1 (0.8)
Pyrexia	18 (15.3)	0
Oedema peripheral	12 (10.2)	0
Investigations	45 (38.1)	11 (9.3)
Alanine aminotransferase increased	18 (15.3)	8 (6.8)
Metabolism and nutrition disorders	38 (32.2)	4 (3.4)
Decreased appetite	14 (11.9)	1 (0.8)
Musculoskeletal and connective tissue disorders	50 (42.4)	7 (5.9)
Arthralgia	17 (14.4)	1 (0.8)

System Organ Class Preferred Term	Total n=118	
	All Grades	Grade 3/4
Nervous system disorders	43 (36.4)	5 (4.2)
Headache	30 (25.4)	3 (2.5)
Dizziness	15 (12.7)	0
Respiratory, thoracic and mediastinal disorders	47 (39.8)	5 (4.2)
Cough	20 (16.9)	0
Pleural effusion	12 (10.2)	2 (1.7)
Skin and subcutaneous tissue disorders	59 (50)	8 (6.8)
Rash	34 (28.8)	5 (4.2)
Pruritus	17 (14.4)	1(0.8)

Note: Totals for 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. The cut-off is applied to the Total All Grades column and only to the adverse event preferred terms.
Source: AE4T-ALLG34-10-CP3L-TOT - 22AUG12 14:01; date of snapshot: 28MAR11 as derived from Study 200 CSR Table 9-29 and Study 200 CSR Table 9-31.

A summary of adverse events for the 52 patients in the *subpopulations with unmet need* is presented in the following table.

Table 18. Summary of Adverse Events: Number (%) of Patients "Unmet Medical Need" CP, AP, and BP CML Subpopulations

Event	Chronic Phase Second Line (n=15)	Chronic Phase Third Line (n=21)	AP Total (n=5)	BP Total (n=11)	Total (N=52)
Any TEAE	15 (100)	21 (100)	5 (100)	11 (100)	52 (100)
Grade 3 or 4 TEAEs	11 (73.3)	12 (57.1)	5 (100)	8 (72.7)	36 (69.2)
TEAEs leading to discontinuation	4 (26.7)	5 (23.8)	1 (20)	3 (27.3)	13 (25)
SAEs	6 (40.0)	10 (47.6)	4 (80.0)	8 (72.7)	28 (53.8)

Abbreviations: AP=accelerated phase patients, BP=blast phase patients; TEAE=treatment-emergent adverse event
Source: Module 5, Table 41, AE4T-BSUM-NICHE - 09AUG12 11:41 and Module 5, Table 36, AE4-SAE-NICHE - 09AUG12 09:22; date of snapshot: 28MAR11

The general adverse event profile and drug related TEAE with an Incidence of ≥5%of bosutinib in *Study 3000 WW* are presented respectively in the tables below.

Table 19. Adverse Event Profile by treatment arm in safety population of study 3000 WW

Event	**Bosutinib N=248 N (%)**	**Imatinib N=251**	**TOTAL N=499**
Any treatment-emergent adverse event (TEAE)	237 (95.6)	238 (94.8)	475 (95.2)
Drug-related TEAEs	(91.5)	(86.9)	
Grade 3 or 4 TEAEs	159 (64.1)	119 (47.4)	278 (55.7)
Serious adverse events (SAEs)	63 (25.4)	34 (13.5)	97 (19.4)
Adverse events leading to discontinuation	48 (19.4)	14 (5.6)	62 (12.4)
Adverse events leading to reduction in test article dose	92 (37.1)	40 (15.9)	132 (26.5)
Adverse events leading to temporary stop in test article dose	150 (60.5)	106 (42.2)	256 (51.3)
Deaths on study treatment (within 28 days of last dose 1)	1(0.4)	3 (1.2)	4 (0.8)

Source: Report AE5_BSUM - 26JAN2011 17:29. **Date of snapshot: 31AUG2010**

Table 20. Number (%) of Subjects Experiencing Drug Related Treatment-Emergent Adverse Events (TEAEs) with an Incidence of ⩾5%: Safety Population of study 3000 WW

	Treatment		
System Organ Class. Preferred Term	**Bosutinib N=248**	**Imatinib N=251**	**Total N=499**
ANY ADVERSE EVENT	227 (91.5)	218 (86.9)	445 (89.2)
Blood and lymphatic system disorders	94 (37.9)	118 (47.0)	212 (42.5)
Thrombocytopenia	65 (26.2)	67 (26.7)	132 (26.5)
Neutropenia	29 (11.7)	65 (25.9)	94 (18.8)
Anaemia	37 (14.9)	45 (17.9)	82 (16.4)
Leukopenia	21 (8.5)	50 (19.9)	71 (14.2)
Eye disorders	8 (3.2)	34 (13.5)	42 (8.4)
Eyelid oedema	2 (0.8)	18 (7.2)	20 (4.0)
Gastrointestinal disorders	181 (73.0)	106 (42.2)	287 (57.5)
Diarrhoea	163 (65.7)	45 (17.9)	208 (41.7)
Nausea	66 (26.6)	81 (32.3)	147 (29.5)
Vomiting	61 (24.6)	22 (8.8)	83 (16.6)
Abdominal pain upper	24 (9.7)	10 (4.0)	34 (6.8)
Abdominal pain	21 (8.5)	7 (2.8)	28 (5.6)
General disorders and administration site conditions	54 (21.8)	68 (27.1)	122 (24.4)
Fatigue	22 (8.9)	22 (8.8)	44 (8.8)
Oedema peripheral	4 (1.6)	21 (8.4)	25 (5.0)
Investigations	123 (49.6)	75 (29.9)	198 (39.7)
Alanine aminotransferase increased	73 (29.4)	14 (5.6)	87 (17.4)
Aspartate aminotransferase increased	59 (23.8)	12 (4.8)	71 (14.2)
Lipase increased	25 (10.1)	20 (8.0)	45 (9.0)
Blood creatine phosphokinase increased	10 (4.0)	22 (8.8)	32 (6.4)
Blood alkaline phosphatase increased	14 (5.6)	9 (3.6)	23 (4.6)
Gamma-glutamyltransferase increased	14(5.6)	1 (0.4)	15 (3.0)
Metabolism and nutrition disorders	39 (15.7)	43 (17.1)	82 (16.4)
Hypophosphataemia	12 (4.8)	25 (10.0)	37 (7.4)
Decreased appetite	19 (7.7)	3 (1.2)	22 (4.4)
Musculoskeletal and connective tissue disorders	19 (7.7)	80 (31.9)	99 (19.8)
Muscle spasms	1 (0.4)	44 (17.5)	45 (9.0)
Myalgia	6 (2.4)	21 (8.4)	27 (5.4)
Bone pain	2 (0.8)	16 (6.4)	18 (3.6)
Nervous system disorders	34 (13.7)	18 (7.2)	52 (10.4)
Headache	13 (5.2)	6 (2.4)	19 (3.8)
Skin and subcutaneous tissue disorders	80 (32.3)	69 (27.5)	149 (29.9)
Rash	45 (18.1)	28 (11.2)	73 (14.6)
Periorbital oedema	0	34 (13.5)	34 (6.8)

System organ class totals are not necessarily the sum of the individual adverse events since a subject may report two or more different adverse events in the same system organ class.

Source: REPORT AE5T_REL_5 -13DEC2010 2:45. Date of snapshot: 31AUG2010

Overall, in the safety population including a total of 870 Ph+ leukaemia patients receiving at least 1 dose of single-agent bosutinib. at least 1 adverse reaction of any toxicity grade was reported for 848 (97.5%) patients. The most frequent adverse reactions reported for ≥20% of patients were diarrhoea

(78.5%), nausea (42.1%), thrombocytopenia (38.5%), vomiting (37.1%), abdominal pain (33.4%), rash (32.4%), anaemia (27.4 %), pyrexia (23.4%), and alanine aminotranserase increased (22.3%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 531 (61.0%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥5% of patients were thrombocytopenia (25.4%), anaemia (12.3%), neutropenia (11.5%), alanine aminotransferase increased (10.2%), diarrhoea (9.1%), rash (6.1%), lipase increased (5.2%) and aspartate aminotransferase increased (5.0%). Adverse reactions are summarised in the table below.

Table 21. Adverse reactions for bosutinib (n=870)

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Infections and infestations	Very common	Respiratory tract infection[a]	99 (11.4)	4 (0.5)	0
	Common	Pneumonia[b]	45 (5.2)	21 (2.4)	5 (0.6)
		Influenza	47 (5.4)	2 (0.2)	0
		Bronchitis	27 (3.1)	1 (0.1)	0
		Nasopharyngitis	81 (9.3)	0	0
Blood and lymphatic system disorders	Very common	Thrombocytopenia	335 (38.5)	127 (14.6)	94 (10.8)
		Neutropenia	141 (16.2)	67 (7.7)	33 (3.8)
		Anaemia	238 (27.4)	82 (9.4)	25 (2.9)
		Leukopenia	94 (10.8)	31 (3.6)	8 (0.9)
	Common	Febrile Neutropenia	13 (1.5)	8 (0.9)	3 (0.3)
	Uncommon	Granulocytopenia	2 (0.2)	0	2 (0.2)
Immune system disorders	Common	Drug hypersensitivity	12 (1.4)	7 (0.8)	0
	Uncommon	Anaphylactic shock	2 (0.2)	0	2 (0.2)
Metabolism and nutrition disorders	Very Common	Decreased appetite	109 (12.5)	4 (0.5)	0
	Common	Dehydration	20 (2.3)	2 (0.2)	0
		Hyperkalaemia	23 (2.6)	2 (0.2)	1 (0.1)
		Hypophosphataemia	54 (6.2)	18 (2.1)	0
Nervous system disorders	Very common	Headache	148 (17.0)	9 (1.0)	3 (0.3)
	Common	Dizziness	74 (8.5)	2 (0.2)	0
		Dysgeusia	18 (2.1)	0	0
Ear and labyrinth disorders	Uncommon	Tinnitus	8 (0.9)	0	0
Cardiac disorders	Common	Pericardial effusion	16 (1.8)	2 (0.2)	1 (0.1)
		Electrocardiogram QT prolonged[c]	10 (1.1)	1 (0.1)	0
	Uncommon	Pericarditis	1 (0.1)	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	Very common	Cough	125 (14.4)	0	0
	Common	Dyspnoea	82 (9.4)	15 (1.7)	3 (0.3)
		Pleural effusion	52 (6.0)	14 (1.6)	1 (0.1)
	Uncommon	Respiratory failure	5 (0.6)	1 (0.1)	1 (0.1)
		Acute pulmonary oedema	3 (0.3)	1 (0.1)	1 (0.1)
		Pulmonary hypertension	4 (0.5)	1 (0.1)	0
Gastrointestinal disorders	Very common	Diarrhoea	683 (78.5)	78 (9.0)	1 (0.1)
		Vomiting	323 (37.1)	25 (2.9)	0
		Nausea	366 (42.1)	10 (1.1)	0
		Abdominal pain[d]	291 (33.4)	15 (1.7)	0
	Common	Gastritis	25 (2.9)	3 (0.3)	1 (0.1)
	Uncommon	Acute pancreatitis	3 (0.3)	2 (0.2)	1 (0.1)
		Gastrointestinal haemorrhage[e]	6 (0.7)	5 (0.6)	0

System Organ Class	*Frequency*	*Adverse reactions*	*All Grades n (%)*	*Grade 3 n (%)*	*Grade 4 n (%)*
Hepatobiliary disorders	Very common	Alanine aminotransferase increased	194 (22.3)	79 (9.1)	10 (1.1)
		Aspartate aminotransferase increased	160 (18.4)	41 (4.7)	3 (0.3)
	Common	Hepatotoxicity[f]	15 (1.7)	5 (0.6)	1 (0.1)
		Hepatic function abnormal	27 (3.1)	8 (0.9)	3 (0.3)
		Blood bilirubin increased	33 (3.8)	8 (0.9)	0
		Gamma-glutamyltransferase increased	29 (3.3)	7 (0.8)	0
	Uncommon	Liver Injury	2 (0.2)	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	Very common	Rash[g]	282 (32.4)	51 (5.9)	2 (0.2)
	Common	Urticaria	26 (3.0)	2 (0.2)	1 (0.1)
		Acne	25 (2.9)	0	0
		Pruritus	71 (8.2)	3 (0.3)	0
	Uncommon	Erythema multiforme	1 (0.1)	0	1 (0.1)
		Exfoliative rash	6 (0.7)	1 (0.1)	0
		Drug eruption	5 (0.6)	1 (0.1)	0
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia	96 (11.0)	3 (0.3)	0
	Common	Myalgia	49 (5.6)	3 (0.3)	0
		Back pain	72 (8.3)	7 (0.8)	1 (0.1)
Renal and urinary disorders	Common	Renal failure	13 (1.5)	2 (0.2)	1 (0.1)
	Uncommon	Renal failure acute	7 (0.8)	3 (0.3)	1 (0.1)
		Renal impairment	8 (0.9)	1 (0.1)	0
General disorders and administration site conditions	Very common	Pyrexia	204 (23.4)	6 (0.7)	1 (0.1)
		Oedema[h]	100 (11.5)	1 (0.1)	0
		Fatigue[i]	169 (19.4)	14 (1.6)	1 (0.1)
	Common	Chest pain[j]	61 (7.0)	4 (0.5)	1 (0.1)
		Pain	41 (4.7)	5 (0.6)	0
		Asthenia	86 (9.9)	7 (0.8)	2.(0.2)
Investigations	Common	Lipase increased	76 (8.7)	41 (4.7)	4 (0.5)
		Blood creatinine increased	42 (4.8)	2 (0.2)	0
		Blood amylase increased	31 (3.6)	7 (0.8)	0
		Blood creatine phosphokinase increased	28 (3.2)	3 (0.3)	2 (0.2)

The following terms have been combined:

[a] Respiratory tract infection, upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, respiratory tract infection viral.

[b] Pneumonia, bronchopneumonia, primary atypical pneumonia, lobar pneumonia.

[c] Electrocardiogram QT prolonged, long QT syndrome.

[d] Abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, abdominal tenderness, gastrointestinal pain.

[e] Gastrointestinal haemorrhage, gastric haemorrhage, upper gastrointestinal haemorrhage.

[f] Hepatotoxicity, toxic hepatitis, cytolytic hepatitis.

[g] Rash, maculopapular rash, macular rash, pruritic rash, generalized rash, papular rash.

[h] Oedema, face oedema, localized oedema, peripheral oedema.

[i] Fatigue, malaise.

[j] Chest pain, chest discomfort.

Serious adverse event / deaths / other significant events

Serious adverse events

In *Study 200-WW*, 35 (29.7%) of the patients had SAEs as of the 28 March 2011 database snapshot. However, in the population of "high medical need" more SAEs were observed. In total 28 (53,8%) of the included patients had SAEs. This is explained at least partially due to inclusion of more heavily pretreated patients and more advanced stages of CML.

The most common SAEs (≥2% incidence) were pleural effusion in 4 (3.4%) patients, and headache and neutropenia each in 3 (2.5%) patients. As of the 15 February 2012 database snapshot, there were no new SAEs with a ≥2% incidence.

Overall, the incidence and types of SAEs appeared to be consistent and comparable with the data previously reported from *study 3000-WW*, where the number of subjects with SAEs was significantly higher in the bosutinib arm (68 subjects; 27.4 %), compared with the imatinib arm (37 subjects; 14.1%) [updated analysis from 15 November 2011]. SAEs considered to be related to treatment were also more frequent in the bosutinib arm (32 subjects; 12.9%) compared with the imatinib arm (13 subjects; 5.1%). Also, SAEs in the bosutinib arm led more frequently to treatment discontinuation (13 subjects, 19.1 %) compared with the imatinib arm (3 subjects, 8.1%). However, SAEs leading to death occurred more often in the imatinib arm (7 subjects, 18.9%) compared with the bosutinib arm (3 subjects, 4.4%). The updated analysis at 24 months in general has confirmed these results.

The most commonly reported SAEs (≥2%) in subjects receiving bosutinib were diarrhoea (9 subjects, 3.6%), ALT increased (7 subjects, 2.8%), pneumonia (6 subjects, 2.4%) and AST increased and pyrexia, (5 subjects, 2.0% each).

The most commonly reported SAEs (≥2%) in subjects receiving imatinib were anaemia (6 subjects; 2.4%; Grade 3+4) and thrombocytopenia (6 subjects; 2.4 %; all Grade 4).

Infection TEAEs and SAEs occurred more often in bosutinib subjects (40.7%) than in imatinib treated subjects (31.1%). There was no association between TEAEs of infection and Grade 3 or Grade 4 neutropenia in either treatment arm. No deaths due to an infection TEAE were reported in either treatment arm.

In 2 subjects in the bosutinib arm of study WW3000 a Grade 4 SAE due to a drug-related anaphylactic reaction was observed. One patient (015436) experienced anaphylactic shock after administration of the first bosutinib dose. The other patient (011677) experienced anaphylactic shock after being on treatment for 56 days; this subject had an anaphylactic response to bosutinib after a treatment interruption for a separate TEAE and on Day 1 of the rechallenge experienced anaphylaxis to bosutinib. Administration of bosutinib was discontinued for both subjects and both recovered completely under supportive care. Anaphylactic reactions have not been reported in any other clinical study with bosutinib.

Deaths

As summarised in the table below, overall, 22 (19%) patients of the high medical need population in study 200-WW died during the study, which included the 2-year follow-up period after discontinuing treatment with bosutinib as of the 28 March 2011 database snapshot.

Table 22. Death Summary
Chronic Phase CML Safety Population: Prior Imatinib and Dasatinib and/or Nilotinib (Third-Line)

Characteristic	IM+(NI+D) or IM + NI Intolerant N=4	IM + D Resistant N=37	IM + D Intolerant N=50	IM + NI Resistant N=27	Total N=118
Number patients who died					
No	3 (75)	27 (73)	43 (86)	23 (85)	96 (81)
Yes	1 (25)	10 (27)	7 (14)	4 (15)	22 (19)
Reason for death					
AE related to test article	0	0	1 (2)	0	1 (1)
AE unrelated to test article	0	3 (8)	5 (10)	0	8 (7)
Disease progression	0	6 (16)	1 (2)	3 (11)	10 (8)
Other unknown[a]	1 (25)	1 (3)	0	1 (4)	3 (3)
Number patients who died within 30 days of last dose					
No	4 (100)	35 (95)	47 (94)	26 (96)	112 (95)
Yes	0	2 (5)	3 (6)	1 (4)	6 (5)
Reason for death within 30 days of last dose					
AE related to test article	0	0	1 (2)	0	1 (1)
AE unrelated to test article	0	0	2 (4)	0	2 (2)
Disease progression	0	2 (5)	0	1 (4)	3 (3)

Abbreviations: AE=adverse event; D=dasatinib; IM=imatinib; NI=nilotinib
a: Causes of death for Other unknown include: complications from Grade 4 GI graft versus host disease after a cord blood transplant; and unknown in 2 patients.
Source: Study 200-WW CSR, Table 9-33, DTH4-CP3L - 29MAR11 21:03; date of snapshot: 28MAR11; and Study 200-WW CSR, Section 14.0 (Errata, Patient 3160A4-200-114-002796)

As of the 15 February 2012 database snapshot, there was 1 new death in the study. One (1) patient, in the dasatinib-intolerant cohort, died because of an unrelated AE (severe heart failure) 123 days after the last dose of bosutinib, after having received bosutinib for over 3 years.

In the 52 patients of the *subpopulation with unmet medical need*, no treatment-related deaths were observed during the study.

Mortality (in total 16 subjects of 499) was relatively low in *Study 3000-WW*. This can be expected in the intended first-line population of subjects with newly diagnosed CP-CML. Fewer deaths occurred in the bosutinib arm (7/249) in comparison with the imatinib arm (13/251). Most of the deaths were related to disease progression and no deaths have been observed as consequence of drug-related SAEs. As the study was not powered to detect difference in mortality, no conclusion can be drawn.

Other significant events

Gastrointestinal disorders

Of the 681 (78%) patients that experienced diarrhoea, 665 patients had drug-related events of diarrhoea and 8 patients discontinued bosutinib due to this event. Concomitant medicines were given to treat diarrhoea in 461 (68%) of patients. The maximum toxicity of diarrhoea was Grade 1 or 2 in 89% of patients, Grade 3 in 11% of patients; one patient (<1%) experienced a Grade 4 event. Among patients with diarrhoea, the median time to first event was 2 days (range, 1 to 594 days) and the median duration of any grade of diarrhoea was 2 days (range, 1 to 910 days).

Among the 681 patients with diarrhoea, 104 patients (15%) were managed with treatment interruption and of these 98 (94%) were rechallenged with bosutinib. Of those who were rechallenged, 95 (97%) did not have a subsequent event or did not discontinue bosutinib due to a subsequent event of diarrhoea.

Cardiac disorders

Three patients (0.3%) experienced QTcF interval prolongation (greater than 500 ms). Eight (0.9%) patients, including 2 of those with QTcF interval prolongation of greater than 500 ms, experienced QTcF increase from baseline exceeding 60 ms.

Immunological events

Hypersensitivity drug-related grade 3 or grade 4 TEAEs were reported for 11 subjects (1.3%). Grade 3 or grade 4 drug hypersensitivity was reported to be drug related for 5 subjects; all reports of grade 3 or grade 4 urticaria and anaphylactic shock were considered to be drug related. Anaphylactic or hypersensitivity reactions may also be due to macrogol (polyethylene glycol) 3350, poloxamer 188, povidone or to any of the excipients. This has been reflected in a contraindication (see SmPC, section 4.4).

Laboratory findings

In the population of study 200-WW on-therapy clinical laboratory test results for events of special interest (ALT, AST, and lipase, total bilirubin, and glucose elevations, and low phosphorus, haemoglobin, ANC, and platelet count) are summarised in the table below.

Table 23. On-Therapy Clinical Laboratory Results by Maximum NCI CTCAE Grade Chronic Phase CML Safety Population: Prior Imatinib and Dasatinib and/or Nilotinib (Third Line)

Parameter	IM + NI +/or D (n=4)	IM + D Resistant (n=37)	IM + D Intolerant (n=50)	IM + NI Resistant (n=27)	Total (N=118)
Blood Chemistry					
Alanine transaminase (High)					
Grade ½	4 (100)	16 (43.2)	18 (36)	12 (44.4)	50 (42.4)
Grade 3	0	1 (2.7)	2 (4)	4 (14.8)	7 (5.9)
Grade 4	0	0	0	1 (3.7)	1 (0.8)
Aspartate aminotransferase (High)					
Grade ½	2 (50)	13 (35.1)	19 (38)	10 (37)	44 (37.3)
Grade 3	0	1 (2.7)	0	2 (7.4)	3 (2.5)
Grade 4	0	0	0	1 (3.7)	1 (0.8)
Total bilirubin (High)					
Grade ½	1 (25)	2 (5.4)	2 (4)	3 (11.1)	8 (6.8)
Grade 3	0	0	2 (4)	1 (3.7)	3 (2.5)
Grade 4	0	0	0	0	0
Lipase (High)					
Grade ½	0	7 (18.9)	12 (24)	1 (3.7)	20 (16.9)
Grade 3	0	2 (5.4)	3 (6)	2 (7.4)	7 (5.9)
Grade 4	0	0	1 (2)	0	1 (0.8)
Phosphorus (Low)					
Grade ½	1 (25)	8 (21.6)	13 (26)	12 (44.4)	34 (28.8)
Grade 3	0	0	2 (4)	1 (3.7)	3 (2.5)
Grade 4	0	0	0	0	0
Glucose (High)					
Grade ½	0	10 (27)	19 (38)	6 (22.2)	35 (29.7)
Grade 3	0	0	1 (2)	0	1 (0.8)
Grade 4	0	0	0	0	0
HAEMATOLOGY					
Haemoglobin (Low)					
Grade ½	3 (75)	27 (73)	38 (76)	21 (77.8)	89 (75.4)

Parameter	IM + NI +/or D (n=4)	IM + D Resistant (n=37)	IM + D Intolerant (n=50)	IM + NI Resistant (n=27)	Total (N=118)
Grade 3	0	4 (10.8)	0	0	4 (3.4)
Grade 4	0	2 (5.4)	3 (6)	1 (3.7)	6 (5.1)
Absolute neutrophils count (Low)					
Grade ½	0	11 (29.7)	13 (26)	7 (25.9)	31 (26.3)
Grade 3	0	4 (10.8)	3 (6)	3 (11.1)	10 (8.5)
Grade 4	1 (25)	3 (8.1)	6 (12)	3 (11.1)	13 (11)
Platelet counts (Low)					
Grade ½	2 (50)	15 (40.5)	9 (18)	13 (48.1)	39 (33.1)
Grade 3	0	6 (16.2)	8 (16)	3 (11.1)	17 (14.4)
Grade 4	0	1 (2.7)	7 (14)	5 (18.5)	13 (11)

Abbreviations: IM=imatinib, D=dasatinib, NI=nilotinib
Note: On-Therapy is defined as the time period between the first dose and last dose date with a 30 day lag
Source: Study 200-WW CSR, Table 9-69, LAB4-MAXTOX-OT-CP3L - 04APR11 16:42; date of snapshot: 28MAR11

As of the 28 March 2011 database snapshot, the majority of patients reported laboratory abnormalities at a maximum toxicity of Grade 1 or Grade 2. Clinical chemistry values reported at a Grade 3 maximum toxicity in ≥5% of patients during treatment were elevated ALT and elevated lipase each in 7 (5.9%) patients. There were no clinical chemistry values of Grade 4 maximum toxicity in ≥5% of patients during treatment.

Haematologic laboratory abnormalities continue to represent the most common potential clinical important Grade 3/4 laboratory abnormalities. Haematology values reported at a Grade 3 maximum toxicity in ≥5% of patients during treatment were low platelet count in 17 (14.4%) patients and low ANC in 10 (8.5%) patients. Haematology values reported at a Grade 4 maximum toxicity in ≥5% of patients during treatment were low ANC and low platelet count each in 13 (11.0%) patients, and low haemoglobin in 6 (5.1%) patients.

Although all reported SAEs of increased AST/ALT in the bosutinib arm are resolved, the high incidence of liver-related TEAEs and liver-enzyme elevation observed for bosutinib in the clinical studies has to be noted. Despite the observed abnormalities in liver function tests, there were no cases of permanent hepatic injury and no liver-related deaths in CML patients treated with bosutinib (confirmed again also by the 15 February 2012 database snapshot). It seems that as in study 3000-WW the majority of liver toxicities were transient laboratory elevations, and were generally managed with dose modifications.

However, in study 2207-WW, a Phase 2 study in metastatic breast cancer, two subjects fulfil the criteria for so called “Hy’s law” indicating intolerable hepatotoxicity for a drug. As these events were observed in a completely different target population in which the disease itself as well as the combination with letrozole might have had an additional effect on liver function and no further cases were observed during the other clinical studies.

Safety in special populations

No formal analyses for the PH+ leukaemia trials were performed to compare the TEAE data on the basis of age, sex or race. However, subgroup analyses were provided to allow some descriptive comparisons of results concerning age, gender and race.

No consistent trends with regard to special populations were observed. Exposure in special populations was limited. There were no subjects under the age of 18 years participating in the pivotal study and the number of subjects ≥ 65 years old were rather small, n = 28 (11.3 %) in the bosutinib group and n = 26 (10.4%) in the imatinib group.

Phase I data suggests that renal impairment is not likely to have a significant impact on bosutinib’s PK. However, as subjects with Creatinine >1,5 ULN were excluded from the phase III studies confirmative information from these trials is absent.

Patients with hepatic impairment had an increased exposure as characterised in phase I study 3160A4-1111-EU and additionally a high rate of QTc-time prolongation related to drug exposure.

Safety related to drug-drug interactions and other interactions

Proton pump inhibitors (PPIs) have been shown to decrease bosutinib's bioavailablity. . When a single oral dose of bosutinib (400 mg) was co-administered with multiple-oral doses of lansoprazole (60 mg) in a study of 24 healthy fasting subjects, bosutinib Cmax and AUC decreased to 54% and 74%, respectively, of the values seen when bosutinib (400 mg) was given alone (see Pharmacokinetic interaction studies).

The most frequently used concomitant medications in the bosutinib arm of study 3000-WW were antidiarrhoeal agents (48.0%); antacids (39.9%), antigout preparations (primarily allopurinol, 38.3%), analgesics (36.3%), and systemic antibacterials (35.5%). For subjects receiving imatinib, the most frequently used concomitant medications on study treatment were antigout preparations (primarily allopurinol) (41.0%), analgesics (30.7%), antibacterials and antacids (28.7% each), and anti-inflammatory and antirheumatic products (25.5%).

Discontinuation due to adverse events

In *Study 200-WW*, 84 (71.2%) patients within this reference CP CML population discontinued study drug as of the 28 March 2011 database snapshot. The primary reasons for discontinuation of bosutinib treatment are summarised in the table below.

Table 24. Summary of Reasons for Treatment Discontinuation
Chronic Phase CML Safety Population: Prior Imatinib and Dasatinib and/or Nilotinib (Third-Line)

Conclusion Status Reason	IM+(NI+D) or IM + NI Intolerant n=4	IM + D Resistant n=37	IM + D Intolerant n=50	IM + NI Resistant n=27	TOTAL N=118
Discontinued	3 (75.0)	31 (83.8)	34 (68.0)	16 (59.3)	84 (71.2)
Unsatisfactory response - efficacy	1 (25.0)	12 (32.4)	7 (14.0)	5 (18.5)	25 (21.2)
Adverse event	0	6 (16.2)	15 (30.0)	3 (11.1)	24 (20.3)
Disease progression	2 (50.0)	8 (21.6)	4 (8.0)	6 (22.2)	20 (16.9)
Death	0	2 (5.4)	2 (4.0)	0	4 (3.4)
Other	0	1 (2.7)	3 (6.0)	0	4 (3.4)
Patient request	0	0	2 (4.0)	1 (3.7)	3 (2.5)
Lost to follow-up	0	2 (5.4)	0	0	2 (1.7)
Investigator request	0	0	0	1 (3.7)	1 (0.8)
Protocol violation	0	0	1 (2.0)	0	1 (0.8)

Abbreviations: IM=imatinib, D=dasatinib, NI=nilotinib
Note: Total discontinued is the sum of individual reasons since they are mutually exclusive by patient.
Source: Study 200-WW CSR, Table 9-1, CPP4-T-CP3L - 29MAR11 01:05 and Module 5, Table 43, CPP1_T_SAFETY; date of Snapshot: 28MAR11

In the updated database snapshot from 15 February 2012, 6 additional patients discontinued treatment. Primary reasons for discontinuation included patient request (3 patients), AE (2 patients), and investigator request (1 patient). The most common primary reasons for treatment discontinuation continue to be AEs (21.8%), unsatisfactory response (21.0%), and disease progression (16.8%). Two (2) patients who discontinued treatment because of thrombocytopenia and 1 patient each because of diarrhoea, anemia, myocardial infarction (MI), and disease progression. Overall, the incidence and

types of AEs that led to discontinuation of treatment appeared to be consistent with the data previously reported.

TEAEs that led to the permanent discontinuation of bosutinib are presented in the table below.

Table 25. Treatment-Emergent Adverse Events That Led to Permanent Discontinuation of Bosutinib Treatment in >1 Patient
Chronic Phase CML Safety Population: Prior Imatinib and Dasatinib and/or Nilotinib (Third-Line)

System Organ Class Preferred Term	IM+(NI+D) or IM + NI Intolerant N=4	IM + D Resistant N=37	IM + D Intolerant N=50	IM + NI Resistant N=27	Total N=118
Any Adverse Event	0	6 (16.2)	15 (30.0)	4 (14.8)	25 (21.2)
Blood and lymphatic system disorders	0	3 (8.1)	5 (10.0)	1 (3.7)	9 (7.6)
Thrombocytopenia	0	1 (2.7)	4 (8.0)	0	5 (4.2)
Neutropenia	0	2 (5.4)	1 (2.0)	1 (3.7)	4 (3.4)
Gastrointestinal disorders	0	1 (2.7)	2 (4.0)	0	3 (2.5)
Vomiting	0	0	2 (4.0)	0	2 (1.7)
Investigations	0	1 (2.7)	2 (4.0)	2 (7.4)	5 (4.2)
Alanine aminotransferase increased	0	0	1 (2.0)	2 (7.4)	3 (2.5)

Abbreviations: D=dasatinib, IM=imatinib, NI=nilotinib
Note: Within each system organ class, events are presented in descending order of incidence based on "Total" incidence. Totals for the number of patients at a higher level are not necessarily the sum of those at the lower levels since a patient may have 2 or more different adverse events within the higher level category.
Source: Study 200-WW CSR, modified Table 9-37, modified AE4T-DISC-CP3L - 28MAR11 17:55; date of snapshot: 28MAR11

In *Study 3000-WW*, AEs that led to the permanent discontinuation of the study drug were thrice more reported for in the bosutinib treatment arm (n=54 /21.8%) than in the imatinib arm (n=16 / 6.4%). A similar unfavourable relation was seen for dose interruptions and dose reduction for bosutinib. These findings confirm a critical safety profile for bosutinib compared with imatinib, which also seems to preclude any first-line administration in CP-CML.

In conclusion, it seems that discontinuation due to safety issues as reflected by discontinuation due to AEs which was observed in about 22 % of the bosutinib treated patients in both main studies. Thus, the difference between both populations is only small.

Post marketing experience

Bosutinib has been recently approved in the United Stated on 4 September 2012 for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy. However, no post-marketing data is available to date.

2.6.1. Discussion on clinical safety

In accordance with signals derived from non-clinical studies, hepatotoxicity, gastrointestinal effects and cardiac arrhythmias were the most important toxicities associated with bosutinib.

Toxicity in comparison with imatinib was too pronounced to justify the use of this product in the first-line indication, particularly as superiority in efficacy was not demonstrated in Study 3000-WW and a direct comparison with other second-generation TKIs approved for first-line CP-CML patients is not possible based on the available data.

The most common TEAEs included gastrointestinal events (predominantly diarrhoea), myelosuppression (mainly thrombocytopenia) and transaminase elevations (particularly ALT). The most common TEAEs in the subpopulations reflecting the recommended indication were also the most common TEAEs in the broader safety population.

In the pivotal Study 200-WW, the safety profile of bosutinib seemed manageable and generally similar across all CML reference populations (CP, AP, and BP). Interestingly, patients who had a history of pleural effusion or of discontinuation of treatment with a previous TKI due to this event appeared to have minimal cross-intolerance with bosutinib treatment.

Diarrhoea was identified consistently as dose dependent and dose limiting for bosutinib. In Study 3000-WW the rate of drug-related diarrhoea in the bosutinib arm (B: 65.7% versus I: 17.9%) was very high. Most cases were of short duration (median:3 days) and started early. However, there is also a relevant subgroup of patients (N= 77 subjects (45.8%) out of 168 with this AEs) that had longer lasting diarrhoea (>28 days, range 1 to 466 days). An additional post-hoc analysis with regard to safety information for diarrhoea frequency will be provided in order to better characterise the formulation to be marketed (see Risk Management Plan).

In Study 3000-WW, a high rate of drug-related vomiting (B: 31.5% versus I: 13.5%) was reported. A higher rate of arrhythmia events in bosutinib treated patients was also observed (B: 8.6 % versus I:6.5%). Hypokalaemia may enhance this effect. A warning with respect to the proarrhythmic potential of bosutinib is included in the SmPC.

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

A high incidence of liver-related TEAEs and liver-enzyme elevations [B: 114 subjects (46.0%) versus I: 35 subjects (13.9%)] observed for bosutinib in the first line population of study 3000-WW, transaminase elevations in the currently proposed target population derived from Study 200-WW were primarily Grade 1 or 2 in severity and were generally managed with dose interruptions and dose reductions. Dose adjustments recommendations in case of elevated liver transaminases are included in section 4.2 of the SmPC.

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

However, it should be noted that t hepatic toxicity has only been evaluated beyond 12-24 months in a small population of about 250 patients in Study 3000-WW.In a terminated Phase 2 study 2207-W with bosutinib in metastatic breast cancer, two subjects fulfilled the criteria for so called “Hy’s law” indicating intolerable hepatotoxicity for a drug. Therefore, the potential for severe drug-induced liver injury has to be considered with bosutinib exposure. Dose adjustments and warning on liver function abnormalities are included in the SmPC. In addition, as patients with hepatic impairment had an increased exposure as characterised in phase I study 3160A4-1111-EU and additionally a high rate of QTc-time prolongation related to drug exposure, a contraindication is included in the SmPC for patients with hepatic impairment.

Phase I data suggests that renal impairment is not likely to have a significant impact on bosutinib’s PK. However, as subjects with Creatinine >1,5 ULN were excluded from the phase III studies confirmative information from these trials is absent. Therefore, the SmPC states that subjects with Creatinine > 1,5

ULN were excluded from clinical studies (see sections 4.2 and 4.4). A study in patients with renal impairment is ongoing and results will be submitted as a post-authorisation measure.

Two cases of anaphylaxis were reported across the bosutinib clinical development program, although none were reported other studies including in Study 200-WW. The SmPC therefore includes a contraindication in case of hypersensitivity to the active substance or to any of the excipients.

The effects of concomitant medication for the management of bosutinib's adverse event profile requires further clarification. A clinical drug-drug interaction study on inhibition of P-gp is requested as a post-authorisation measure. Warnings with respect to interactions have been included in the SmPC, including with antiemetics, which are known to induce QTc prolongation.

The antiemetic agent, domperidone, has the potential to increase QT interval prolongation and to induce "torsade de pointes"- arrhythmias; therefore, co-administration with domperidone should be avoided. It should only be used, if other medicinal products are not efficacious. In these situations an individual benefit-risk assessment is mandatory and patients should be monitored for occurrence of QT prolongation (see SmPC section 4.4).

Infection TEAEs and SAEs occurred more often in bosutinib subjects (40.7%) than in imatinib-treated subjects (31.1%). Whether this reflects a direct lymphocytotoxic effect of bosutinib, as postulated from animal model data, could not be further clarified by the data submitted. A warning that bosutinib may predispose to infections has been included in the product information.

Bosutinib is a substrate of CYP3A and is susceptible to interaction with strong CYP3A inhibitors as well as with strong CYP3A4 inducers. Known drug interactions are adequately reflected in the product information.

With respect to concomitant medication it seems that antidiarrhoeal agents were frequently needed. They had to be given for gastrointestinal toxicity in nearly every second subject with bosutinib at least for a short time. The SmPC includes recommendation for dose adjustments as well as a warning with respect to diarrhoea and vomiting. A post-hoc analysis of diarrhoea incidence after study patients switch to the commercial formulation is planned as a post-authorisation measure.

As antidiarrhoeal drugs act by lowering gastrointestinal motility, the risk of higher exposure to bosutinib was assessed. As diarrhoea is dose-dependent, such an effect might lead to a paradoxical increase of diarrhoea events. A warning has been included in the product information to address this issue (see SmPC section 4.4).

The overall safety in the last-line indication was derived only from a small number of patients. However, based on additional analyses, no unexplained difference in safety profile became obvious during a comparison between the new target population and the total study populations of 200-WW or 3000-WW.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

The safety profile of bosutinib seems to be adequately characterised. Nevertheless the study to be conducted as a specific obligation in order to better characterise the efficacy in the last-line population will also provide further information on the safety of bosutinib.

2.6.2. Conclusions on the clinical safety

Bosutinib was associated with pronounced toxicities, particularly hepatotoxicity and gastrointestinal toxicity. However, the available safety data seems to indicate that bosutinib has a manageable safety profile in the subpopulation with an “unmet medical need”.

The CHMP considered the following measures necessary to address the missing safety data in the context of a conditional MA :

- To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.
    - Submission of protocol: 30 May 2013
    - Final clinical study report: 30 September 2018

The benefit to public health of the immediate availability on the market of bosutinib outweighs the risk implicit in the fact that additional data are still required.

2.7. Pharmacovigilance

Summary of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 26. Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Important Identified Risks		
Hepatotoxicity	• Routine Pharmacovigilance, including the use of a hepatic events follow-up questionnaire	As described in the SmPC in sections 4.2 (dose interruptions for elevated transaminases), 4.4 (associated with elevations in serum transaminases), and 4.8 (ALT or AST elevations discussed as ADRs).
Gastrointestinal toxicities	• Routine Pharmacovigilance • A post-hoc analysis of diarrhoea incidence after study patients switch to the commercial formulation is planned for post approval.	As described in the SmPC in sections 4.2 (dose interruptions for diarrhoea), 4.4 (associated with diarrhoea and vomiting), and 4.8 (diarrhoea, nausea, and vomiting discussed as ADRs).
Hypersensitivity Reactions, Including Anaphylaxis	• Routine Pharmacovigilance	As described in the SmPC in sections 4.3 (hypersensitivity to active substance or excipients) and 4.8 (included as ADR).
Fluid retention	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for non-haematological toxicity), 4.4 (associated with fluid retention), and 4.8 (included as ADR).
Myelosuppression	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2

		(dose interruptions for neutropenia and thrombocytopenia), 4.4 (associated with anaemia, neutropenia, and thrombocytopenia), and 4.8 (anaemia, neutropenia and thrombocytopenia discussed as ADRs).
QT prolongation	• Routine Pharmacovigilance	As described in the SmPC in sections 4.4 (QTc prolongation without arrhythmia), 4.5 (potential for interactions), 4.8 (QT interval prolongation discussed as ADR), 5.1 (QT data discussed), and 5.3 (nonclinical effect on QTc interval discussed).
Respiratory Tract Infections	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for non-haematological toxicity) and 4.8 (included as ADR).
Bleeding Events	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for haematological toxicity) and 4.8 (included as ADR, as well as the Package Leaflet, section 2.
Rash	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for non-haematological toxicity) and 4.8 (included as ADR).
Pancreatitis / Increased lipase	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for non-haematological toxicity), 4.4 (elevation in lipase observed), and 4.8 (included as ADR).
Important Potential Risks		
Cardiac toxicity (excluding QT prolongation)	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (patients excluded) and 4.4 (patients with uncontrolled or significant cardiac disease).
Interstitial lung disease	• Routine Pharmacovigilance	No risk minimisation activities are planned currently
Thyroid dysfunction	• Routine Pharmacovigilance	No risk minimisation activities are planned currently
Tumour lysis syndrome	• Routine Pharmacovigilance	No risk minimisation activities are planned currently
Effect on bone turnover / bone mineral metabolism disorders	• Routine Pharmacovigilance	As described in the SmPC in section 4.8 (hypophosphataemia included as ADR).
Immunotoxicity	• Routine Pharmacovigilance	Myelosuppression and infections, as described in the SmPC in sections 4.2, (dose interruptions for haematologic and non-haematological toxicity), 4.4 and 4.8 (anaemia, neutropenia and thrombocytopenia and infections discussed as ADRs).
Important Missing Information		
Paediatric safety	• Routine Pharmacovigilance • Paediatric Investigation Plan approved. A summary of the paediatric investigational plan is provided in Annex 3. The initiation of this study is deferred.	As described in the SmPC in section 4.2 (no data available) and 5.2 (not yet studied).
Safety in elderly patients	• Routine Pharmacovigilance	As described in the SmPC in section 4.2 (no dose recommendation) and 5.2 (no clinically relevant effects of age).
Safety in non-white and non-Asian patients	• Routine Pharmacovigilance	As described in the SmPC in section 5.2 (no clinically relevant effects of race).
Renal Impairment	• Routine Pharmacovigilance The ongoing study (B1871020) in	As described in the SmPC in section 4.2 (patients excluded) and 4.4 (trend to

	subjects with renal impairment is clinically complete; the clinical study report is being prepared and will be submitted when available.	increasing AUC).
Safety in patients with hepatic impairment	• Routine Pharmacovigilance	As described in the SmPC in section 4.3 (included as contraindication).
Safety in patients with cardiac impairment	• Routine Pharmacovigilance	As described in the SmPC in section 4.2 (patients excluded) and 4.4 (uncontrolled or significant cardiac disease).
Safety in patients with recent or ongoing clinically significant gastrointestinal disorders	• Routine Pharmacovigilance	As described in the SmPC in sections 4.2 (dose interruptions for diarrhoea), 4.4 (associated with diarrhoea and vomiting), and 4.8 (diarrhoea, nausea, and vomiting discussed as ARDs).
Pregnancy and lactation	• Routine Pharmacovigilance, including the use of a pregnancy follow-up questionnaire	As described in the SmPC in sections 4.6 (pregnancy and lactation) and 5.3 (nonclinical reproductive and development toxicity discussed).
Carcinogenicity	• Routine Pharmacovigilance A carcinogenicity study with bosutinib has been conducted.	As described in the SmPC in section 5.3 (nonclinical carcinogenicity study discussed).
Long-term safety	• Routine Pharmacovigilance	As described in the SmPC in sections 4.8 (median treatment noted) and 5.3 (6-month rat and 9-month dog studies discussed).
Interactions of bosutinib with P-gp substrates	• Routine Pharmacovigilance • This interaction will be examined in a clinical, post-authorisation, drug-drug interaction study.	As described in the SmPC in section 4.5 (potential to increase concentrations P-gp substrates)
Safety in patients with background diseases	• Routine Pharmacovigilance	No risk minimisation activities are planned currently
Efficacy and safety information in the proposed indication	• Routine Pharmacovigilance including data from the proposed post-authorization study	No risk minimisation activities are planned currently

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Final Clinical Study Report: 30 September 2018
Clinical drug-drug interaction study on inhibition of P-gp	Study synopsis: 30 April 2013
Post-hoc analysis of diarrhoea incidence after study patients switch to the commercial formulation.	Synopsis of the plan to provide the data: 30 April 2013
Clinical study of absolute bioavailability study using the commercial formulation tablet in fed state in healthy volunteers	Study synopsis: 30 April 2013

Description	Due date
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Final Clinical Study Report: 30 September 2018
Study (B1871020) in subjects with renal impairment	Final Clinical Study Report: 30 March 2013

No additional risk minimisation activities were required beyond those included in the product information.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- Results for the carcinogenicity study have been submitted and do not indicate that further investigations are required. Carcinogenicity is no longer considered important missing information. The summary information on carcinogenicity provided in section 1.1.4 of the RMP should be updated to include information on the results of the study.
- Annex 3 of the RMP should be amended to include information on the clinical studies as detailed above.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

The applicant requested to have a combined package leaflet for the 100 mg and 500 mg strengths. This was considered acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Bosutinib is a second generation TKI that binds the kinase domain of Bcr-Abl, which is characteristic for Ph+ CML, in an intermediate conformation thereby inhibiting Abl kinase activity in vitro with an IC50 of 1 nM. In cell lines transfected with both wild type and imatinib-resistant mutant BCR-ABL it suppresses proliferation. In imatinib-sensitive CML cell lines, the in-vitro inhibitory activity of bosutinib is up to 100-fold that of imatinib, with IC_{50} values ranging from 1 to 20 nM. In imatinib-resistant cell lines (with or without mutations) bosutinib inhibited proliferation up to 114-fold that of imatinib. Bosutinib has been shown to inhibit phosphorylation of various signalling proteins and downstream substrates of Bcr-Abl, most notably the transcription factor Stat5 and the docking protein CrkL.

Bosutinib could not be considered approvable for a 1st line indication in CML. as the pivotal Study 300-WW failed to achieve the primary objective CCyR at 12 months and the updated analysis at 24 months showed that imatinib was actually numerically superior to bosutinib.

According the relevant CHMP guideline-document a comparative study for bosutinib against the EU-approved second line TKIs (dasatinib and nilotinib) is necessary for approval. However, such data was not available during the procedure and insofar, only a last line indication based on data in post-hoc defined subpopulation of patients with an "Unmet Medical Need" from study 200-WW could be further discussed for approval.

Consequently, results of study 200-WW were considered as pivotal to support an indication of Bosulif in a last-line CML indication "*for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) previously treated with one or more tyrosine kinase inhibitor(s) (TKIs) and for whom imatinib, nilotinib or dasatinib are not considered appropriate treatment options".*

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

In this study, efficacy was seen in the subpopulation of CP, AP, and BP CML patients who, based on clearly defined criteria, may not be candidates for treatment with at least 1 of the currently approved TKI due to intolerance, mutations, or comorbidities. Although these subpopulations were small, the efficacy is further supported by the results seen in the larger reference populations within Study 200-WW.

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

There was also a subpopulation of 16 advanced phase patients (5 AP CML and 11 BP CML patients) that failed treatment with either imatinib alone or imatinib in addition to one or both second-generation TKIs (dasatinib and nilotinib) and for whom, based on the presence of co-morbidities, a history of TKI intolerance, or a BCR-ABL resistance mutation, the remaining approved TKI(s) were not considered appropriate treatment options. Of these, 4 of the 5 AP patients had notable treatment duration with a range from 46 to 114 weeks with responses including CMR (1 patient), CCyR (2 patients) and major haematologic response (MaHR) (1 patient) with 1 patient still on treatment. Among the 11 BP CML patients, 3 patients remained on treatment for more than 24 weeks with notable responses (2 patients with a CCyR and 1 patient with a MaHR) and a treatment duration ranging from 46 to 118 weeks with one patient still on treatment.

Uncertainty in the knowledge about the beneficial effects.

Although the second generation TKI Bosutinib is clearly efficacious in CML patients, efficacy for the currently proposed last-line indication is only shown in a very limited population selected retrospectively from an exploratory study. Thus, this efficacy needs to be confirmed prospectively in a larger population. The applicant has committed to perform an adequately designed study as a specific obligation for approval in order to generate sufficient data on efficacy and safety in the last line indication.

Risks

Unfavourable effects

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

In the pivotal Study 200-WW, the safety profile of bosutinib seemed manageable and generally similar across all CML reference populations (CP, AP, and BP). But based on results from Study 3000-WW, it was concluded that toxicity in the first-line CP-CML patients was more pronounced than with imatinib.

Gastrointestinal toxicity of Bosutinib is pronounced and diarrhoea was identified consistently as dose-dependent and dose-limiting for bosutinib in all clinical studies.

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

Hepatic toxicity with bosutinib seemed primarily to involve isolated transaminase elevations, which occurred most frequently within the first 6 months of treatment. The subjects remained asymptomatic despite the laboratory abnormalities and the majority of subjects did not require treatment discontinuation, even though almost 30% of patients in bosutinib arm reported hepatic-related AEs that led to treatment interruption. There were no cases of permanent hepatic injury and no liver-related deaths in CML patients treated with bosutinib. However, Hy's law cases associated with the use of bosutinib were documented. From the assessment of the AST/ALT/Bilirubin data provided in the response, it can be confirmed now that no further case fulfilling Hy's law occurred in the CML population.

Two cases of anaphylaxis were reported across the bosutinib clinical development program, although none were reported in other studies including Study 200-WW. The SmPC therefore includes a contraindication in case of hypersensitivity to the active substance or to any of the excipients.

Pharmacokinetic studies have shown 2-fold increases of bosutinib exposure and elimination half-life in patients with hepatic impairment. Additionally, a high rate of QTc-time prolongation related to drug exposure. A contraindication is included in the SmPC for patients with hepatic impairment.

Uncertainty in the knowledge about the unfavourable effects

All reported SAEs of increased AST/ALT in the bosutinib arm are reported as resolved; this might indicate that hepatotoxicity with adequate controls might be manageable. Consequently, recommendations for monitoring of liver function have been included in section 4.4 of the SmPC as well as recommendations for dose interruptions and adjustements in section 4.2 of the SmPC.

Diarrhoea events in the bosutinib arm were reported to be manageable; however, the overall impact of concomitant antidiarrhoeal medication on these events should be further described. A post-hoc analysis of diarrhoea incidence after study patients switch to the commercial formulation is planned as a post-authorisation measure.

Diarrhoea and vomiting may lead to electrolyte disturbances (e.g. diarrhoea induced hypokalaemia and QTc prolongation); insufficient bioavailability (inadequate PK data on influence of diarrhoea); increase of bosutinib exposure secondary to antidiarrhoeal drugs, which may produce paradoxical worsening of the diarrhoea events in a vicious circle manner; more gastrointestinal infections. Diarrhoea and vomiting should be managed through dose adjustments and in accordance to the warnings in the SmPC (see sections 4.2 and 4.4

A proarrhythmic potential of bosutinib could not be ruled out although the thorough QT study was negative, because in other studies clinically relevant QTc prolongations have been observed and patients with cardiac risk factors had been excluded from the clinical studies. Consequently bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation and monitoring for an effect on the QTc interval is recommended (see section 4.4 of the SmPC).

The safety profile of bosutinib has been adequately characterised. Nevertheless the study to be conducted as a specific obligation in order to better characterise the efficacy in the last-line population will also provide further information on the safety of bosutinib.

Benefit-risk balance

Importance of favourable and unfavourable effects

While available TKIs provide noteworthy clinical benefit, many patients ultimately develop intolerance or resistance to treatment, or experience disease transformation to advanced leukaemia. The presence of resistance mutations, intolerance to specific TKI toxicities, and pre-existing comorbidities are key considerations for selecting one TKI over another for a specific patient. For these patients, there are currently limited or no treatment options and bosutinib may offer a valuable alternative treatment option. The unique efficacy and safety profiles of currently available TKIs therefore drive the choice of initial and subsequent sequential treatments. A sizeable proportion of patients fail to achieve responses with imatinib, dasatinib or nilotinib. Furthermore, intolerance due to intolerable toxicity with the available TKIs is becoming a growing problem in the clinical management of CML patients.

The available data from study 200-WW indicate that bosutinib is a possible treatment option for these patients and has shown that CP and advanced CML patients, who are resistant and/or intolerant to imatinib, dasatinib and nilotinib, have a clinically relevant benefit from treatment with this drug.

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

Benefit-risk balance

In Study 200-WW bosutinib was associated with a clinically significant benefit in the subpopulations of CP, AP, and BP CML patients, who were previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib were not considered appropriate. As bosutinib is currently the only available TKI treatment option in this subpopulation, the toxicity profile is deemed acceptable. Thus, a positive benefit-risk balance in this subpopulation can be concluded.

Discussion on the benefit-risk balance

Due to the limited evidence currently supporting the last-line indication, additional comprehensive clinical data are needed from a clinical interventional study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Approximately 150 patients will be enrolled primarily at large medical centres in Europe and the United States, with the intent to enroll up to 75 patients in the 4th or later line setting. Efficacy endpoint assessment should be performed centralized and mutation analysis is expected.

The primary efficacy endpoint will be Major Cytogenetic Response (MCyR) rate (chronic phase) and Confirmed Overall Haematological Response (OHR) rate (accelerated and blast phase) by one year. Efficacy data will be collected at regularly scheduled time-points at 3, 6, 9 and 12 months in the different CML patient populations.

It is expected that this study will further support the efficacy of bosutinib in the last-line treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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.

The safety profile of bosutinib seems to be adequately characterised. Nevertheless the study to be conducted as a specific obligation will also provide further information on the safety of bosutinib.

Such a study is considered appropriate to allow a conditional marketing authorisation and to confirm the preliminary results observed in the target population as approved by CHMP.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Bosulif in the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) 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 is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreeed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To conduct a single-arm open-label, multi-centre efficacy and safety study of bosutinib in patients with Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.	Final Clinical Study Report: 30 September 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that bosutinib monohydrate is qualified as a new active substance.