Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bosutinib Clonmel 400 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg bosutinib.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange oval (width: 9 mm; length: 17 mm) biconvex, film-coated tablet debossed with "C19" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Bosutinib Clonmel is indicated for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- CP, accelerated phase (AP), and blast phase (BP) Ph+ CML previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

Posology

Newly-diagnosed CP Ph+ CML
The recommended dose is 400 mg bosutinib once daily.

CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy
The recommended dose is 500 mg bosutinib once daily.

In clinical trials for both indications, treatment with bosutinib continued until disease progression or intolerance to therapy.

Dose adjustments

In the Phase 1/2 clinical study in patients with CML who were resistant or intolerant to prior therapy dose escalations from 500 mg to 600 mg once daily with food were allowed in patients who failed to demonstrate complete haematological response (CHR) by Week 8 or complete cytogenetic response (CCyR) by Week 12 and did not have Grade 3 or higher adverse events possibly-related to the investigational product. In the Phase 3 clinical study in patients with newly-diagnosed CP CML treated with bosutinib 400 mg, dose escalations by 100 mg increments to a maximum of 600 mg once daily with food were permitted if the patient failed to demonstrate breakpoint cluster region-Abelson (BCR-ABL) transcripts ≤ 10% at Month 3, did not have a Grade 3 or 4 adverse reaction at the time of escalation, and all Grade 2 non-haematological toxicities were resolved to at least Grade 1. In the Phase 4 clinical study in patients with Ph+ CML previously treated with 1 or more TKI(s), dose escalations from 500 mg to 600 mg once daily with food were allowed in patients with unsatisfactory response or with signs of disease progression in the absence of any Grade 3 or 4 or persistent Grade 2 adverse events.

In the Phase 1/2 study in patients with CML who were resistant or intolerant to prior therapy who started treatment at ≤ 500 mg, 93 (93/558; 16.7%) patients had dose escalations to 600 mg daily.

In the Phase 3 study in patients with newly-diagnosed CP CML who started bosutinib treatment at 400 mg, a total of 58 patients (21.6%) received dose escalations to 500 mg daily. In addition, 10.4% of patients in the bosutinib treatment group had further dose escalations to 600 mg daily.

In the Phase 4 study in patients with Ph+ CML previously treated with 1 or more TKI(s) who started bosutinib treatment at 500 mg daily, 1 patient (0.6%) had a dose escalation up to 600 mg daily.

Doses greater than 600 mg/day have not been studied and, therefore, should not be given.

Dose adjustments for adverse reactions

Non-haematological adverse reactions
If clinically significant moderate or severe non-haematological toxicity develops, bosutinib should be interrupted, and may be resumed at a dose reduced by 100 mg taken once daily after the toxicity has resolved. If clinically appropriate, re-escalation to the dose prior to the dose reduction taken once daily should be considered (see section 4.4). Doses less than 300 mg/day have been used in patients; however, efficacy has not been established.

Elevated liver transaminases: If elevations in liver transaminases > 5 × institutional upper limit of normal (ULN) occur, bosutinib should be interrupted until recovery to ≤ 2.5 × ULN and may be resumed at 400 mg once daily thereafter. If recovery takes longer than 4 weeks, discontinuation of bosutinib should be considered. If transaminase elevations ≥ 3 × ULN occur concurrently with bilirubin elevations > 2 × ULN and alkaline phosphatase < 2 × ULN, bosutinib should be discontinued (see section 4.4).

Diarrhoea: For NCI Common Terminology Criteria for Adverse Events (CTCAE) Grade 3-4 diarrhoea, bosutinib should be interrupted and may be resumed at 400 mg once daily upon recovery to grade ≤ 1 (see section 4.4).

Haematological adverse reactions
Dose reductions are recommended for severe or persistent neutropenia and thrombocytopenia as described in Table 1:

Table 1 – Dose adjustments for neutropenia and thrombocytopenia

ANC[a] < 1.0×10^9/L and/or Platelets < 50 × 109/L	Hold bosutinib until ANC ≥ 1.0×10^9/L and platelets ≥ 50×10^9/L. Resume treatment with bosutinib at the same dose if recovery occurs within 2 weeks. If blood counts remain low for > 2 weeks, upon recovery reduce dose by 100 mg and resume treatment. If cytopoenia recurs, reduce dose by an additional 100 mg upon recovery and resume treatment. Doses less than 300 mg/day have been used; however, efficacy has not been established.

[a]ANC = absolute neutrophil count

Special populations

Elderly patients (≥ 65 years)
No specific dose recommendation is necessary in the elderly. Since there is limited information in the elderly, caution should be exercised in these patients.

Renal impairment
Patients with serum creatinine > 1.5×ULN were excluded from CML studies. Increasing exposure (area under curve [AUC]) in patients with moderate and severe renal impairment during studies was observed.

Newly-diagnosed CP Ph+ CML
In patients with moderate renal impairment (creatinine clearance [CLCr] 30 to 50 ml/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily with food (see sections 4.4 and 5.2).

In patients with severe renal impairment (CLCr < 30 ml/min, estimated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 200 mg daily with food (see sections 4.4 and 5.2).

Dose escalation to 400 mg once daily with food for patients with moderate renal impairment or to 300 mg once daily for patients with severe renal impairment may be considered if they do not experience severe or persistent moderate adverse reactions and if they do not achieve an adequate haematological, cytogenetic, or molecular response.

CP, AP, or BP Ph+ CML with resistance or intolerance to prior therapy
In patients with moderate renal impairment (CLCr 30 to 50 ml/min, calculated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 400 mg daily (see sections 4.4 and 5.2).

In patients with severe renal impairment (CLCr < 30 ml/min, calculated by the Cockcroft-Gault formula), the recommended dose of bosutinib is 300 mg daily (see sections 4.4 and 5.2).

Dose escalation to 500 mg once daily for patients with moderate renal impairment or to 400 mg once daily in patients with severe renal impairment may be considered in those who did not experience severe or persistent moderate adverse reactions, and if they do not achieve an adequate haematological, cytogenetic, or molecular response.

Cardiac disorders
In clinical studies, patients with uncontrolled or significant cardiac disease (e.g., recent myocardial infarction, congestive heart failure or unstable angina) were excluded. Caution should be exercised in patients with relevant cardiac disorders (see section 4.4).

Recent or ongoing clinically significant gastrointestinal disorder
In clinical studies, patients with recent or ongoing clinically significant gastrointestinal disorder (e.g., severe vomiting and/or diarrhoea) were excluded. Caution should be exercised in patients with recent or ongoing clinically significant gastrointestinal disorder (see section 4.4).

Paediatric population
The safety and efficacy of bosutinib in children and adolescents less than 18 years of age have not been established. No data are available.

Method of administration
Bosutinib Clonmel should be taken orally once daily with food (see section 5.2). If a dose is missed by more than 12 hours, the patient should not be given an additional dose. The patient should take the usual prescribed dose on the following day.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hepatic impairment (see sections 5.1 and 5.2).

4.4 Special warnings and precautions for use

Liver function abnormalities
Treatment with bosutinib is associated with elevations in serum transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]).

Transaminase elevations generally occurred early in the course of treatment (of the patients who experienced transaminase elevations of any grade, > 80% experienced their first event within the first 3 months). Patients receiving bosutinib should have liver function tests prior to treatment initiation and monthly for the first 3 months of treatment, and as clinically indicated.

Patients with transaminase elevations should be managed by withholding bosutinib temporarily (with consideration given to dose reduction after recovery to Grade 1 or baseline), and/or discontinuation of bosutinib. Elevations of transaminases, particularly in the setting of concomitant increases in bilirubin, may be an early indication of drug-induced liver injury and these patients should be managed appropriately (see sections 4.2 and 4.8).

Diarrhoea and vomiting
Treatment with bosutinib is associated with diarrhoea and vomiting; therefore, patients with recent or ongoing clinically significant gastrointestinal disorder should use this medicinal product with caution and only after a careful benefit-risk assessment as respective patients were excluded from the clinical studies. Patients with diarrhoea and vomiting should be

managed using standard-of-care treatment, including an antidiarrhoeal or antiemetic medicinal product and/or fluid replacement. In addition, diarrhoea and vomiting can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8). The antiemetic agent, domperidone, has the potential to increase QT interval (QTc) 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 QTc prolongation.

Myelosuppression
Treatment with bosutinib is associated with myelosuppression, defined as anaemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month and then monthly thereafter, or as clinically indicated. Myelosuppression should/can be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8).

Fluid retention
Treatment with bosutinib may be associated with fluid retention including pericardial effusion, pleural effusion, pulmonary oedema and/or peripheral oedema. Patients should be monitored and managed using standard-of-care treatment. In addition, fluid retention can also be managed by withholding bosutinib temporarily, dose reduction, and/or discontinuation of bosutinib (see sections 4.2 and 4.8).

Serum lipase
Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, bosutinib should be interrupted and appropriate diagnostic measures considered to exclude pancreatitis (see section 4.2).

Infections
Bosutinib may predispose patients to bacterial, fungal, viral, or protozoan infections.

Proarrhythmic potential
Automated machine-read QTc prolongation without accompanying arrhythmia has been observed. Bosutinib should be administered with caution to patients who have a history of or predisposition for QTc prolongation, who have uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia, or who are taking medicinal products that are known to prolong the QTc (e.g., anti-arrhythmic medicinal products and other substances that may prolong QTc [see section 4.5]). The presence of hypokalaemia and hypomagnesaemia may further enhance this effect.

Monitoring for an effect on the QTc is advisable and a baseline electrocardiogram (ECG) is recommended prior to initiating therapy with bosutinib and as clinically indicated. Hypokalaemia or hypomagnesaemia must be corrected prior to bosutinib administration and should be monitored periodically during therapy.

Renal impairment
Treatment with bosutinib may result in a clinically significant decline in renal function in CML patients. A decline over time in estimated glomerular filtration rate (eGFR) has been observed in patients treated with bosutinib in clinical studies. In patients with newly-diagnosed CP CML treated with 400 mg, the median decline from baseline in eGFR was 11.1 ml/min/1.73 m^2 at 1 year and 14.1 ml/min/1.73 m^2 at 5 years for patients on treatment. Treatment-naïve CML patients treated with 500 mg showed a median eGFR decline of 9.2 ml/min/1.73 m^2 at 1 year, 12.0 ml/min/1.73 m^2 at 5 years and 16.6 ml/min/1.73 m^2 at 10 years for patients on treatment. In pre-treated patients with CP and advanced stage CML treated with 500 mg the median eGFR decline was 7.6 ml ml/min/1.73 m^2 at 1 year, 12.3 ml/min/1.73 m^2 at 5 years and 15.9 ml/min/1.73 m^2 at 10 years for patients on treatment. In patients with Ph+ CML previously treated with 1 or more TKI(s) treated with 500 mg, the median eGFR decline from baseline was 9.2 ml/min/1.73 m^2 at 1 year and 14.5 ml/min/1.73 m^2 at 4 years for patients on treatment.

It is important that renal function is assessed prior to treatment initiation and closely monitored during therapy with bosutinib, with particular attention in those patients who have pre-existing renal compromise or in those patients exhibiting risk factors for renal dysfunction, including concomitant use of medicinal products with potential for nephrotoxicity, such as diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs).

In a renal impairment study, bosutinib exposures were increased in subjects with moderately and severely impaired renal function. Dose reduction is recommended for patients with moderate or severe renal impairment (see sections 4.2 and 5.2).

Patients with serum creatinine > 1.5 × ULN were excluded from the CML studies. Based on a population pharmacokinetic analysis increasing exposure (AUC) in patients with moderate and severe renal impairment at initiation of treatment during studies was observed (see sections 4.2 and 5.2).

Clinical data are very limited (n = 3) for CML patients with moderate renal impairment receiving an escalated dose of 600 mg bosutinib.

Asian race
According to population pharmacokinetic analyses, Asians had a lower clearance resulting in increased exposure. Therefore, these patients should be closely monitored for adverse reactions especially in case of dose escalation.

Severe skin reactions
Bosutinib can induce severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Bosutinib should be permanently discontinued in patients who experience a severe skin reaction during treatment.

Tumour lysis syndrome
Due to the possible occurrence of tumour lysis syndrome (TLS), correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiation of bosutinib (see section 4.8).

Hepatitis B reactivation
Reactivation of hepatitis B (HBV) in patients who are chronic carriers of this virus has occurred after these patients received BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Patients should be tested for HBV infection before initiating treatment with bosutinib. Experts in liver disease and in the treatment of HBV should be consulted before treatment is initiated in patients with positive HBV serology (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with bosutinib should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Photosensitivity
Exposure to direct sunlight or ultraviolet (UV) radiation should be avoided or minimised due to the risk of photosensitivity associated with bosutinib treatment. Patients should be instructed to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Cytochrome P-450 (CYP)3A inhibitors
The concomitant use of bosutinib with strong or moderate CYP3A inhibitors should be avoided, as an increase in bosutinib plasma concentration will occur (see section 4.5).

Selection of an alternate concomitant medicinal product with no or minimal CYP3A inhibition potential, if possible, is recommended.

If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered.

CYP3A inducers
The concomitant use of bosutinib with strong or moderate CYP3A inducers should be avoided as a decrease in bosutinib plasma concentration will occur (see section 4.5).

Food effect
Grapefruit products, including grapefruit juice and other foods that are known to inhibit CYP3A should be avoided (see section 4.5).

Dietary sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg, 400 mg, or 500 mg tablet. Patients on low sodium diets should be informed that this product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on bosutinib

CYP3A inhibitors
The concomitant use of bosutinib with strong CYP3A inhibitors (including, but not limited to itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, telithromycin, nefazodone, mibefradil, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, boceprevir, telaprevir, grapefruit products including grapefruit juice) or moderate CYP3A inhibitors (including, but not limited to fluconazole, ciprofloxacin, erythromycin, diltiazem, verapamil, amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir, aprepitant, crizotinib, imatinib) should be avoided, as an increase in bosutinib plasma concentration will occur.

Caution should be exercised if mild CYP3A inhibitors are used concomitantly with bosutinib.

Selection of an alternate concomitant medicinal product with no or minimal CYP3A enzyme inhibition potential, if possible, is recommended.

If a strong or moderate CYP3A inhibitor must be administered during bosutinib treatment, an interruption of bosutinib therapy or a dose reduction in bosutinib should be considered.

In a study of 24 healthy subjects in whom 5 daily doses of 400 mg ketoconazole (a strong CYP3A inhibitor) were co-administered with a single dose of 100 mg bosutinib under fasting conditions, ketoconazole increased bosutinib Cmax by 5.2-fold, and bosutinib AUC in plasma by 8.6-fold, as compared with administration of bosutinib alone.

In a study of 20 healthy subjects, in whom a single dose of 125 mg aprepitant (a moderate CYP3A inhibitor) was co-administered with a single dose of 500 mg bosutinib under fed conditions, aprepitant increased bosutinib Cmax by 1.5-fold, and bosutinib AUC in plasma by 2.0-fold, as compared with administration of bosutinib alone.

CYP3A inducers
The concomitant use of bosutinib with strong CYP3A inducers (including, but not limited to carbamazepine, phenytoin, rifampicin, St. John's Wort), or moderate CYP3A inducers (including, but not limited to bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided, as a decrease in bosutinib plasma concentration will occur.

Based on the large reduction in bosutinib exposure that occurred when bosutinib was co-administered with rifampicin, increasing the dose of bosutinib when co-administering with strong or moderate CYP3A inducers is unlikely to sufficiently compensate for the loss of exposure.

Caution is warranted if mild CYP3A inducers are used concomitantly with bosutinib.

Following concomitant administration of a single dose bosutinib with 6 daily doses of 600 mg rifampicin, in 24 healthy subjects in fed state bosutinib exposure (C_{max} and AUC in plasma) decreased to 14% and 6%, respectively, of the values when bosutinib 500 mg was administered alone.

Proton pump inhibitors (PPIs)

Caution should be exercised when administering bosutinib concomitantly with PPIs. Short-acting antacids should be considered as an alternative to PPIs and administration times of bosutinib and antacids should be separated (i.e. take bosutinib in the morning and antacids in the evening) whenever possible. Bosutinib displays pH-dependent aqueous solubility *in vitro*. 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 C_{max} and AUC decreased to 54% and 74%, respectively, of the values seen when bosutinib (400 mg) was given alone.

Effects of bosutinib on other medicinal products
In a study of 27 healthy subjects, in whom a single dose of 500 mg bosutinib was co-administered with a single dose of 150 mg dabigatran etexilate mesylate (a P-glycoprotein [P-gp] substrate) under fed conditions, bosutinib did not increase C_{max} or AUC of dabigatran in plasma, as compared with administration of dabigatran etexilate mesylate alone. The study results indicate that bosutinib does not exhibit clinically relevant P-gp inhibitory effects.

An *in vitro* study indicates that drug-drug interactions are unlikely to occur at therapeutic doses as a result of induction by bosutinib on the metabolism of medicinal products that are substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4.

In vitro studies indicate that clinical drug-drug interactions are unlikely to occur at therapeutic doses as a result of inhibition by bosutinib on the metabolism of medicinal products that are substrates for CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5.

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

Anti-arrhythmic medicinal products and other substances that may prolong QT
Bosutinib should be used with caution in patients who have or may develop prolongation of QT, including those patients taking anti-arrhythmic medicinal products such as amiodarone, disopyramide, procainamide, quinidine and sotalol or other medicinal products that may lead to QT prolongation such as chloroquine, halofantrine, clarithromycin, domperidone, haloperidol, methadone, and moxifloxacin (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Women of childbearing potential should be advised to use effective contraception during treatment with bosutinib and for at least 1 month after the last dose and to avoid becoming pregnant while receiving bosutinib. In addition, the patient should be advised that vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption.

Pregnancy
There are limited amount of data in pregnant women from the use of bosutinib. Studies in animals have shown reproductive toxicity (see section 5.3). Bosutinib is not recommended for use during pregnancy, or in women of childbearing potential not using contraception. If bosutinib is used during pregnancy, or the patient becomes pregnant while taking bosutinib, she should be apprised of the potential hazard to the foetus.

Breast-feeding
It is unknown whether bosutinib and its metabolites are excreted in human milk. A study of [^{14}C] radiolabelled bosutinib in rats demonstrated excretion of bosutinib-derived radioactivity in breast milk (see section 5.3). A potential risk to the breast-feeding infant cannot be excluded. Breast-feeding should be discontinued during treatment with bosutinib.

Fertility
Based on non-clinical findings, bosutinib has the potential to impair reproductive function and fertility in humans (see section 5.3). Men being treated with bosutinib are advised to seek advice on conservation of sperm prior to treatment because of the possibility of decreased fertility due to therapy with bosutinib.

4.7 Effects on ability to drive and use machines

Bosutinib has no or negligible influence on the ability to drive and use machines. However, if a patient taking bosutinib experiences dizziness, fatigue, visual impairment or other undesirable effects with a potential impact on the ability to drive or use machines safely, the patient should refrain from these activities for as long as the undesirable effects persist.

4.8 Undesirable effects

Summary of safety profile
A total of 1,372 leukaemia patients received at least 1 dose of single-agent bosutinib. The median duration of therapy was 26.30 months (range: 0.03 to 170.49 months). These patients were either newly-diagnosed, with CP CML or were resistant or intolerant to prior therapy with chronic, accelerated, or blast phase CML or Ph+ acute lymphoblastic leukaemia (ALL). Of these patients, 268 (400 mg starting dose) and 248 (500 mg starting dose) are from the 2 Phase 3 studies in previously untreated CML patients, 60 (400 mg starting dose) are from a Phase 2 study in previously untreated CML patients, 570 and 63 (Phase 2: 500 mg starting dose) are from 2 Phase 1/2 studies in previously treated Ph+ leukaemias, and 163 (500 mg starting dose) are from a Phase 4 study in previously treated CML. The median duration of therapy was 55.1 months (range: 0. 2 to 60.05 months), 61.6 months (0.03 to 145.86 months), 15.3 months (range: 0.3 to 21.8 months), 11.1 months (range: 0.03 to 170.49 months), 30.2 months (range: 0.2 to 85.6 months), and 37.80 months (range: 0.16 to 50.0 months), respectively. The safety analyses included data from a completed extension study.

At least 1 adverse reaction of any toxicity grade was reported for 1,349 (98.3%) patients. The most frequent adverse reactions reported for ≥ 20% of patients were diarrhoea (80.4%), nausea (41.5%), abdominal pain (35.6%), thrombocytopenia (34.4%), vomiting (33.7%), rash (32.8%), ALT increased (28.0%), anaemia (27.2%), pyrexia (23.4%), AST increased (22.5%), fatigue (32.0%), and headache (20.3%). At least 1 Grade 3 or Grade 4 adverse reaction was reported for 943 (68.7%) patients. The Grade 3 or Grade 4 adverse reactions reported for ≥ 5% of patients were thrombocytopenia (19.7%), ALT increased (14.6%), neutropenia (10.6%), diarrhoea (10.6%), anaemia (10.3%), lipase increased (10.1%), AST increased (6.7%), and rash (5.0%).

Tabulated list of adverse reactions

The following adverse reactions were reported in patients in bosutinib clinical studies (Table 2). These represent an evaluation of the adverse reaction data from 1,372 patients with either newly-diagnosed CP CML or with chronic, accelerated, or blast phase CML resistant or intolerant to prior therapy or Ph+ ALL who have received at least 1 dose of single-agent bosutinib. These adverse reactions are presented by system organ class and frequency. Frequency categories are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 - Adverse reactions for bosutinib

Infections and infestations	
Very common	Respiratory tract infection (including Lower respiratory tract infection, Respiratory tract infection viral, Upper respiratory tract infection, Viral upper respiratory tract infection), Nasopharyngitis
Common	Pneumonia (including Atypical pneumonia, Pneumonia bacterial, Pneumonia fungal, Pneumonia necrotising, Pneumonia streptococcal), Influenza (including Influenza H1N1), Bronchitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Uncommon	Tumour lysis syndrome**
Blood and lymphatic system disorders	
Very common	Thrombocytopenia (including Platelet count decreased), Neutropenia (including Neutrophil count decreased), Anaemia (including haemoglobin decreased, Red blood cell count decreased)
Common	Leukopenia (including White blood cell count decreased)
Uncommon	Febrile neutropenia, Granulocytopenia
Immune system disorders	
Common	Drug hypersensitivity
Uncommon	Anaphylactic shock
Metabolism and nutrition disorders	
Very common	Decreased appetite
Common	Dehydration, Hyperkalaemia (including Blood potassium increased), Hypophosphataemia (including Blood phosphorus decreased)
Nervous system disorders	
Very common	Dizziness, Headache
Common	Dysgeusia
Ear and labyrinth disorders	
Common	Tinnitus
Cardiac disorders	
Common	Pericardial effusion
Uncommon	Pericarditis
Vascular disorders	
Common	Hypertension (including Blood pressure increased, Blood pressure systolic increased, Essential hypertension, Hypertensive crisis)
Respiratory, thoracic and mediastinal disorders	
Very common	Pleural effusion, Dyspnoea, Cough
Common	Pulmonary hypertension (including Pulmonary arterial hypertension, Pulmonary arterial pressure increased), Respiratory failure
Uncommon	Acute pulmonary oedema (including Pulmonary oedema)
Not known	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhoea, Vomiting, Nausea, Abdominal pain (including Abdominal discomfort, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness, Gastrointestinal pain)
Common	Gastrointestinal haemorrhage (including Anal haemorrhage, Gastric haemorrhage, Intestinal haemorrhage,

	Lower gastrointestinal haemorrhage, Rectal haemorrhage, Upper gastrointestinal haemorrhage), Pancreatitis (including Pancreatitis acute), Gastritis
Hepatobiliary disorders	
Common	Hepatotoxicity (including Hepatitis, Hepatitis toxic, Liver disorder), Hepatic function abnormal (including Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, Transaminases increased)
Uncommon	Liver injury (including Drug-induced liver injury, Hepatocellular injury)
Skin and subcutaneous tissue disorders	
Very common	Rash (including Rash macular, Rash maculo-papular, Rash papular, Rash pruritic), Pruritus
Common	Photosensitivity reaction (including Polymorphic light eruption), Urticaria, Acne
Uncommon	Erythema multiforme, Exfoliative rash, Drug eruption
Not known	Stevens-Johnson Syndrome**, Toxic epidermal necrolysis**
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, Back pain
Common	Myalgia
Renal and urinary disorders	
Common	Acute kidney injury, Renal failure, Renal impairment
General disorders and administration site conditions	
Very common	Oedema (including Eyelid oedema, Face oedema, Generalised oedema, Localised oedema, Oedema peripheral, Periorbital oedema, Periorbital swelling, Peripheral swelling, Swelling, Swelling of eyelid), Pyrexia, Fatigue (including Asthenia, Malaise)
Common	Chest pain (including Chest discomfort), Pain
Investigations	
Very common	Lipase increased (including Hyperlipasaemia), Alanine aminotransferase increased (including Alanine aminotransferase abnormal), Aspartate aminotransferase increased, Blood creatinine increased
Common	Electrocardiogram QT prolonged (including Long QT syndrome) , Amylase increased (including Hyperamylasaemia), Blood creatine phosphokinase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased (including Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased)

** Adverse reaction identified post marketing.

Description of selected adverse reactions

The descriptions included below are based on the safety population of 1,372 patients who received at least 1 dose of bosutinib and had either newly-diagnosed CP CML or were resistant or intolerant to prior therapy with CP, AP, or BP CML, or Ph+ ALL.

Blood and lymphatic system disorders

Of the 372 (27.1%) patients with reports of adverse reactions of anaemia, 6 patients discontinued bosutinib due to anaemia. Maximum toxicity of Grade 1 occurred in 95 (25.5%) patients, Grade 2 in 135 (36.3%) patients, Grade 3 in 113 patients (30.4%), and Grade 4 in 29 (7.8%) patients. Among these patients, the median time to first event was 29 days (range: 1 to 3,999 days) and the median duration per event was 22 days (range: 1 to 3,682 days).

Of the 209 (15.2%) patients with reports of adverse reactions of neutropenia, 19 patients discontinued bosutinib due to neutropenia. Maximum toxicity of Grade 1 occurred in 19 patients (9.1%), Grade 2 in 45 (21.5%) patients, Grade 3 in 95 (45.5%) patients, and Grade 4 in 50 (23.9%) patients. Among these patients, the median time to first event was 56 days (range: 1 to 1,769 days), and themedian duration per event was 15 days (range: 1 to 913 days).

Of the 472 (34.4%) patients with reports of adverse reactions of thrombocytopenia, 42 patients discontinued bosutinib due to thrombocytopenia. Maximum toxicity of Grade 1 occurred in 114 (24.2%) patients, Grade 2 in 88 (18.6%) patients, Grade 3 in 172 (36.4%) patients, and Grade 4 in 98 (20.8%) patients. Among these patients, the median time to first event was 28 days (range: 1 to 1,688 days), and median duration per event was 15 days (range: 1 to 3,921 days).

Hepatobiliary disorders

Among patients with reports of adverse reactions of elevations in either ALT or AST (all grades), the median time of onset observed was 29 days with a range of onset 1 to 3,995 days for ALT and AST. The median duration of an event was 17 days (range: 1 to 1,148 days), and 15 days (range: 1 to 803 days) for ALT and AST, respectively.

Two cases consistent with drug-induced liver injury (defined as concurrent elevations in ALT or AST ≥ 3 × ULN with total bilirubin > 2 × ULN and with alkaline phosphatase < 2 × ULN) without alternative causes have occurred in 2/1,711 (0.1%) subjects treated with bosutinib.

Hepatitis B reactivation
Hepatitis B reactivation has been reported in association with BCR-ABL TKIs. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section 4.4).

Gastrointestinal disorders
Of the 1,103 (80.4%) patients that experienced diarrhoea, 14 patients discontinued bosutinib due to this event. Concomitant medicinal products were given to treat diarrhoea in 756 (68.5%) patients. Maximum toxicity of Grade 1 occurred in 575 (52.1%) patients, Grade 2 in 383 (34.7%) patients, Grade 3 in 144 (13.1%) patients; 1 patient (0.1%) experienced a Grade 4 event. Among patients with diarrhoea, the median time to first event was 2 days (range: 1 to 2,702 days) and the median duration of any grade of diarrhoea was 2 days (range: 1 to 4,247 days).

Among the 1,103 patients with diarrhoea, 218 patients (19.8%) were managed with treatment interruption and of these 208 (95.4%) were rechallenged with bosutinib. Of those who were rechallenged, 201 (96.6%) did not have a subsequent event or did not discontinue bosutinib due to a subsequent event of diarrhoea.

Cardiac disorders
Seven patients (0.5%) experienced QTcF prolongation (greater than 500 ms). Eleven (0.8%) patientsexperienced QTcF increase> 60 ms from baseline. Patients with uncontrolled or significant cardiovascular disease including QTc prolongation, at baseline, were not included in clinical studies (see sections 5.1 and 5.3).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Experience with bosutinib overdose in clinical studies was limited to isolated cases. Patients who take an overdose of bosutinib should be observed and given appropriate supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EA04.

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

In *in vitro* studies, bosutinib inhibits proliferation and survival of established CML cell lines, Ph+ ALL cell lines, and patient-derived primary primitive CML cells. Bosutinib inhibited 16 of 18 imatinib-resistant forms of BCR-ABL expressed in murine myeloid cell lines. Bosutinib treatment reduced the size of CML tumours growing in nude mice and inhibited growth of murine myeloid tumours expressing imatinib-resistant forms of BCR-ABL. Bosutinib also inhibits receptor tyrosine kinases c-Fms, EphA and B receptors, Trk family kinases, Axl family kinases, Tec family kinases, some members of the ErbB family, the non-receptor tyrosine kinase Csk, serine/threonine kinases of the Ste20 family, and 2 calmodulin-dependent protein kinases.

Pharmacodynamic effects
The effect of bosutinib 500 mg administration on corrected QTc was evaluated in a randomised, single-dose, double-blind (with respect to bosutinib), crossover, placebo- and open-label moxifloxacin-controlled study in healthy subjects.

The data from this study indicate that bosutinib does not prolong the QTc in healthy subjects at the dose of 500 mg daily with food, and under conditions that give rise to supratherapeutic plasma concentrations. Following administration of a single oral dose of bosutinib 500 mg (therapeutic dose) and bosutinib 500 mg with ketoconazole 400 mg (to achieve supratherapeutic concentrations of bosutinib) in healthy subjects, the upper bound of the 1-sided 95% confidence interval (CI) around the mean

change in QTc was less than 10 ms at all post-dose time points, and no adverse events suggestive of QTc prolongation were observed.

In a study in liver impaired subjects, an increasing frequency of QTc prolongation > 450 ms with declining hepatic function was observed. In the Phase 1/2 clinical study in patients with previously treated Ph+ leukaemias treated with bosutinib 500 mg, QTcF increase > 60 ms from baseline was observed in 9 (1.6%) of 570 patients. In the Phase 3 clinical study in patients with newly-diagnosed CP CML treated with bosutinib 400 mg, there were no patients in the bosutinib treatment group (N=268) with a QTcF increase of > 60 ms from baseline. In the Phase 3 clinical study in patients with newly-diagnosed Ph+ CP CML treated with bosutinib 500 mg, QTcF increase > 60 ms from baseline was observed in 2 (0.8%) of 248 patients receiving bosutinib. In the Phase 4 clinical study in patients with Ph+ CML previously treated with 1 or more TKI(s) treated with bosutinib 500 mg (N=163), there were no patients with a QTcF increase > 60 ms from baseline. A proarrhythmic potential of bosutinib cannot be ruled out.

Clinical efficacy and safety

Clinical study in CP previously untreated CML

Bosutinib 400 mg study
A 2-arm, Phase 3, open-label, multicentre superiority trial was conducted to investigate the efficacy and safety of bosutinib 400 mg once daily alone compared with imatinib 400 mg once daily alone in adult patients with newly-diagnosed Ph+ CP CML. The trial randomised 536 patients (268 in each treatment group) with Ph+ or Ph- newly-diagnosed CP CML (intent-to-treat population [ITT]) including 487 patients with Ph+ CML harbouring b2a2 and/or b3a2 transcripts and baseline BCR-ABL copies> 0 (modified intent-to-treat [mITT] population).

The primary efficacy endpoint was the proportion demonstrating a major molecular response (MMR) at 12 months (48 weeks) in the bosutinib treatment group compared with that in the imatinib treatment group in the mITT population. MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts as assessed by the central laboratory.

Key secondary endpoints included complete cytogenetic response (CCyR) by 12 months, duration of CCyR, duration of MMR, event-free survival (EFS), and overall survival (OS). CCyR by Month 12, was defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥ 20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable. The p-values for endpoints other than MMR at 12 months and CCyR by 12 months have not been adjusted for multiple comparisons.

Baseline characteristics for the mITT population were well balanced between the 2 treatment groups with respect to age (median age was 52 years for the bosutinib group and 53 years for the imatinib group with 19.5% and 17.4% of patients 65 years of age or older, respectively); gender (women 42.3% and 44.0%, respectively); race (Caucasian 78.0% and 77.6%, Asian 12.2% and 12.4%, Black or African American 4.1% and 4.1%, and Other 5.7% and 5.4%, respectively, and 1 unknown in the imatinib group); and Sokal risk score (low risk 35.0% and 39.4%, intermediate risk 43.5% and 38.2%, high risk 21.5% and 22.4%, respectively).

After 60 months of follow-up in the mITT population, 60.2% of patients treated with bosutinib (N=246) and 59.8% of patients treated with imatinib (N=239) were still receiving first-line treatment.

After 60 months of follow-up in the mITT population, discontinuations due to disease progression to AP or BP CML for bosutinib-treated patients were 0.8% compared to 1.7% for imatinib-treated patients. Six (2.4%) bosutinib patients and 7 (2.9%) imatinib patients transformed to AP CML or BP CML. Discontinuations due to suboptimal response or treatment failure as assessed by the investigator occurred for 5.3% of patients in the bosutinib-treated group compared to 15.5% of patients in the imatinib-treated group. Twelve (4.9%) patients on bosutinib and 14 (5.8%) patients on imatinib died while on study. No additional transformations occurred in the ITT population, there were 2 additional deaths in the bosutinib arm in the ITT population.

The efficacy results of MMR and CCyR are summarised in Table 3.

Table 3 - Summary of MMR at Months 12 and 18 and CCyR by Month 12, by treatment group in the mITT population

Response	**Bosutinib** (N=246)	**Imatinib** (N=241)	**Odds ratio (95% CI)[a]**
Major molecular response	116 (47.2)[b]	89 (36.9)	1.55 (1.07,2.23)

MMR at Month 12, n (%) (95% CI)	(40.9,53.4)	(30.8,43.0)	
1-sided p-value	0.0100[b]		
MMR at Month 18, n (%) (95% CI)	140 (56.9) (50.7,63.1)	115 (47.7) (41.4,54.0)	1.45 (1.02,2.07)
1-sided p-value	0.0208[c]		
Complete cytogenetic response CCyR by Month 12, n (%) (95% CI)	190 (77.2)[b] (72.0,82.5)	160 (66.4) (60.4,72.4)	1.74 (1.16,2.61)
1-sided p-value	0.0037[b]		

Note: MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio by international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory. Complete cytogenetic response was defined as the absence of Ph+ metaphases in chromosome banding analysis of ≥ 20 metaphases derived from bone marrow aspirate or MMR if an adequate cytogenetic assessment was unavailable.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CCyR=complete cytogenetic response; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number of patients; Ph+=Philadelphia chromosome-positive.
[a] Adjusted for geographical region and Sokal score at randomisation.
[b] Statistically significant comparison at the pre-specified significance level; based on CMH test stratified by geographical region and Sokal score at randomisation.
[c] Based on CMH test stratified by geographical region and Sokal score at randomisation.

At Month 12, the MR^4 rate (defined as ≤ 0.01% BCR-ABL [corresponding to ≥ 4 log reduction from standardised baseline] with a minimum of 9,800 ABL transcripts) was higher in the bosutinib treatment group compared to the imatinib treatment group in the mITT population (20.7% [95% CI: 15.7%, 25.8%] versus 12.0% [95% CI: 7.9%, 16.1%], respectively, odds ratio (OR) 1.88 [95% CI: 1.15, 3.08], 1-sided p-value=0.0052).

At Months 3, 6, and 9, the proportion of patients with MMR was higher in the bosutinib treatment group compared to the imatinib treatment group (Table 4).

Table 4 - Comparison of MMR at Months 3, 6, and 9 by treatment in the mITT population

Time	Number (%) of subjects with MMR		
	Bosutinib (N=246)	Imatinib (N=241)	Odds ratio (95% CI)[a]
Month 3 (95% CI)	10 (4.1) (1.6,6.5)	4 (1.7) (0.0,3.3)	2.48 (0.77,7.98)
1-sided p-value[b]	0.0578		
Month 6 (95% CI)	86 (35.0) (29.0,40.9)	44 (18.3) (13.4,23.1)	2.42 (1.59,3.69)
1-sided p-value[b]	<0.0001		
Month 9 (95% CI)	104 (42.3) (36.1,48.4)	71 (29.5) (23.7,35.2)	1.78 (1.22,2.60)
1-sided p-value[b]	0.0015		

Note: Percentages were based on number of patients in each treatment group. MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio on international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; mITT=modified intent-to-treat; MMR=major molecular response; N=number of patients.
[a] Adjusted for geographical region and Sokal score at randomisation.
[b] Based on CMH test stratified by geographical region and Sokal score at randomisation.

By Month 60 in the mITT population, the proportion of patients with MMR, MR^4 and $MR^{4.5}$ was higher in the bosutinib group compared to the imatinib group (Table 5). MMR rates by Month 60 across Sokal risk subgroups are summarised in Table 6.

Table 5 - Summary of molecular response by Month 60 in the mITT population

Response	Bosutinib (N=246)	Imatinib (N=241)	Odds ratio (95% CI)[a]
Molecular responseby Month 60, n (%) (95% CI)			
MMR	182 (74.0) (68.5,79.5)	158 (65.6) (59.6,71.6)	1.52 (1.02,2.25)
MR^4	145 (58.9) (52.8,65.1)	120 (49.8) (43.5,56.1)	1.46 (1.02,2.09)
$MR^{4.5}$	119 (48.4) (42.1,54.6)	93 (38.6) (32.4,44.7)	1.50 (1.05,2.16)

Note: MMR/MR^4/$MR^{4.5}$ were defined as ≤ 0.1/0.01/0.0032% BCR-ABL/ABL ratio on international scale (corresponding to ≥ 3/4/4.5 log reduction from standardised baseline) with a minimum of 3,000/9,800/30,990 ABL transcripts assessed by the central laboratory.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; mITT=modified intent-to-treat; MMR=major molecular response; MR=molecular response; N/n=number of patients.
[a] Adjusted for geographical region and Sokal score at randomisation.

Table 6 - Summary of MMR by Month 60 by Sokal risk score in the mITT population

Response	Bosutinib	Imatinib	Odds ratio (95% CI)
Low Sokal risk MMR, n (%) (95% CI)	N=86 67 (77.9) (69.1,86.7)	N=95 68 (71.6) (62.5,80.6)	1.40 (0.71,2.76)
Intermediate Sokal risk MMR, n (%) (95% CI)	N=107 79 (73.8) (65.5,82.2)	N=92 62 (67.4) (57.8,77.0)	1.37 (0.74,2.52)
High Sokal risk MMR, n (%) (95% CI)	N=53 36 (67.9) (55.4,80.5)	N=54 28 (51.9) (38.5,65.2)	1.97 (0.90,4.32)

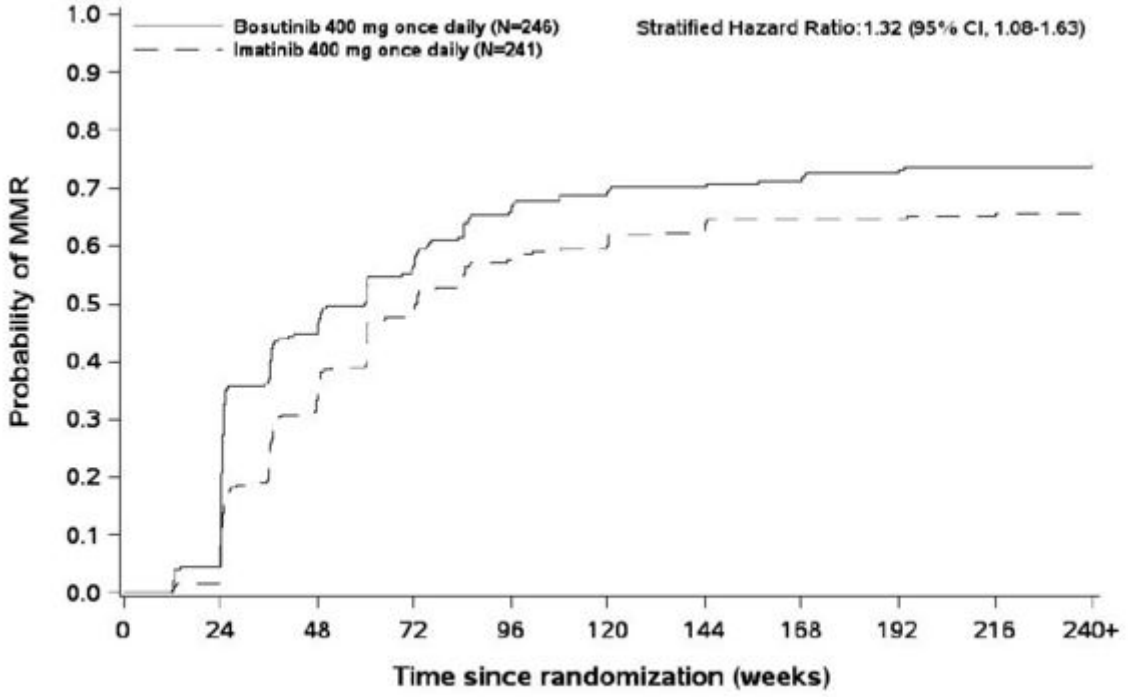
Note: Percentages were based on number of patients in each treatment group. MMR was defined as ≤ 0.1% BCR-ABL/ABL ratio on international scale (corresponding to ≥ 3 log reduction from standardised baseline) with a minimum of 3,000 ABL transcripts assessed by the central laboratory.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; mITT=modified intent-to-treat; MMR=major molecular response; N/n=number of patients.

The cumulative incidence of CCyR adjusted for the competing risk of treatment discontinuation without CCyR was higher in the bosutinib treatment group compared to the imatinib treatment group in the mITT population (83.3% [95% CI: 78.1%, 87.4%] versus 76.8% [95% CI: 70.9%, 81.6%] at Month 60; hazard ratio [HR] from a stratified proportional sub distributional hazards model: 1.35, [95% CI: 1.11, 1.64]). The median time to CCyR (responders only) was 24.0 weeks (range: 11.4 to 120.7) in the bosutinib group compared to the 24.3 weeks (range: 11.4 to 96.6) in the imatinib group.

The median time to MMR, MR^4 and $MR^{4.5}$ (responders only) was 36.1 weeks (range: 11.9 to 241.9), 83.7 weeks (range: 12.4 to 244.3), and 108.0 weeks (range: 24.1 to 242.1), respectively, for the bosutinib treatment group versus 47.7 weeks (range: 12.1 to 216.1), 84.4 weeks (range: 23.6 to 241.9), and 120.4 weeks (range: 24.6 to 240.7), respectively, for the imatinib treatment group in the mITT population.

The cumulative incidence of MMR, MR^4 and $MR^{4.5}$ adjusted for the competing risk of treatment discontinuation without the event was higher with bosutinib compared to imatinib as shown in Figures 1 to 3.

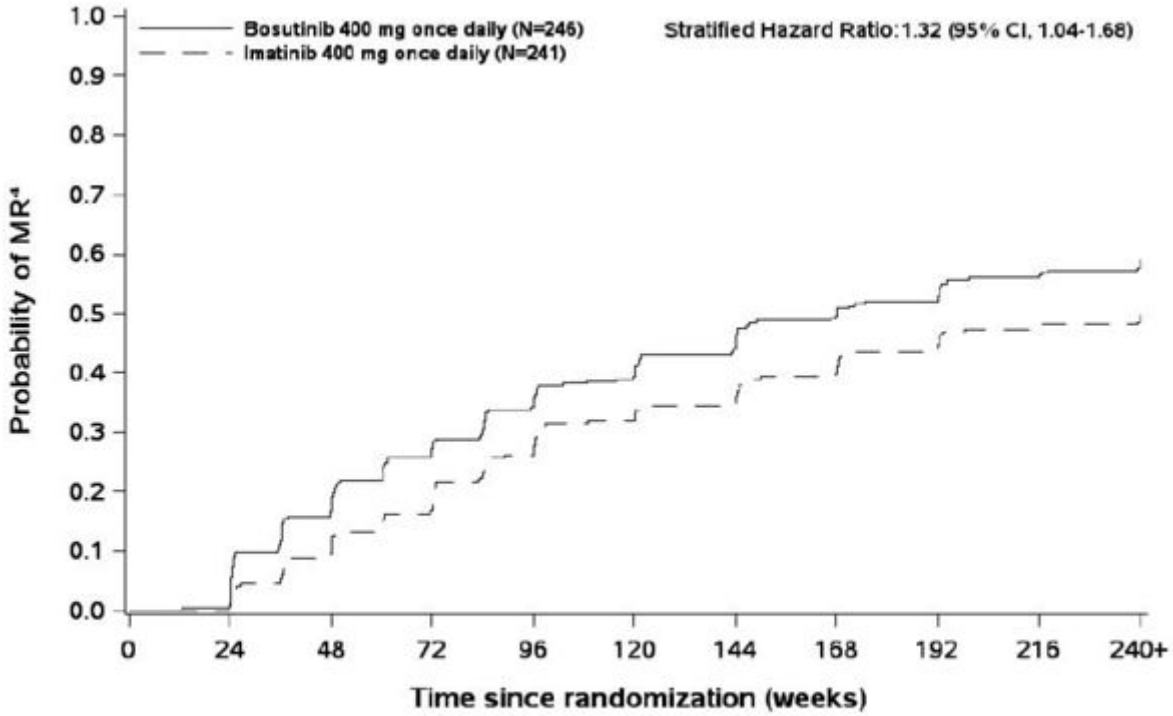
Figure 1 - Cumulative incidence of MMR (mITT population)



Number at risk (Cumulative Events):

Bosutinib	246(0)	206(20)	94(111)	58(139)	30(162)	19(170)	12(173)	10(175)	6(179)	4(181)	3(182)
Imatinib:	241(0)	204(11)	116(81)	62(116)	29(139)	23(145)	16(153)	10(156)	10(156)	8(157)	5(158)

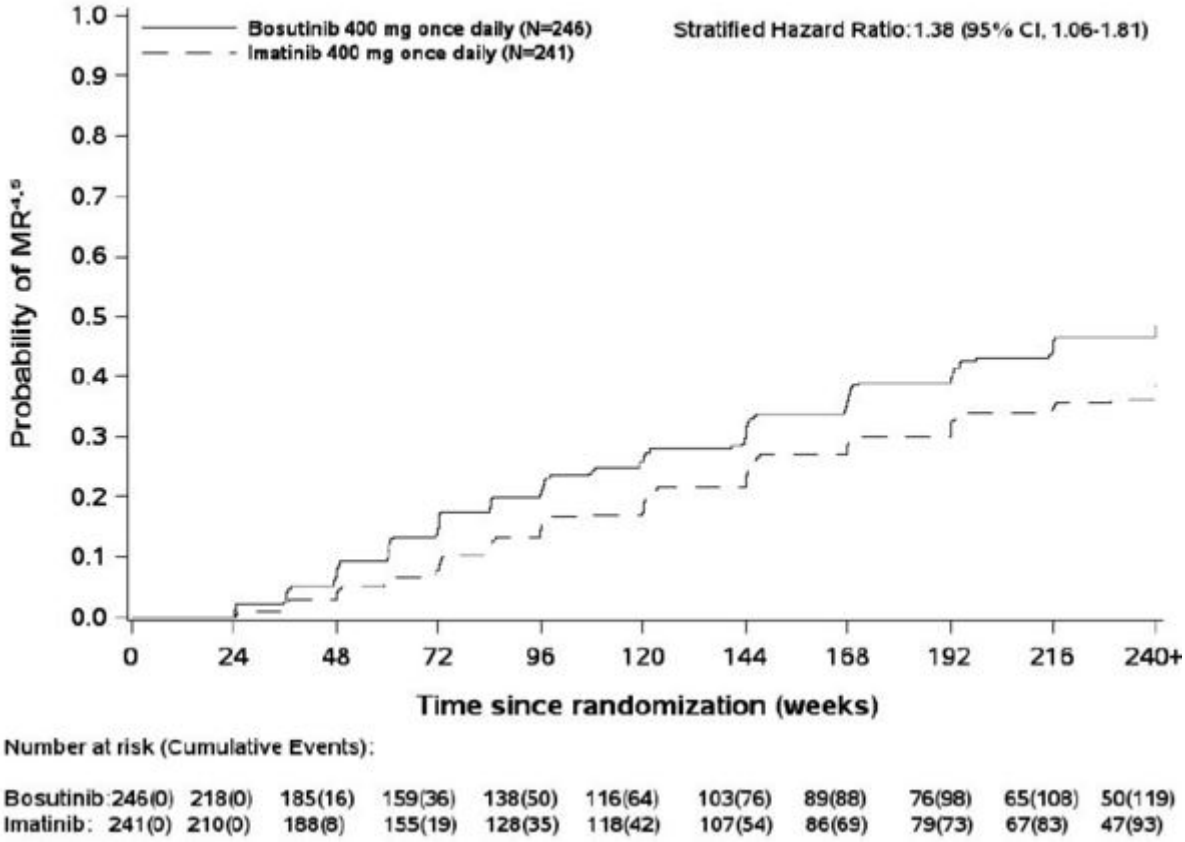
Figure 2 - Cumulative incidence of MR[4] (mITT population)



Number at risk (Cumulative Events):

Bosutinib	246(0)	216(2)	160(42)	127(67)	104(85)	86(97)	70(112)	56(122)	50(129)	39(138)	28(145)
Imatinib:	241(0)	209(3)	172(25)	133(41)	101(65)	86(77)	78(85)	61(96)	49(107)	39(115)	28(120)

Figure 3 - Cumulative incidence of MR[4.5] (mITT population)



In the mITT population, among patients who achieved CCyR, the Kaplan-Meier estimate of maintaining a response at Year 4 was 97.4% (95% CI: 93.9%, 98.9%) and 93.7% (95% CI: 88.9%, 96.5%) in the bosutinib and imatinib groups (HR 0.39 [95% CI: 0.14, 1.13]), respectively. Among patients who achieved MMR, the Kaplan-Meier estimate of maintaining a response at Year 4 was 92.2% (95% CI: 86.8%, 95.4%) and 92.0% (95% CI: 85.9%, 95.5%) in the bosutinib and imatinib groups (HR 1.09 [95% CI: 0.49, 2.44]), respectively.

By Month 60, 43.9% (95% CI: 37.7%, 50.1%) and 38.6% (95% CI: 32.4%, 44.7%) of bosutinib- and imatinib-treated patients (OR 1.24 [95% CI: 0.87, 1.78]) in the mITT population, respectively, had sustained MR[4] defined by the following criteria: treatment for at least 3 years with at least MR[4] at all assessments during a 1-year period.

The cumulative incidence of on-treatment EFS events at Month 60 in the mITT population was 6.9% (95% CI: 4.2%, 10.5%) in the bosutinib arm and 10.4% (95% CI: 6.9%, 14.6%) in the imatinib arm (HR 0.64, 95% CI: 0.35, 1.17).

The Kaplan-Meier estimates of OS at Month 60 for bosutinib and imatinib patients in the mITT population were 94.9% (95% CI: 91.1%, 97.0%) and 94.0% (95% CI: 90.1%, 96.4%), respectively (HR 0.80, 95% CI: 0.37, 1.73).

In a retrospective analysis, among evaluable patients in the ITT population, more patients in the bosutinib arm 200/248 (80.6%) achieved early molecular response (BCR-ABL transcripts ≤ 10% at 3 months) compared to patients in the imatinib arm 153/253 (60.5%), OR 2.72 (95% CI: 1.82, 4.08). MMR and EFS at Month 60 in bosutinib patients with and without early molecular response are summarised in Table 7.

Table 7 - Outcomes at Month 60 in bosutinib patients with BCR-ABL ≤ 10% vs > 10% at Month 3 in the ITT population

Bosutinib (N=248)	**Patients with BCR-ABL ≤ 10% at 3 Months** (N=200)	**Patients with BCR-ABL > 10% at 3 Months** (N=48)	**Hazard Ratio (95% CI)[a]**
Cumulative incidence of MMR, % (95% CI)	84.0 (78.1,88.4)	56.5 (41.1,69.4)	2.67 (1.90,3.75)
Cumulative incidence of EFS events, % (95% CI)	5.5 (2.9,9.3)	12.5 (5.1,23.4)	0.40 (0.14,1.17)

Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CI=confidence interval; ITT=intent-to-treat; MMR=major molecular response; EFS=event free survival; N=number of patients with ≥ 3000 ABL copies at Month 3.

[a] Adjusted for geographical region and Sokal score at randomisation.

Fewer patients in the bosutinib arm [6 (2.4%) bosutinib and 12 (5.0%) imatinib] had newly detectable mutations at 60 months in the mITT population.

Phase 1/2 Clinical study in imatinib-resistant or intolerant CML in CP, AP, and BP A single-arm, Phase 1/2 open-label, multicentre trial was conducted to evaluate the efficacy and safety of bosutinib 500 mg once daily in patients with imatinib-resistant or -intolerant CML with separate cohorts for chronic, accelerated, and blast phase disease previously treated with 1 prior TKI (imatinib) or more than 1 TKI (imatinib followed by dasatinib and/or nilotinib).

There were 570 patients treated with bosutinib in this trial including CP CML patients previously treated with only 1 prior TKI (imatinib), CP CML patients previously treated with imatinib and at least 1 additional TKI (dasatinib and/or nilotinib), CML patients in accelerated or blast phase previously treated with at least 1 TKI (imatinib) and patients with Ph+ ALL previously treated with at least 1 TKI (imatinib).

The primary efficacy endpoint of the study was the major cytogenetic response (MCyR) rate at Week 24 in patients with imatinib-resistant CP CML previously treated with only 1 prior TKI (imatinib). Other efficacy endpoints include the cumulative cytogenetic and molecular response rates, time to and duration of cytogenetic and molecular responses, response in baseline mutations, transformation to AP/BP, progression free survival and OS for all cohorts.

Patients who were still receiving bosutinib at the end of the Phase 1/2 study and were benefiting from bosutinib treatment as judged by the investigator, as well as those patients who had already discontinued bosutinib as part of the Phase 1/2 study and were in long-term follow-up for survival or had completed the Phase 1/2 study, were eligible for enrollment into the extension study. Each patient remained in the extension study, either on bosutinib treatment or in long-term survival follow-up, until the last patient reached 10 years of follow-up, as calculated from the date of his/her first dose of bosutinib administered in the Phase 1/2 study.

Extension study efficacy endpoints included duration of cytogenetic and molecular responses, transformation to AP/BP, progression free survival, and OS.

The efficacy analyses included data from this completed extension study.
CP CML Patients
The efficacy results for Ph+ CP CML patients previously treated with imatinib and at least 1 additional TKI (minimum follow-up 120 months, median treatment duration of 9 months (range: 0.23 to 164.28 months) and 20.2% and 7.6% still on-treatment at 60 and 120 months, respectively) and the results for Ph+ CP CML patients previously treated with only imatinib (minimum follow-up 120 months, median treatment duration of 26 months (range: 0.16 to 170.49 months) and 40.5% and 19.4% still on-treatment at 60 and 120 months, respectively) are presented in Table 8.

AP and BP CML patients
The efficacy results for AP (minimum follow-up 120 months, median treatment duration of 10 months (range: 0.10 to 156.15 months) and 12.7% and 7.6% still on-treatment at 60 and 120 months, respectively) and BP (minimum follow-up 120 months, median treatment duration of 2.8 months (range: 0.03 to 71.38 months) and 3.1% and 0% still on-treatment at 60 and 120 months, respectively) Ph+ CML patients are present in Table 8.

Table 8 - 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=262	N=112	N=72	N=54
MCyR, % (95% CI)	59.9	42.0	40.3	37.0
CCyR, % (95% CI)	(53.7,65.9)	(32.7,51.7)	(28.9,52.5)	(24.3,51.3)
	49.6	32.1	30.6	27.8

	(43.4,55.8)	(23.6,41.6)	(20.2,42.5)	(16.5,41.6)
Cumulative molecular response[a] **MMR, % (95% CI)** **MR[4], % (95% CI)**	N=197 42.1 (35.1,49.4) 37.1 (30.3,44.2)	N=107 17.8 (11.0,26.3) 15.0 (8.8,23.1)	N=54 16.7 (7.9,29.3) 13.0 (5.4,24.9)	N=48 10.4 (3.5,22.7) 10.4 (3.5,22.7)
Time to MCyR for responders only[b], median (range), weeks	12.3 (4.0,346.0)	12.3 (3.9,550.6)	12.0 (3.9,144.7)	8.2 (3.9,25.1)
Duration of MCyR[b] **K-M at year 5, % (95% CI)** **K-M at year 10, % (95% CI)** **Median, weeks (95% CI)**	N=157 70.7 (63.1,78.3) 65.3 (56.6,74.0) N/R	N=47 66.6 (51.5,81.7) 55.3 (36.3,74.4) N/R	N=29 40.8 (20.9,60.7) 40.8 (20.9,60.7) 84.0 (24.0,N/E)	N=20 21.2 (0.1,42.3) N/E 29.1 (11.9,38.3)
Time to CCyR for responders only[b], median (range), weeks	24.0 (7.7,240.6)	24.0 (11.6,216.0)	23.8 (4.1,120.0)	8.4 (3.9,25.1)
Duration of CCyR[b] **K-M at year 5, % (95% CI)** **K-M at year 10, % (95% CI)** **Median, weeks (95% CI)**	N=130 69.7 (61.3,78.2) 63.4 (54.0,72.8) N/R	N=36 54.4 (36.7,72.1) 40.8 (22.0,59.6) 252.0 (24.0,N/E)	N=22 40.0 (18.5,61.5) 40.0 (18.5,61.5) 72.0 (36.1,N/E)	N=15 24.9 (0.9,48.9) N/E 20.0 (9.1,29.6)
Time to MMR for responders only[b], median (range), weeks	35.6 (3.1,367.1)	12.4 (4.0,171.7)	36.1 (12.1,144.1)	4.7 (3.9,168.9)
Duration of MMR[b] **K-M at year 5, % (95% CI)** **K-M at year 10, % (95% CI)** **Median, weeks (95% CI)**	N=83 74.1 (64.2,83.9) 63.4 (50.2,76.6) N/R	N=19 70.0 (47.5,92.5) 70.0 (47.5,92.5) N/R	N=9 66.7 (35.9,97.5) 66.7 (35.9,97.5) N/R	N=5 60.0 (17.1,100.0) N/E N/R
Time to MR[4] for responders onlyb, median (range), weeks	28.0 (3.1,583.1)	23.8 (4.0,240.1)	24.1 (22.9,96.0)	4.7 (3.9,284.9)
Duration of MR[4b,e] **K-M at year 5, % (95% CI)** **K-M at year 10, % (95% CI)** **Median, weeks (95% CI)**	N=73 74.7 (64.2,85.2) 60.8 (46.1,75.4) N/R	N/A	N/A	N/A
Transformation to AP/ BP[c] **On-treatment transformation, n**	N=284 15	N=119 5	N=79 3	N/A
Progression-free survival[c] **CumInc at year 5, % (95% CI)[d]** **CumInc at year 10, % (95% CI)[d]**	N=284 19.7 (15.6,24.9) 23.9 (19.5,29.5)	N=119 24.4 (17.8,33.4) 26.9 (20.0,36.2)	N=79 41.8 (32.2,54.2) 41.8 (32.2,54.2)	N=64 67.2 (56.6,79.7) N/E
Overall survival[c] **K-M at year 5, % (95% CI)** **K-M at year 10, % (95% CI)** **Median, months (95% CI)**	N=284 83.5 (78.7,88.3) 71.5 (64.4,78.7) N/R	N=119 74.1 (64.8,83.4) 60.4 (47.2,73.7) N/R	N=79 58.5 (46.9,70.2) 50.7 (36.5,65.0) N/R	N=64 22.5 (7.1,37.9) 22.5 (7.1,37.9) 10.9 (8.7,19.7)

Snapshot date: Phase 1/2 Study 02Oct2015, Extension Study 02Sep2020.

Cytogenetic Response criteria: MCyR included Complete [0% Ph+ metaphases from bone marrow or < 1% positive cells from fluorescent in situ hybridisation (FISH)] or partial (1%-35%) cytogenetic responses. Cytogenetic responseswere 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. In the extension study, CCyR was imputed from MMR if a valid cytogenetic assessment was not available on a specific date.
Molecular response criteria: In the Phase 1/2 Study, MMR/MR[4] was defined as ≤0.1/0.01% BCR-ABL transcripts as assessed by a central laboratory (not on the international scale). In the extension study, responders had MMR/MR[4] denoted on the case report form as assessed by a local laboratory.
Abbreviations: AP=accelerated phase; BP=blast phase; Ph+=Philadelphia chromosome-positive; CP=chronic phase; CML=chronic myelogenous leukaemia; K-M=Kaplan-Meier; N/n=number of patients; N/A=not applicable; N/R=not reached as of minimum follow-up; N/E=not estimable; CI=confidence interval; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; CumInc=cumulative incidence; MMR=major molecular response; BCR-ABL=breakpoint cluster region-Abelson.
[a] Includes patients (N) with a valid baseline assessment for cytogenetic and patients not from China, South Africa, India, or Russia for molecular as samples could not be exported for molecular assessment in those countries. 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 120 months.
[b] Includes patients (N) who attained or maintained response.
[c] Including patients (N) who received at least 1 dose of bosutinib.
[d] Cumulative incidence analysis adjusting for the competing risk of treatment discontinuation without the event.
[e] Not analysed for groups with limited numbers.

The Overall Survival in the CP, AP and BP cohorts is displayed graphically in Figure 4.

Figure 4 - Kaplan-Meier Estimate of Overall Survival (OS) in CP2L, CP3L, AP, and BP

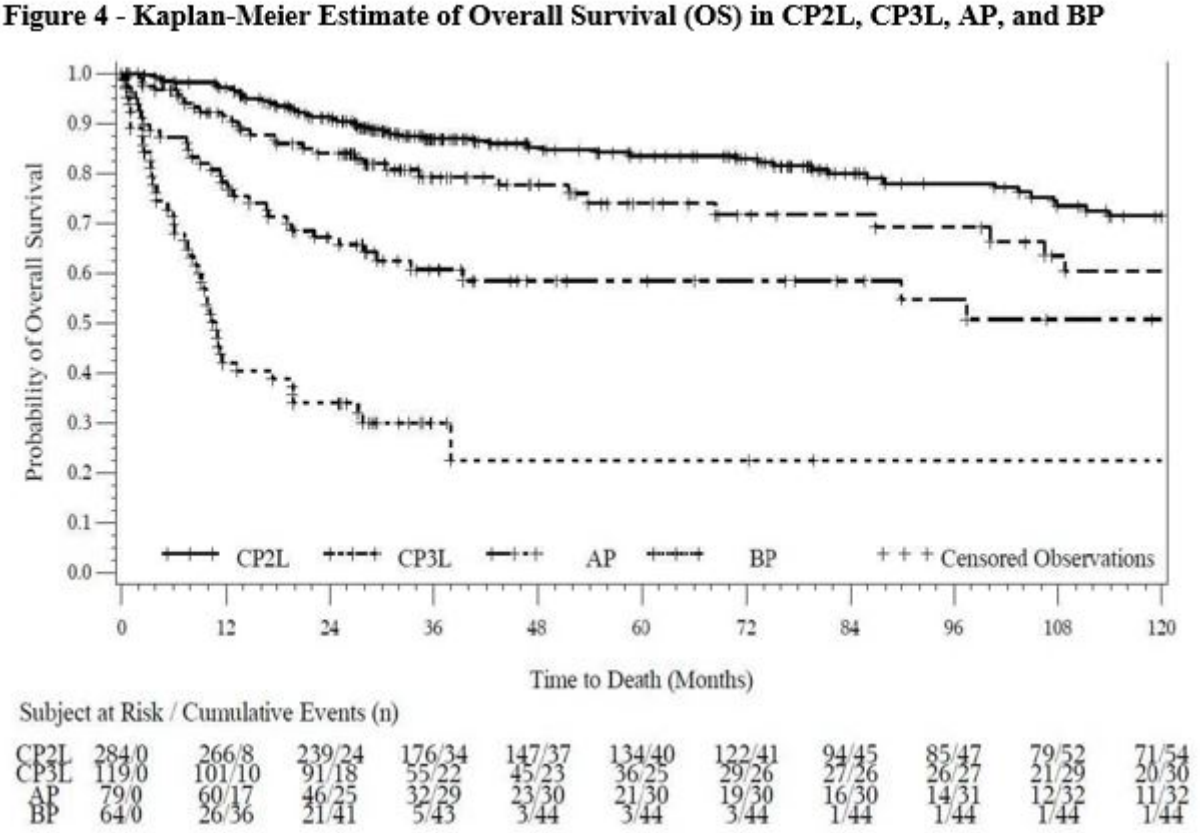


Table 9 - Response by baseline BCR-ABL mutation status in CP CML evaluable population: prior imatinib and dasatinib and/or nilotinib (third-line)

BCR-ABL mutation status at baseline	Incidence at baseline n (%)[a]	MCyR attained or maintained Resp/Eval[b] (%) N=112
Mutation assessed	98 (100.0)	36/92 (39.1)
No mutation	59 (60.2)	23/55 (41.8)
At least 1 mutation	39 (39.8)	13/37 (35.1)
Dasatinib resistant mutations	10 (10.2)	1/9 (11.1)
E255K/V	2 (2.0)	0/2
F317L	8 (8.2)	1/7 (14.3)
Nilotinib resistant mutations[c]	13 (13.3)	8/13 (61.5)

Y253H	6 (6.1)	5/6 (83.3)
E255K/V	2 (2.0)	0/2
F359C/I/V	7 (7.1)	5/7 (71.4)

Snapshot date: Phase 1/2 Study 02Oct2015, Extension Study 02Sep2020
Note: Baseline mutations were identified before the patient's first dose of study drug.
Abbreviations: BCR-ABL=breakpoint cluster region-Abelson; CP=chronic phase; CML=chronic myelogenous leukaemia; MCyR=major cytogenetic response; N/n=number of patients; Resp=responders; Eval=evaluable.
[a] The percentage is based on number of patients with baseline mutation assessment.
[b] The evaluable population includes patients who had a valid baseline disease assessment.
[c] 2 patients had more than 1 mutation in this category.

One patient with the E255V mutation previously treated with nilotinib achieved CHR as best response.
In vitro testing indicated that bosutinib had limited activity against the T315I or the V299L mutation.
Therefore, clinical activity in patients with these mutations is not expected.

Phase 4 Clinical study in Ph+ CML previously treated with 1 or more TKI(s)
A single-arm, Phase 4 open-label, non-randomised, multi-centre study was conducted to evaluate the efficacy and safety of bosutinib 500 mg once daily in patients with TKI-resistant or TKI-intolerant CML with separate cohorts for CP, AP or BP disease previously treated with 1 or more prior TKIs.

There were 163 patients treated with bosutinib in this trial including 46 patients with CP Ph+ CML and treated previously with 1 prior TKI (imatinib or dasatinib or nilotinib), 61 CP Ph+ CML patients previously treated with 2 prior TKIs (imatinib and/or dasatinib and/or nilotinib), 49 CP Ph+ CML patients treated with 3 prior TKIs (imatinib and dasatinib and nilotinib), 4 patients with AP Ph+ CML previously treated with at least 1 TKI (2 patients treated with 2 prior TKIs and 2 patients treated with 3 prior TKIs) and 3 patients with Ph- CML treated with at least 1 prior TKI.

The primary efficacy endpoint was cumulative confirmed MCyR by 1 year (Week 52) in patients with CP Ph+ CML previously treated with 1 or 2 prior TKIs and patients with CP Ph+ CML previously treated with 3 prior TKIs. For patients with AP and BP Ph+ CML with any prior TKI therapy, the primary efficacy endpoint was cumulative confirmed overall haematological response (OHR) by 1 year (Week 52). Other efficacy endpoints in Ph+ CP CML patients include cumulative cytogenetic and molecular response, the duration of cytogenetic and molecular responses, response in baseline mutations, transformation to AP/BP, PFS, and OS. Additional endpoints in the Ph+ AP/BP cohort include cumulative cytogenetic and molecular responses rates, PFS and OS.

CP CML patients
The primary endpoint of cumulative confirmed MCyR (95% CI) rate by 1 year (52 weeks) was 76.5% (66.9, 84.5) in patients treated with 1 or 2 prior TKIs and 62.2% (46.5, 76.2) in patients treated with 3 prior TKIs.

Additional efficacy results at study closure, after a minimum follow-up of 3 years, in Ph+ CP CML patients treated with 1 (median treatment duration 47.5 months (range: 0.9 to 50.1 months) and 60.9% still on-treatment), 2 (median treatment duration 41.9 months (range: 0.4 to 48.9 months) and 45.9% still on-treatment) and 3 (median treatment duration 20.0 months (range: 0.2 to 48.9 months) and 38.8% still on-treatment) prior TKIs are presented in Table 10.

Table 10 – Efficacy results in previously treated patients with chronic phase Ph+ CML

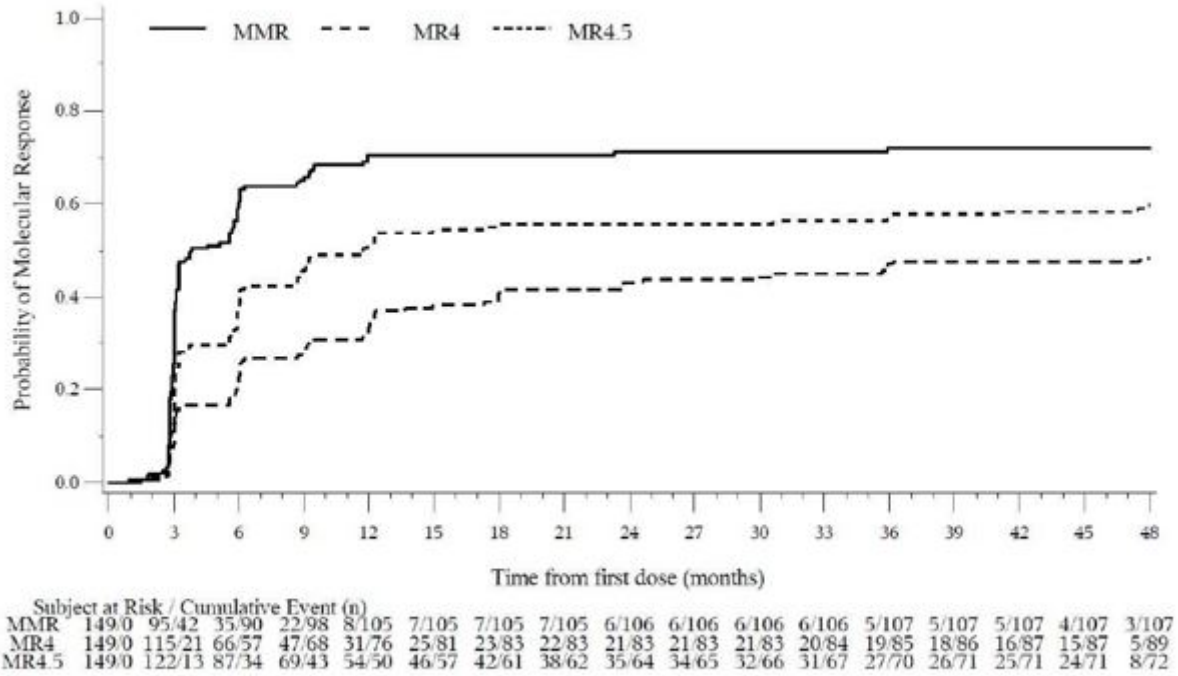
	Ph+ CP CML treated with 1 prior TKI	**Ph+ CP CML treated with 2 prior TKIs**	**Ph+ CP CML treated with 3 prior TKIs**	**Total Ph+ CP CML cohort**
Cumulative confirmed MCyR[a] by 1 year, % (95% CI)	N=43 83.7 (69.3,93.2)	N=55 70.9 (57.1,82.4)	N=45 62.2 (46.5,76.2)	N=143 72.0 (63.9,79.2)
Cumulative cytogenetic response [a,b] **MCyR, % (95% CI)** **CCyR, % (95% CI)**	N=46 88.4 (74.9,96.1) 86.0 (72.1,94.7)	N=55 85.5 (73.3,93.5) 83.6 (71.2,92.2)	N=45 77.8 (62.9,88.8) 73.3 (58.1,85.4)	N=143 83.9 (76.9,89.5) 81.1 (73.7,87.2)
Cumulative molecular response[a,b] **MMR, % (95% CI)**	N=46 82.6 (68.6,92.2)	N=55 76.4 (63.0,86.8)	N=48 56.3 (41.2.,70.5)	N=149 71.8 (63.9,78.9)

MR4, % (95% CI)	73.9 (58.9,85.7)	63.6 (49.6,76.2)	41.7 (27.6,56.8)	59.7 (51.4,67.7)
MR4.5, % (95% CI)	58.7 (43.2,73.0)	50.9 (37.1,64.6)	35.4 (22.2,50.5)	48.3 (40.1,56.6)
Time to cytogenetic response for responders only[b], median (range), months'				
MCyR	3.0 (1.0,11.8)	2.9 (0.3,6.4)	3.0 (1.8,8.8)	3.0 (0.3,11.8)
CCyR	3.0 (1.0,17,6)	2.9 (0.3,6.4)	3.0 (1.8,8.8)	3.0 (0.3,17.6)
Duration of cytogenetic response[b]				
MCyR, K-M at year 3, % (95% CI)	96.6 (77.9,99.5)	94.4 (79.2,98.6)	96.9 (79.8,99.6)	95.6 (88.7,98.4)
CCyR, K-M at year 3, % (95% CI)	94.4 (77.2,99.5)	94.4 (79.2,98.6)	100.0 (100.0,100.0)	96.5 (89.5,98.9)
Time to molecular response for responders only, median (range), months				
MMR	3.0 (2.8,23.3)	3.0 (1.0,35.9)	3.1 (1.8,9.3)	3.0 (1.0,35.9)
MR^4	6.0 (2.8,47.4)	3.1 (1.0,36.1)	3.2 (1.8,47.9)	5.5 (1.0,47.9)
$MR^{4,5}$	9.2 (2.8,47.6)	6.0 (2.8,36.2)	5.8 (1.8,18.0)	6.0 (1.8,47.6)
Duration of molecular response[b]				
MMR, K-M at year 3, % (95% CI)	90.7 (73.9,96.9)	81.5 (63.2,91.3)	90.2 (65.9,97.5)	87.2 (78.0,92.7)
MR^4, K-M at year 3, % (95% CI)	89.5 (70.9,96.5)	68.7 (48.0,82.5)	85.2 (51.9,96.2)	80.7 (69.4,88.1)

Snapshot date: 23Nov2020.
Abbreviations: Ph+=Philadelphia chromosome-positive; CP=chronic phase; CML=chronic myelogenous leukaemia; K-M=Kaplan Meier; N=number of patients; CI=confidence interval; MCyR=major cytogenetic response; CCyR=complete cytogenetic response; MMR=major molecular response; MR^4=≥ 4 log-reduction in BCR-ABL transcripts from standardised baseline; $MR^{4.5}$=≥ 4.5 log-reduction in BCR-ABL transcripts from standardised baseline.
Cumulative Confirmed MCyR criteria: Response is confirmed with 2 consecutive evaluations at least 28 days apart.
To be considered a responder, the patient must have maintained a baseline response for at least 52 weeks or improved from baseline. Patients with partial cytogenetic response (PCyR) at baseline must attain CCyR on-treatment to be counted as a cytogenetic responder. Patients with at least MMR and a deeper molecular response than baseline are counted as confirmed CCyR.
Cumulative Cytogenetic Response criteria: Major Cytogenetic Response included Complete [0% Ph+ metaphases from bone marrow or < 1% positive cells from fluorescent in situ hybridisation (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 to assess CCyR if ≥ 20 metaphases were not available. Patients without a valid bone marrow or FISH assessment and with at least MMR are counted as CCyR. Cumulative Molecular Response criteria: MMR, MR^4, and $MR^{4.5}$ were defined as ≤ 0.1%, ≤ 0.01%, and ≤ 0.0032% BCR-ABL/ABL ratio on international scale, respectively (corresponding to ≥ 3, ≥ 4, and ≥ 4.5 log-reduction from standardised baseline) with a minimum of 10,000, 10,000, and 32,000 ABL transcripts assessed by the central laboratory, respectively.
[a] Includes patients (N) with a valid baseline assessment. Minimum follow-up time (time from last patient first dose to data snapshot date) of 36 months.
[b] Includes patients (N) who attained or maintained response.

The cumulative incidence of MMR, MR^4 and $MR^{4,5}$ adjusted for the competing risk of treatment discontinuation without the event are shown in Figure 5.

Figure 5 - Cumulative Incidence of Molecular Response (CP Evaluable Population)



Achieved molecular responses by line of treatment are shown in Table 11.

Table 11 – Achieved molecular responses

	Ph+ CP CML treated with 1 prior TKI	Ph+ CP CML treated with 2 prior TKIs	Ph+ CP CML treated with 3 prior TKIs	Total Ph+ CP CML cohort
Patients without MMR at baseline[a]	N=25	N=28	N=26	N=79
MMR, % (95% CI)	76.0 (54.9,90.6)	64.3 (44.1,81.4)	38.5 (20.2,59.4)	59.5 (47.9,70.4)
Patients without MR^4 at baseline[a]	N=37	N=38	N=37	N=112
MR^4, % (95% CI)	70.3 (53.0,84.1)	55.3 (38.3,71.4)	32.4 (18.0,49.8)	52.7 (43.0,62.2)
Patients without $MR^{4.5}$ at baseline[a]	N=42	N=46	N=43	N=131
$MR^{4.5}$, % (95% CI)	54.8 (38.7,70.2)	43.5 (28.9,58.9)	30.2 (17.2,46.1)	42.7 (34.1,51.7)
Patients with MMR at baseline[a]	N=21	N=27	N=22	N=70
Deeper MR, % (95% CI)	85.7 (63.7,97.0)	66.7 (46.0,83.5)	63.6 (40.7,82.8)	71.4 (59.4,81.6)

Snapshot date: 23Nov2020.
Abbreviations: Ph+=Philadelphia chromosome-positive; CP=chronic phase; CML=chronic myelogenous leukaemia; N=number of patients; CI=confidence interval; MMR=major molecular response; MR=molecular response; MR^4=≥ 4 log-reduction in BCR-ABL transcripts from standardised baseline; $MR^{4.5}$=≥ 4.5 log-reduction in BCR-ABL transcripts from standardised baseline.
[a] Includes patients (N) with a valid baseline assessment. To be considered a responder, patients must have achieved an improved response from baseline. Molecular Response criteria: MMR, MR^4, and $MR^{4.5}$ were defined as ≤ 0.1%, ≤ 0.01%, and ≤ 0.0032% BCR-ABL/ABL ratio on international scale, respectively (corresponding to ≥ 3, ≥ 4, and ≥ 4.5 log-reduction from standardised baseline) with a minimum of 10,000, 10,000, and 32,000 ABL transcripts assessed by the central laboratory, respectively.

In CP patients, there were no on-treatment progressions to AP or BP CML.

AP CML patients
In patients with Ph+ AP CML, the median duration of treatment was 22.1 months (range: 1.6 to 50.1 months), the cumulative confirmed OHR by 1 year (52 weeks) was 75.0% (95% CI: 19.4, 99.4), as was the cumulative CCyR rate, all 3 patients maintained their CCyR on treatment.

Response by BCR-ABL Mutations at baseline

Ten patients in the CP cohort had mutations at baseline (A365V, E453K, E255K, E255V, Q252H, L298V [n=1 each], Y253F and G250E [n=2 each]). One patient in the CP cohort had a F359I mutation identified on study day 8. One patient in the AP cohort had 2 mutations (F311L and L387F) at baseline. In the CP cohort, among patients with mutations, molecular responses were observed in 4/11 (36.4%) patients, 1 patient with a E255V mutation achieved MMR and 3 patients with F359I, Y253F and A365V respectively achieved MR4.5. The patient with mutations in the AP cohort did not achieve any response.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with the reference medicinal product containing bosutinib in one or more subsets of the paediatric population in CML (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following administration of a single dose of bosutinib (500 mg) with food in healthy subjects, the absolute bioavailability was 34%. Absorption was relatively slow, with a median time-to-peak concentration (tmax) reached after 6 hours. Bosutinib exhibits dose proportional increases in AUC and C_{max}, over the dose range of 200 to 600 mg. Food increased bosutinib C_{max} 1.8-fold and bosutinib AUC 1.7-fold compared to the fasting state. In CML patients at steady state, C_{max} (geometric mean, coefficient of variation [CV]%) was 145 (14) ng/mL, and AUCss (geometric mean, CV%) was 2,700 (16) ng•h/mL after daily administration of bosutinib at 400 mg with food. After 500 mg bosutinib daily with food, C_{max} was 200 (6) ng/mL and AUCss was 3,640 (12) ng•h/mL. The solubility of bosutinib is pH-dependent and absorption is reduced when gastric pH is increased (see section 4.5).

Distribution
Following administration of a single intravenous dose of 120 mg bosutinib to healthy subjects, bosutinib had a mean (% coefficient of variation [CV]) volume of distribution of 2,331 (32) L, suggesting that bosutinib is extensively distributed to extra vascular tissue.

Bosutinib was highly bound to human plasma proteins *in vitro* (94%) and *ex vivo* in healthy subjects (96%), and binding was not concentration-dependent.

Biotransformation
In vitro and *in vivo* studies indicated that bosutinib (parent compound) undergoes predominantly hepatic metabolism in humans. Following administration of single or multiple doses of bosutinib (400 or 500 mg) to humans, the major circulating metabolites appeared to be oxydechlorinated (M2) and *N*-desmethylated (M5) bosutinib, with bosutinib *N*-oxide (M6) as a minor circulating metabolite. The systemic exposure of *N*-desmethylated metabolite was 25% of the parent compound, while the oxydechlorinated metabolite was 19% of the parent compound. All 3 metabolites exhibited activity that was 5% that of bosutinib in a Src-transformed fibroblast anchorage-independent proliferation assay. In faeces, bosutinib and *N*-desmethyl bosutinib were the major drug-related components. *In vitro* studies with human liver microsomes indicated that the major cytochrome P450 isozyme involved in the metabolism of bosutinib is CYP3A4 and drug interaction studies have shown that ketoconazole and rifampicin had marked effect on the pharmacokinetics of bosutinib (see section 4.5). No metabolism of bosutinib was observed with CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A5.

Elimination
In healthy subjects given a single intravenous dose of 120 mg bosutinib, the mean (%CV) terminal elimination half-life was 35.5 (24) hours, and the mean (%CV) clearance was 61.9 (26) L/h. In a ass-balance study with oral bosutinib, an average of 94.6% of the total dose was recovered in 9 days; faeces (91.3%) was the major route of excretion, with 3.29% of the dose recovered in urine. Seventy-five percent of the dose was recovered within 96 hours. Excretion of unchanged bosutinib in urine was low with approximately 1% of the dose in both healthy subjects and those with advanced malignant solid tumours.

Special populations

Hepatic impairment
A 200 mg dose of bosutinib administered with food was evaluated in a cohort of 18 hepatically impaired subjects (Child-Pugh classes A, B, and C) and 9 matched healthy subjects. Cmax of bosutinib in plasma increased 2.4-fold, 2-fold, and 1.5-fold, respectively, in Child-Pugh classes A, B, and C; and bosutinib AUC in plasma increased 2.3-fold, 2-fold, and 1.9-fold, respectively. The t½ of bosutinib increased in hepatic impaired patients as compared to the healthy subjects.

Renal impairment

In a renal impairment study, a single dose of 200 mg bosutinib was administered with food to 26 subjects with mild, moderate, or severe renal impairment and to 8 matching healthy volunteers. Renal impairment was based on CLCr (calculated by the Cockcroft-Gault formula) of < 30 ml/min (severe renal impairment), 30 CLCr 50 ml/min (moderate renal impairment), or 50 < CLCr ≤ 80 ml/min (mild renal impairment). Subjects with moderate and severe renal impairment had an increase in AUC over healthy volunteers of 35% and 60%, respectively. Maximal exposure Cmax increased by 28% and 34% in the moderate and severe groups, respectively. Bosutinib exposure was not increased in subjects with mild renal impairment. The elimination half-life of bosutinib in subjects with renal impairment was similar to that in healthy subjects.

Dose adjustments for renal impairment were based on the results of this study, and the known linear pharmacokinetics of bosutinib in the dose range of 200 to 600 mg.

Age, gender and race
No formal studies have been performed to assess the effects of these demographic factors. Population pharmacokinetic analyses in patients with Ph+ leukaemia or malignant solid tumour and in healthy subjects indicate that there are no clinically relevant effects of age, gender or body weight. Population pharmacokinetic analyses revealed that Asians had a 18% lower clearance corresponding to an approximately 25% increase in bosutinib exposure (AUC).

Paediatric population
Bosutinib has not yet been studied in children and adolescents less than 18 years of age.

5.3 Preclinical safety data

Bosutinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies.

Safety pharmacology
Bosutinib did not have effects on respiratory functions. In a study of the central nervous system (CNS), bosutinib treated rats displayed decreased pupil size and impaired gait. A no observed effect level (NOEL) for pupil size was not established, but the NOEL for impaired gait occurred at exposures approximately 11-times the human exposure resulting from the clinical dose of 400 mg and 8-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). Bosutinib activity *in vitro* in hERG assays suggested a potential for prolongation of cardiac ventricular repolarisation (QTc). In an oral study of bosutinib in dogs, bosutinib did not produce changes in blood pressure, abnormal atrial or ventricular arrhythmias, or prolongation of the PR, QRS, or QTc of the ECG at exposures up to 3-times the human exposure resulting from the clinical dose of 400 mg and 2-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). A delayed increase in heart rate was observed. In an intravenous study in dogs, transient increases in heart rate and decreases in blood pressure and minimal prolongation of the QTc (< 10 msec) were observed at exposures ranging from approximately 6-times to 20-times the human exposure resulting from the clinical dose of 400 mg and 4-times to 15-times the human exposure resulting from the clinical dose of 500 mg (based on unbound C_{max} in the respective species). The relationship between the observed effects and medicinal product treatment were inconclusive.

Repeated-dose toxicity
Repeated-dose toxicity studies in rats of up to 6 months in duration and in dogs up to 9 months in duration revealed the gastrointestinal system to be the primary target organ of toxicity of bosutinib. Clinical signs of toxicity included foecal changes and were associated with decreased food consumption and body weight loss which occasionally led to death or elective euthanasia.

Histopathologically, luminal dilation, goblet cell hyperplasia, haemorrhage, erosion, and oedema of the intestinal tract, and sinus erythrocytosis and haemorrhage in the mesenteric lymph nodes, were observed. The liver was also identified as a target organ in rats. Toxicities were characterised by an increase in liver weights in correlation with hepatocellular hypertrophy which occurred in the absence of elevated liver enzymes or microscopic signs of hepatocellular cytotoxicity, and is of unknown relevance to humans. The exposure comparison across species indicates that exposures that did not elicit adverse events in the 6- and 9-month toxicity studies in rats and dogs, respectively, were similar to the human exposure resulting from a clinical dose of 400 mg or 500 mg (based on unbound AUC in the respective species).

Genotoxicity
Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of bosutinib.

Reproductive toxicity and development toxicity

In a rat fertility study, fertility was slightly decreased in males. Females were observed with increased embryonic resorptions, and decreases in implantations and viable embryos. 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-times and 0.3-times, respectively, the human exposure resulting from the clinical dose of 400 mg, and 0.5-times and 0.2-times, respectively, the human exposure resulting from the clinical dose of 500 mg (based on unbound AUC in the respective species). An effect on male fertility cannot be excluded (see section 4.6).

Foetal exposure to bosutinib-derived radioactivity during pregnancy was demonstrated in a placental transfer study in gravid Sprague-Dawley rats. In a rat pre- and postnatal development study, there were reduced number of pups born at ≥ 30 mg/kg/day, and increased incidence of total litter loss and decreased growth of offspring after birth occurred at 70 mg/kg/day. The dose at which no adverse development effects were observed (10 mg/kg/day) resulted in exposures equal to 1.3-times and 1.0-times human exposure resulting from the clinical dose of 400 mg and 500 mg, respectively (based on unbound AUC in the respective species). In a rabbit developmental toxicity study at the maternally toxic dose, there were foetal anomalies observed (fused sternebrae, and 2 foetuses had various visceral observations), and a slight decrease in foetal body weight. The exposure at the highest dose tested in rabbits (10 mg/kg/day) that did not result in adverse foetal effects was 0.9-times and 0.7-times the human exposure resulting from the clinical dose of 400 mg or 500 mg, respectively (based on unbound AUC in the respective species).

Following a single oral (10 mg/kg) administration of [14C] radiolabelled bosutinib to lactating Sprague-Dawley rats, radioactivity was readily excreted into breast milk as early as 0.5 hr after dosing. Concentration of radioactivity in milk was up to 8-fold higher than in plasma. This allowed measurable concentrations of radioactivity to appear in the plasma of nursing pups.

Carcinogenicity
Bosutinib was not carcinogenic in the 2-year rat and 6-month rasH2 mouse carcinogenicity studies.

Phototoxicity
Bosutinib has demonstrated the ability to absorb light in the UV-B and UV-A range and is distributed into the skin and uveal tract of pigmented rats. However, bosutinib did not demonstrate a potential for phototoxicity of the skin or eyes in pigmented rats exposed to bosutinib in the presence of UV radiation at bosutinib exposures up to 3-times and 2-times the human exposure resulting from the clinical dose of 400 or 500 mg, respectively (based on unbound Cmax in the respective species).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, microcrystalline (E460)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous
Magnesium stearate

Film coating
Poly(vinyl alcohol) (E1203)
Macrogols
Talc (E553b)
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are packaged in Alu/PVC/Alu/OPA blister packs or Alu/PVC/Alu/OPA perforated unit dose blister packs.

Bosutinib Clonmel 400 mg film-coated tablets
Each carton contains 28 or 112 tablets
Each carton contains 28x1 or 112x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/369/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th April 2024

10 DATE OF REVISION OF THE TEXT