CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203341Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

203341Clinical Pharmacology Review

NDA	203-341
Submission Date:	17 November, 2011
Brand Name:	Bosulif™
Generic Name:	Bosutinib
Formulation:	100 and 500 mg film coated tablets
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Hematology Products
Applicant:	Pfizer/ Wyeth
Submission Type; Code:	0000/1
Dosing regimen:	A single oral daily dose of 500 mg once daily with food
Indication:	The treatment of chronic, accelerated or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy

The OCP Briefing was held on 18th June, 2012.

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1 Executive Summary

Bosutinib is a tyrosine kinase inhibitor (TKI), specifically an inhibitor of Bcr-Abl and the Src-family kinases including Src, Lyn and Hck. Bosutinib is proposed for the treatment of chronic phase (CP), accelerated phase (AP) or blast phase (BP) Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. The proposed oral dosing regimen is 500 mg once daily taken with food.

A pivotal phase 1/2 trial and a supportive phase 3 trial were submitted to support the proposed indication and dosing regimen. The pivotal trial evaluated the efficacy of bosutinib 500 mg in 2nd line CP CML (N=288), 3rd line CP CML (N=118) and in AP and BP Ph+ CML (N=164). The primary efficacy endpoint was major cytogenetic response (MCyR) rate at Week 24 in imatinib-resistant 2nd line CP CML patients. The MCyR rate was 35.5% (90% CI: 29.7, 41.7) with a 1-sided $p<0.001$. The supportive trial (3160A4-3000-WW) was a phase 3 trial comparing the efficacy and safety of bosutinib to that of imatinib in patients with newly diagnosed (1st line) CP CML. In this trial, bosutinib failed to show superiority to imatinib with an adjusted odds ratio estimate of complete cytogenetic response (CCyR) at 1 year of 1.10 (95% CI: 0.74, 1.63). Data from a total of 15 single and multiple dose trials were submitted to support the Clinical Pharmacology Section of the NDA.

Bosutinib exhibits approximately linear PK in the dose range of 200 – 800 mg. No exposure-response relationships for effectiveness or safety were observed at the dose of 500 mg. In a food-effect trial, a high-fat meal increased bosutinib exposure 2-fold. Bosutinib showed better tolerability when co-administered with food; as a result bosutinib was co-administered with food in patient trials. Bosutinib is primarily metabolized by CYP3A4. Clinical trials showed that the strong CYP3A4 inhibitor ketoconazole increased bosutinib AUC 9-fold while the strong CYP3A4 inducer rifampin decreased bosutinib AUC by 94%. A 2-fold increase in exposures was observed in patients with hepatic impairment. In a thorough QT trial, bosutinib did not cause significant changes in placebo adjusted, baseline-corrected QTc.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 5, Pharmacometrics and Pharmacogenomics have reviewed the information contained in NDA 203-341. This NDA is considered acceptable from a clinical pharmacology perspective.

1.2 Post Marketing Requirement

1. Conduct a drug-drug interaction trial to evaluate the effect of a moderate CYP3A4 inhibitor (e.g. erythromycin) on the pharmacokinetics of bosutinib. The proposed protocol must be submitted for review prior to trial initiation.

1.3 Summary of Clinical Pharmacology Findings

Bosutinib is a tyrosine kinase inhibitor (TKI), specifically an inhibitor of Bcr-Abl and the Src-family kinases including Src, Lyn and Hck. Bosutinib is proposed for the treatment of chronic phase (CP), accelerated phase (AP) or blast phase (BP) Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. The proposed oral dosing regimen is 500 mg once daily taken with food.

A pivotal phase 1/2 trial and a supportive phase 3 trial were submitted to support the proposed indication and dosing regimen. Data from a total of 15 single and multiple dose trials were submitted to support the Clinical Pharmacology Section of the NDA. The single dose trials were performed in healthy volunteers and consisted of three bioequivalence trials, a dose escalation trial, a food effect trial, a mass balance trial, a thorough QT trial, a hepatic impairment trial and four drug interaction trials. Multiple dose PK data were available from two dose escalation trials in patients with solid tumors and sparse PK data were also available from the pivotal phase 2 trial.

Bosutinib exhibits approximately linear PK in the dose range of 200 – 800 mg. The median T_{max} in cancer patients ranged from 3 to 6 hours. The mean elimination half-life of bosutinib after a single dose in patients ranged from 19 to 30 hours. The mean accumulation ratio observed ranged from 2 – 3 at steady-state. In a food-effect trial, a high-fat meal caused a 2-fold increase in exposure. Food also increased tolerability to bosutinib in a dose escalation trial, as such, bosutinib was co-administered with food in patient trials. Based on an oral mass balance trial, radioactivity recoveries in feces and urine were 91% and 3%, respectively. The absolute bioavailability of bosutinib has not been determined.

Bosutinib is primarily metabolized by CYP3A4. Concomitant ketoconazole (strong CYP3A4 inhibitor) increased bosutinib C_{max} 5-fold and AUC 9-fold. Concomitant rifampin (strong CYP3A4 inducer) decreased the C_{max} and AUC of bosutinib by 86% and 94%, respectively. Therefore, the use of strong and moderate CYP3A4 inhibitors and inducers should be avoided. Simulation with Simcyp predicted that moderate CYP3A4 inhibitors could increase exposure to bosutinib 2 - 5 fold. A PMR will be issued in order to evaluate, in humans, the influence of moderate CYP3A4 inhibitors on the exposure to bosutinib so as to identify an appropriate dose for concomitant administration with such drugs. *In vitro*, bosutinib is a substrate and an inhibitor of P-gp. A 2-fold increase in exposures was observed in patients with hepatic impairment. A dose adjustment to 200 mg is recommended in patients with mild, moderate and severe hepatic impairment.

No exposure-response relationships for effectiveness or safety were observed. No exposure-response relationship was observed for the primary endpoint of MCYR at 24 weeks in CML patients randomized to receive 500 mg bosutinib. No clinically meaningful exposure-response relationships were identified for grade 3 or higher rash, diarrhea, neutropenia, thrombocytopenia, nausea, vomiting and increases in liver transaminase levels. In a thorough QT trial bosutinib did not cause significant changes in placebo adjusted, baseline-corrected QTc.

Signatures:

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2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

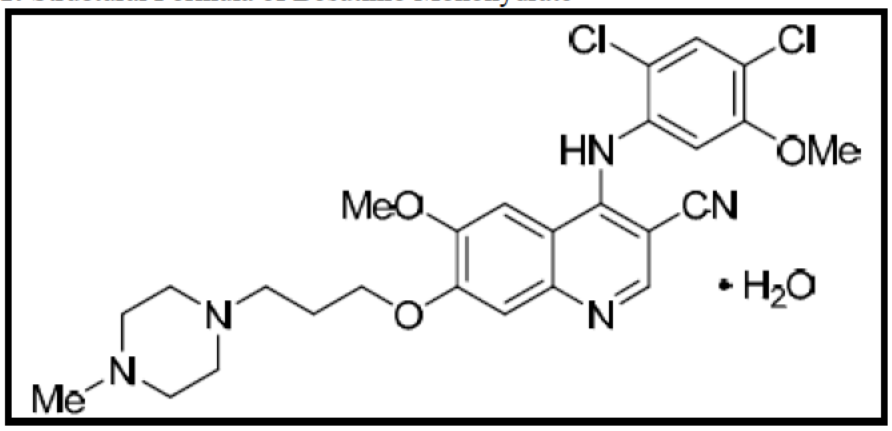
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology and biopharmaceutics review?

Bosutinib is planned to be available as 100 and 500 mg debossed film-coated tablets for oral administration.

Physical-chemical properties

Structural formula:

Figure 1: Structural Formula of Bosutinib Monohydrate



Established names: Bosutinib monohydrate
Molecular Weight: 548.46 (monohydrate)
Molecular Formula: $C_{26}H_{29}C_{12}N_5O_3 \bullet H_20$ (monohydrate)
Partition coefficient (log P): 3.1
Dissociation Constant (pKa): 7.9 (pK_{a1})
Chemical Name: 3-Quinolinecarbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate
Melting Point Range: 100°C to 160°C
Solubility: Bosutinib monohydrate has pH dependent solubility across the physiological pH range. Bosutinib is soluble at or below pH 5 and the solubility reduces above pH 5.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Bosutinib is proposed for the treatment of chronic phase (CP), accelerated phase (AP) or blast phase (BP) Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. CML is causally linked to a cytogenetic abnormality resulting from a reciprocal translocation between the long arms of chromosomes 9 and 22. This results in the production of the Bcr-Abl oncoprotein, which exhibits constitutive tyrosine kinase activity.

Bosutinib is a tyrosine kinase inhibitor, specifically an inhibitor of Bcr-Abl and the Src-family kinases including Src, Lyn and Hck. In CML, bosutinib is believed to exert pharmacological action through the inhibition of Bcr-Abl kinase.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes an oral dosing regimen of 500 mg once daily to be taken with food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical trials used to support dosing or claims?

To support the approval of bosutinib, the sponsor submitted two key clinical trials; a pivotal trial phase 1/2 trial and a supportive phase 3 trial (**Table 1**). The pivotal trial was a two part phase 1/2 trial. Part 1 was performed to identify the maximum tolerated dose (MTD) in patients with Ph+ CML (N=18) and evaluated bosutinib at the oral daily doses of 400, 500 and 600 mg. In part 1 of the trial, 500 mg once daily was identified as the MTD. Part 2 was performed to evaluate the efficacy of bosutinib 500 mg once daily in 2nd line CP CML (N=288), 3rd line CP CML (N=118) and in AP and BP Ph+ CML (N=164). The primary efficacy endpoint was major cytogenetic response (MCyR) rate at Week 24 in imatinib-resistant 2nd line CP CML patients. The supportive trial (3160A4-3000-WW) was a phase 3 trial comparing the efficacy and safety of bosutinib (N=248) to that of imatinib (N=251) in patients with newly diagnosed (1st line) CP CML.

Table 1: Summary of the Pivotal and the Supportive Efficacy Trials

Trial Number	Trial Description	Treatment Groups	Trial Endpoints
3160A4-200-WW (pivotal)	Phase 1/2 open-label 2- part study in patients with Ph+ leukemia Part 1: dose escalation in CP CML (N=18) Part 2: efficacy study at the selected Phase 2 dose - CP CML 2nd line (N=288) - CP CML 3rd line (N=118) - AP and BP Ph+ CML (N=164)	Part 1: Bosutinib 400, 500 and 600 mg Part 2: Bosutinib 500 mg	Part 1: MTD Part 2: CP CML 2nd/3rd line primary endpoint: Major cytogenetic response (MCyR) at 24 weeks AP and BP Ph+ CML primary endpoint: Overall hematologic response (OHR) by 48 weeks.
3160A4-3000-WW (supportive)	Randomized, open-label, phase 3 study to compare the efficacy and safety of bosutinib to that of imatinib in subjects with newly diagnosed CP CML	Bosutinib 500 mg QD (N=248) Imatinib 400 mg QD (N=251)	Rate of complete cytogenetic response (CCyR) at 1 year

Pharmacokinetic data are available from 15 trials conducted in healthy volunteers (HV) and

patients including sparse PK in the pivotal trial.

Table 2: Overview of Clinical Pharmacology Related Trials Submitted in the NDA

Trial Number (Population)	Trial Description	Treatment Regimen
3160A4-1109-US (Healthy)	Relative BA of 3 new formulation tablets and a reference capsule and an oral solution given under fed conditions (N=40)	Single 500 mg dose of each formulation
3160A4-1115-US (Healthy)	BE comparing the proposed commercial test formulation to the phase 3 reference formulation given under fasting conditions (N=30)	Single dose of each: 100 mg x 3 Commercial test 100 mg x 3 Phase 3 reference
3160A4-1120-US (Healthy)	BE comparing the 500 mg proposed commercial test formulation to the Phase 3 reference formulation (N=31)	Single dose of each: 500 mg Commercial test 100 mg x 5 Phase 3 reference
3160A1-103-EU (Healthy)	Single dose PK and preliminary food effect study (N=41)	Bosutinib 200 - 800 mg
3160A4-1110-US (Healthy)	Food effect study (N=24)	Single doses of 400 mg (4 x 100 mg) under fed or fasting conditions
3160A1-100-US (Patients)	Dose-escalation study in patients with advanced malignant solid tumors with expansion cohorts (N=151)	Part 1 (dose-escalation): 50 to 600 mg daily (N=51) Part 2 (expansion): 400 mg QD (N=100)
3160A1-102-JA (Patients)	Dose-escalation study in Japanese patients with advanced malignant solid tumors (N=25)	Daily doses taken with food ranging from 100 - 400 mg
3160A4-1112-US(Healthy)	Mass balance study (N=6)	A single 500 mg oral dose of bosutinib containing 0.01 µCi [^{14}C] bosutinib
3160A4-105-US (Healthy)	Thorough QT study (N=60)	Part A: A single dose of bosutinib 500 mg, placebo or moxifloxacin 400 mg in a fed state. Part B: A single dose of bosutinib 500 mg or placebo with both given concomitantly with ketoconazole 400 mg in a fed state.
3160A4-1111-EU (Healthy)	Hepatic impairment study (N=27). The study enrolled six subjects in each group of Child Pugh A, B and C and 9 matched healthy volunteers in the control group	Single 200 mg dose
3160A4-104-US (Healthy)	Ketoconazole DDI (CYP3A4 Inhibitor) (N=24)	Single dose of bosutinib 100 mg administered either alone or with ketoconazole (400 mg dose for 5 days) under fasting conditions
3160A4-1114-EU (Healthy)	Ketoconazole DDI (CYP3A4 Inhibition) (N=48)	Single dose of bosutinib 100 - 600 mg co-administered with multiple doses of ketoconazole (400 mg tablets) under fed conditions
3160A4-1106-US (Healthy)	Rifampin DDI (CYP3A4 Induction) (N=24)	A single dose of bosutinib 500 mg administered either alone or with rifampin (600 mg for 8 days).
3160A4-1108-US (Healthy)	Lansoprazole DDI (pH altering proton-pump inhibitor) (N=24)	A single dose of 400 mg bosutinib alone or co-administered with multiple doses of 60 mg lansoprazole under fasting conditions

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical trials?

The primary endpoint for the pivotal trial was MCyR at 24 weeks in the imatinib-resistant second-line CP CML population. MCyR was the primary endpoint used in the pivotal trials for both currently approved tyrosine kinase inhibitors (dasatinib and nilotinib) in CP CML after prior imatinib failure. In the submitted pivotal trial, cytogenetic status was determined based on the ratio of the number of Ph+ cells to the number of cells analyzed. MCyR at week 24 considered those with a partial and complete response at that specific time point.

MCyR at 24 weeks was also used as the efficacy endpoint in third line CP CML. Overall hematologic response (OHR) was used as the efficacy end point in AP and BP Ph+ CML. OHR included complete hematologic responses (CHR), no evidence of leukemia (NEL), minor hematologic response (MiHR) and return to chronic phase (RCP). Hematologic responses were based on peripheral blood assessments and clinical assessments of extramedullary disease.

In the pivotal trial, the primary efficacy endpoint was MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects. The MCyR rate was 35.5% (90% CI: 29.7, 41.7) with a 1-sided $p<0.001$. For third-line CP CML patients, the MCyR at Week 24 was 26.9%. The overall hematologic response rate at 48 weeks was 55.1% in AP CML patients and 28.3% in BP CML patients. The supportive trial (3160A4-3000-WW) was a phase 3 trial in the 1st line setting in which bosutinib failed to show superiority to imatinib with an adjusted odds ratio estimate of complete cytogenetic response (CCyR) at 1 year of 1.10 (95% CI: 0.74, 1.63).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Plasma samples from clinical trials were assessed for the parent drug (bosutinib) which is the active moiety. Several of the clinical trials assessed exposures to the major metabolites, M2 and M5, which are inactive (*please refer to the pharmacology review for more details*). M2 and M5 were the major metabolites found in plasma in the mass balance trial and pharmacokinetic trials such as 3160A4-1106-US. The mean AUC ratio of metabolites to parent drug was 0.196 for M2 and 0.251 for M5.

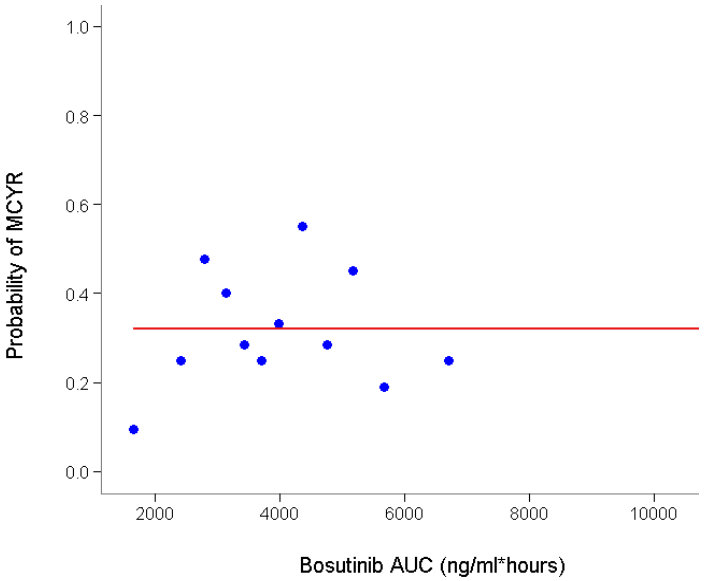
Exposure Response

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

No exposure-response relationship was observed for the primary endpoint of major cytogenetic response (MCYR) at 24 weeks (**Figure 2**) in CML patients randomized to receive 500 mg bosutinib. The efficacy analysis for the pivotal trial # 3160A4-200-WW used patients that were imatinib resistant or imatinib intolerant and had evaluable PK data (266 subjects). The sponsor conducted a logistic regression analysis of the data and their final logistic model indicates there

is no increase in the probability of response with increasing exposure. Details of the logistic regression analysis and exposure metric calculation are discussed starting on page 49 in the pharmacometrics review (**Appendix 1**).

Figure 2: Plot Showing that Probability of Major Cytogenetic Response at 24 Weeks Does Not Increase With Increasing Bosutinib Exposure



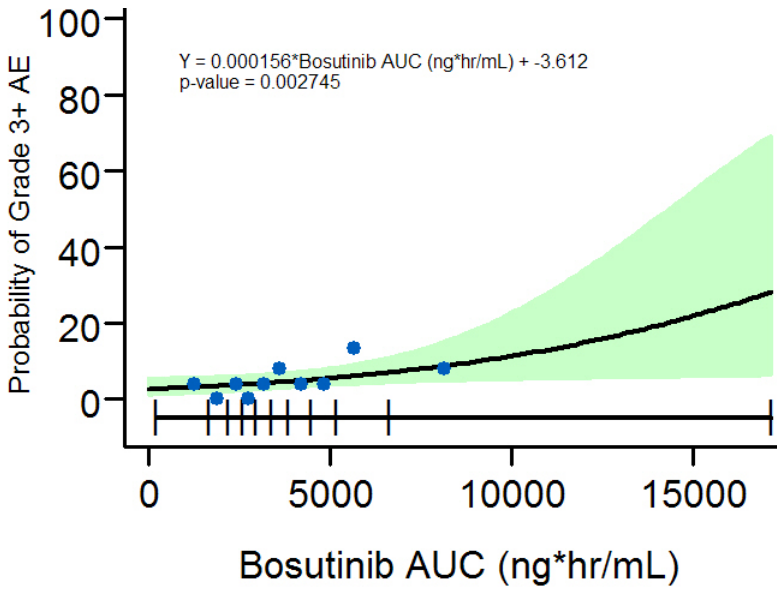
Symbols represent the calculated probability for each exposure bin. The red line is the sponsor's model prediction

(Source: Sponsor's Study Report PMAR-217, Figure 33)

2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

An exposure-response relationship was observed for Grade 3+ rash (**Figure 3**). Logistic regression was applied to model the probability of having a Grade 3 or higher adverse event (e.g. rash) versus bosutinib exposure (AUC) using data from both trials 200 and 3000. Details of these clinical trials are described further on page 46 in the pharmacometrics review (**Appendix 1**).

Figure 3: Exposure-Response Plot for Grade 3+ Rash



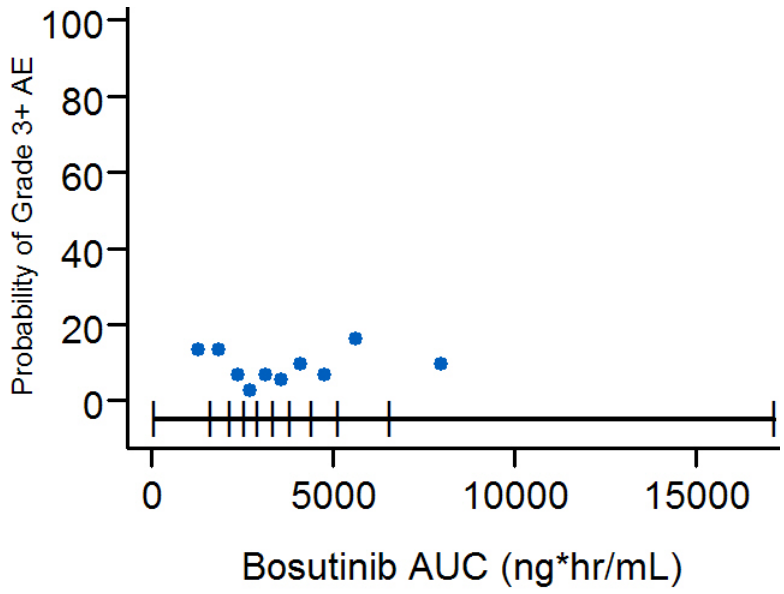
Text on the plot describes the logistic model equation and p-value for the coefficient on bosutinib exposure. Blue symbols are the probability of having grade 3+ rash by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. The solid line and green shaded area indicate the logistic model prediction and 90% confidence interval of the model prediction. Vertical bars denote the range of bosutinib AUC values in each exposure bin

Grade 3+ diarrhea events did not increase with increasing bosutinib exposures (**Figure 4**). Whereas, the sponsor's analysis suggests there is an exposure-response relationship for Grade 1+ diarrhea events (**Figure 5**). This may potentially be explained by the lower number of patients with Grade 3+ events (n=68) compared with the Grade 1+ events (n=567) creating more uncertainty in the analysis.

The primary differences between the reviewers and sponsor's analyses were:

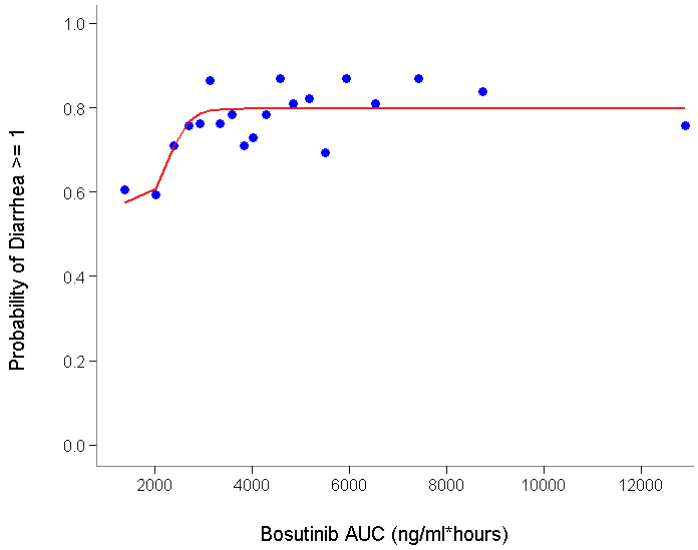
- The reviewer's analysis evaluated Grade 3 events or higher
- The reviewer's analysis calculated the individual bosutinib AUC values based on the time-averaged dose prior to the occurrence of the adverse event.
  $AUC_i = Dose_i/CL_i$
  where the subscript i refers to the individual, Dose refers to the time-average dose prior to the adverse event and CL refers to bosutinib clearance.
  The sponsor's analysis used the mode dose for the individual regardless of when the adverse event occurred.

Figure 4: Plot Showing That an Exposure-Response Relationship for Grade 3+ Diarrhea Was Observed



Blue symbols are the probability of having grade 3+ diarrhea by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

Figure 5: A Plot Showing the Sponsor's Exposure-Response Analysis for Diarrhea that Suggests an Exposure-Response Relationship Exists

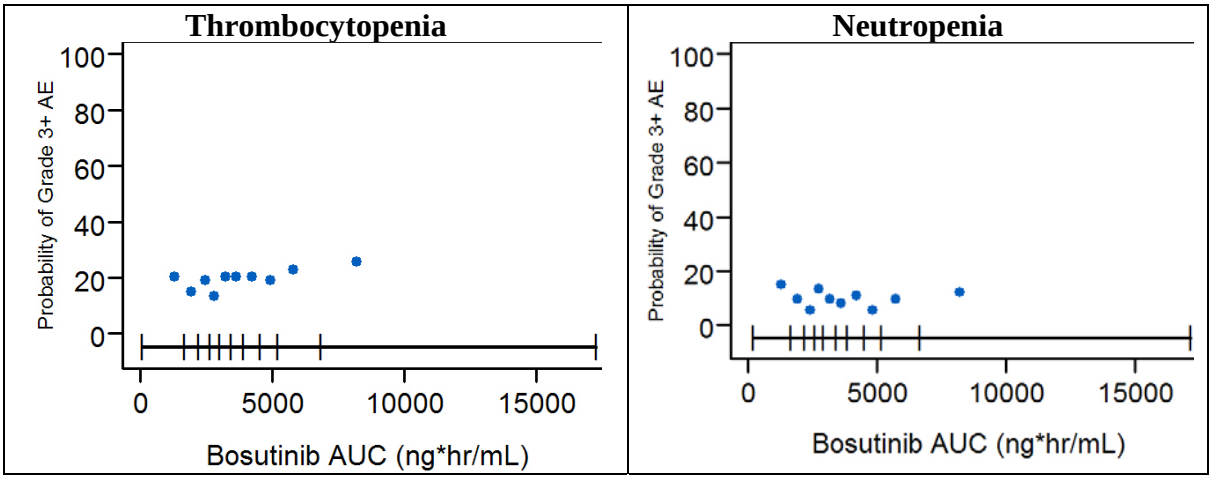


Symbols are calculated probability of Diarrhea grade 1+ for each AUC bin for pooled data from Studies 200 and 3000. Solid lines are predictions of the best model fittings.
(Source: Sponsor's Study Report PMAR-217, Figure 5)

No exposure-response was observed for grade 3+ thrombocytopenia (**Figure 6**), neutropenia (**Figure 6**), nausea (**Figure 7**), vomiting (**Figure 7**), increases in aspartate aminotransferases (**Figure 8**) or increases in alanine aminotransferases (**Figure 8**). These results are consistent

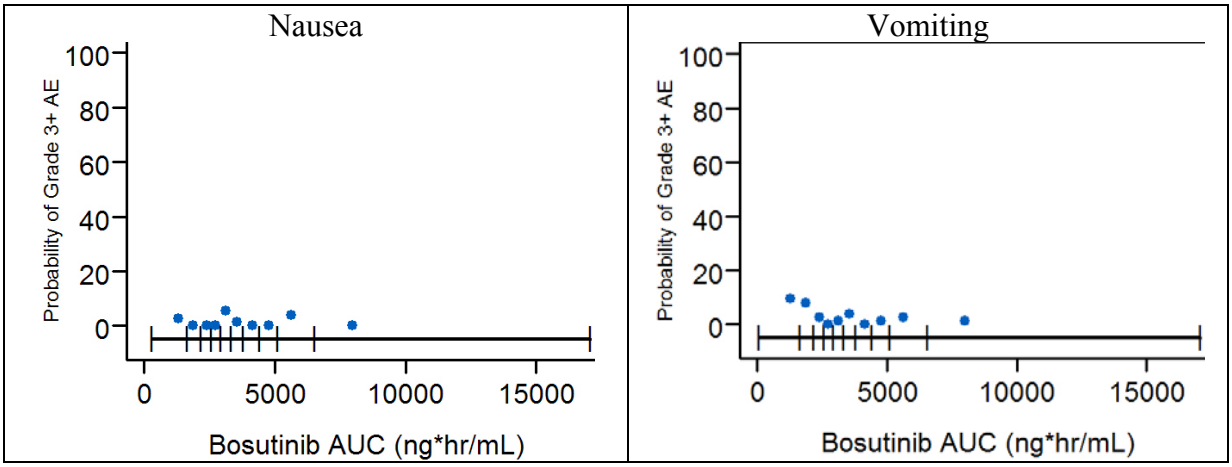
with the sponsor's results for Grade 1+ events.

Figure 6: Plots Showing No Exposure-Response Relationships Were Observed for Grade 3+ Thrombocytopenia (Left Panel) or Neutropenia (Right Panel)



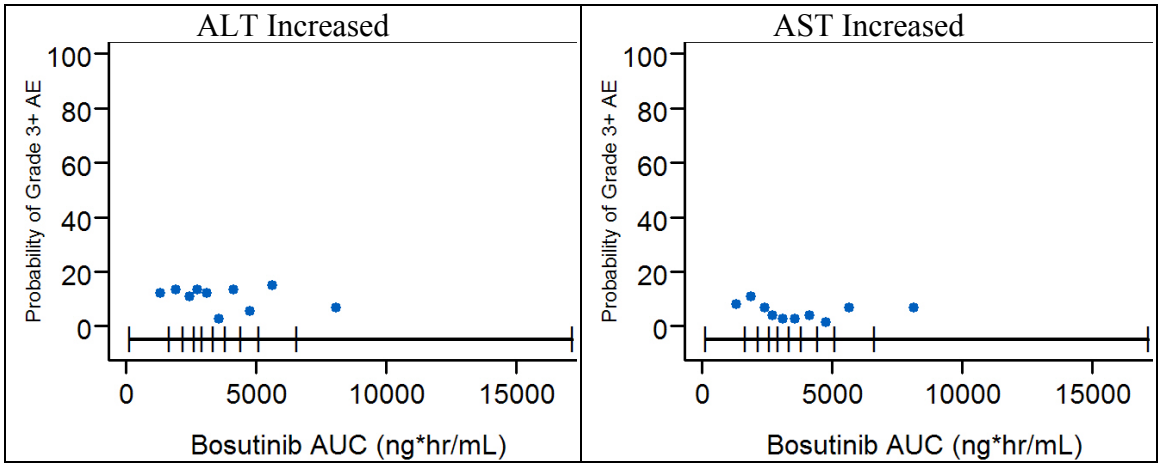
Blue symbols are the probability of having grade 3+ adverse event by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

Figure 7: Plots Showing No Exposure-Response Relationships Were Observed for Grade 3+ Nausea (Left Panel) or Vomiting (Right Panel)



Blue symbols are the probability of having Grade 3+ adverse events by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

Figure 8: Plot Showing No Exposure-Response Relationships Were Observed for Grade 3+ Increases in Alanine Aminotransferases (ALT, Left Panel) or Aspartate Aminotransferases (AST, Right Panel)



Blue symbols are the probability of having grade 3+ adverse event by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

2.2.6 Does this drug prolong the QT or QTc interval?

Bosutinib does not appear to prolong the QTc interval at clinically relevant exposures. The QT/IRT review concluded that in a study with a demonstrated ability to detect small effects, no significant changes in placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) were observed.

QT prolongation was assessed in Trial 3160A4-105-US, a single-dose, crossover, placebo and moxifloxacin controlled two part trial. Part A (therapeutic dose portion) consisted of 3 periods in which volunteers received a single dose of either bosutinib 500 mg (C), moxifloxacin 400 mg (B) or placebo (A), all given under a fed state. Part B (supra-therapeutic dose portion) consisted of 2 periods in which volunteers received a single dose of either bosutinib 500 mg (E) or placebo (D), both given in combination with ketoconazole 400 mg in a fed state.

Volunteers (N=70) were randomly assigned to one of 12 sequences which were different combinations of the 5 treatment arms (ACBDE, ACBED, ABCDE, ABCED, CABDE, CABED, CBADE, CBAED, BACDE, BACED, BCADE, BCAED). Bosutinib and placebo were given in a double-blind manner and moxifloxacin and ketoconazole were given in an open-label manner. In Part A, a washout period of 5 days was used between each treatment. A washout period of 8 days was used before Part B of the trial began and a four day wash-out period was used between the two periods in Part B.

A statistically significant increase in heart-rate (HR) was seen with the use of bosutinib and ketoconazole compared to placebo and ketoconazole at time-points after 3 hours. Based on the applicant and the FDA QT/IRT analyses, QTcF was a better correction method compared to QTcN, QTcI, and QTcB which were slightly associated with heart rate. Assay sensitivity was

established using moxifloxacin which had a largest lower bound of the 2-sided 90% CI for change in QTcF of greater than 5 msec.

The largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg and placebo was 4.5 msec. However, the largest upper bound of the 2-sided 90% CI for the mean difference between bosutinib 500 mg plus ketoconazole and placebo plus ketoconazole was 10.3 ms (higher than the threshold of 10 ms). Although exposures at steady state will be higher than those seen after a single dose due to a 2 - 3 fold accumulation in the PK of bosutinib, the risk of QTc prolongation greater than 10 msec is mitigated by labeling language to avoid the use of strong and moderate CYP3A4 inhibitors. In this trial, ketoconazole increased the C_{max} of bosutinib 2.9 fold and the AUC 6.5 fold. More detailed discussion of the PK parameters with or without ketoconazole can be found in **Section 2.4.3**.

QT/IRT proposed the following labeling language:

> *The effect of single dose of bosutinib 500 mg and 500 mg with ketoconazole on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) two or three-period crossover thorough QT study in 70 healthy subjects. In a study with demonstrated ability to detect small effects, no significant changes in placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) were observed. The exposure of bosutinib with ketoconazole was 2.9-fold that with bosutinib alone. The dose of 500 mg bosutinib with ketoconazole covers the high exposure clinical scenario.*

2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant selected the daily dose of 500 mg taken with food based on the following:

- In the dose escalation trial 3160A1-103-EU, food increased tolerability of single dose bosutinib despite higher exposures with the high-fat meal (2 fold increased exposure). Dose-escalation in the fasting cohorts was stopped at 400 mg due to 67% moderate to severe adverse events. On the other hand, when bosutinib was given with food it was possible to escalate the bosutinib dose up to 800 mg at which point dose escalation was stopped because all the five patients experienced GI toxicities.

- The MTD was determined to be 500 mg taken with food in the phase 1 dose escalation trial in patients with advanced malignant solid tumors (3160A1-100-US). However, because of an approximately 30% incidence of Grade 2 gastrointestinal toxicity at the 500 mg dose level, the 400 mg dose was chosen for evaluation in expanded cohorts of the trial and as the starting dose of the Phase 1/2 trial 3160A4-200-WW (the pivotal trial in this submission). This pivotal trial had a dose escalation portion (Part 1), in which the doses of 400, 500 and 600 mg were evaluated.

- A 500 mg dose taken with food was selected for evaluation in Part 2 of the pivotal trial and in

the supportive phase 3 trial (3160A4-3000-WW).

2.2.8 Do the exposure response relationships for efficacy and safety support the proposed dose adjustments for safety events??

Yes. (b) (4) The exposure-response for effectiveness analysis (**Figure 2**) supports reducing the dose for safety events. The mean AUC for the 400 and 500 mg doses are 4087 ng•mL/hr and 5216 ng•mL/hr, respectively. Based on **Figure 2**, dose decreases to 400 mg for safety events are not likely to reduce the effectiveness of bosutinib.

Pharmacokinetic characteristics of the drug and its major metabolites

2.2.9 What are the single dose and multiple dose PK parameters?

Single Dose PK in Healthy Volunteers

Single dose PK is available from 12 clinical trials in healthy volunteers in the dose range of 100 – 800 mg. The PK data was not pooled for all the different trials as different administration conditions were used for dosing. A high-fat meal was used in Trial 1114-EU, a medium fat meal was used in Trials 1111-EU, 1109-US, 1120-US, 1106-US and 105-US and bosutinib was given after an overnight fast in Trials 1115-US, 1108-US and 104-US (the trials are summarized in **Table 2**). Food effect was assessed comparing a high-fat meal and to an overnight fast in Trials 103-EU and 1110-US. **Table 3** summarizes the PK parameters of bosutinib based on data from four clinical trials that used monotherapy bosutinib.

Single Dose PK in Cancer Patients

Single dose PK parameters of bosutinib are summarized (**Table 4**) based on data from two dose escalation trials. The first trial was in patients with advanced malignant solid tumors (3160A1-100-US) and the second trial was the dose escalation portion of the pivotal CML trial (3160A4-200-WW). The doses ranged from 50 to 600 mg. In these trials, bosutinib was given with food.

Table 3: Pharmacokinetic Parameters of Single Dose Bosutinib in Healthy Volunteers

Trial	Dose Regimen	N	C_{max} (ng/mL)	AUC (ng*hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	CL/F (L/hr)
103-EU Caps	200 mg (Fasted)	6	16.9 ± 11.3	474 ± 116	6 (3-36)	42.0 ± 3.4	443 ± 102
	200 mg (High fat)	6	42.5 ± 10.3	1080 ± 326	6 (3-8)	39.1 ± 12.7	199 ± 61
	400 mg (Fasted)	12	62.1 ± 40.8	1150 ± 625	3 (2-6)	37.3 ± 10.1	462 ± 266
	400 mg (High fat)	6	88.0 ± 23.1	1770 ± 292	6 (4-6)	32.4 ± 8.6	231 ± 34
	600 mg (High fat)	6	141 ± 48.2	2960 ± 681	6 (4-24)	32.6 ± 6.7	214 ± 58
	800 mg (High fat)	5	216 ± 85.8	4000 ± 1530	6 (4-8)	33.8 ± 8.2	246 ± 156
1110-US Tablet	400 mg (fasted)	24	55.9 ± 29.6	1310 ± 598	6 (3-8)	35.5 ± 11.2	369 ± 168
	400 mg (High fat)	23	89.5 ± 24.1	2060 ± 448	6 (2-8)	31.9 ± 5.9	204 ± 45
1115-US Tablet	300 mg (fasted) Commercial	27	43.9 ± 18.3	1160 ± 424	6 (2-8)	36.6 ± 10.8	294 ± 106
	300 mg (fasted) Clinical tablet	28	44.9 ± 20.9	1200 ± 498	6 (2-7)	35.5 ± 7.5	330 ± 295
1120-US Tablet	500 mg (medium-fat) Commercial	31	89.0 ± 35.8	2140 ± 837	3 (1-7)	31.5 ± 6.4	277 ± 125
	500 mg (medium-fat) Clinical tablet	30	83.2 ± 36.6	2070 ± 749	3.5 (1-12)	32.5 ± 5.7	277 ± 111

PK parameters presented as Mean ± SD except T_{max} is presented as Median (min- max)

Table 4: Summary of (Mean±SD) Pharmacokinetic Parameters of Single Dose Bosutinib in Cancer Patients

Trial	Dose (mg)	N	C_{max} (ng/mL)	AUC (ng*hr/mL)	T_{max}[a] (hr)	$T_{1/2}$ (hr)	CL/F (L/hr)
100-US	50	4	4.89 ± 3.69	129 ± 131[b]	6 (4-8)	12.9 ± 7.4[b]	721 ± 535[b]
	100	4	17.0 ± 9.8	284 ± 73	4 (2-6)	18.6 ± 4.9	366 ± 75
	200	6	43.1 ± 26.9	920 ± 338	6 (2-8)	20.8 ± 6.1	242 ± 81
	300	7	63.7 ± 34.7	1200 ± 736	6 (3-6)	17.1 ± 6.0	419 ± 412
	400	54	117 ± 69	2340 ± 1230[c]	4 (1-9)	18.6 ± 7.7[c]	260 ± 318[c]
	500	13	125 ± 63	2950 ± 1470	4 (2-8)	21.9 ± 7.4	207 ± 89
	600	10	206 ± 190	4300 ± 3310	6 (1-8)	19.9 ± 5.5	207 ± 118
200-WW (Pivotal Trial)	400	3	89.3 ± 50.0	2530[d]	4 (3-48)	22.9[d]	177[d]
	500	3	101 ± 35.6	2760 ± 687	6 (6-6)	22.5 ± 1.7	189 ± 48
	600	12	120 ± 40.2	2420 ± 457[f]	4 (2-49)	22.2 ± 5.0[f]	258 ± 61[f]

[a]Median (min - max); [b]N = 3; [c]N = 47; [d]N = 2, SD not calculated and [e]N = 8

Multiple Dose PK in Cancer Patients

Multiple dose PK (**Table 5**) is summarized from the two trials discussed under the section on single dose PK in patients. The dose ranges included were 50 – 600 mg daily. Following multiple dose administration, the mean accumulation ratio observed compared to single dose PK ranged from 2 – 3. Overall, the PK parameters showed high inter-subject variability.

Table 5: Summary of (Mean±SD) Pharmacokinetic Parameters of Multiple Dose Bosutinib in Cancer Patients

Trial	Dose (mg)	N	C_{max} (ng/mL)	AUC (ng*hr/mL)	T_{max}[a] (hr)	$T_{1/2}$ (hr)	CL/F (L/hr)
100-US	50	3	6.9 ± 3.1	114 ± 33	4 (3-6)	25.8 ± 12.3	467 ±148
	100	4	19.6 ± 3.3	329 ± 58	3.5 (2-4)	64.7 ± 67.3	310 ±49
	200	5	95.4 ± 60.0	1670 ± 1130	4 (3-6)	30.0 ± 20.1	162 ±93
	300	5	76.6 ± 37.0	1170 ± 699[b]	4 (3-6)	19.4 ± 7.5[b]	361 ±264[b]
	400	69	190 ± 116	2900 ± 1700[d]	4 (1-8)	19.9 ± 16.7[c]	180 ±103[d]
	500	10	273 ± 197	3580 ± 1820[e]	5 (1-8)	23.3 ± 15.0[e]	186 ±113[e]
	600	2	182, 425	3160, 5280	3.5 (3-4)	21.4, 11.2	190, 114
200-WW (Pivotal Trial)	400	3	146 ± 20	2720 ± 442	4 (3-6)	46.0 ± 32.3	150 ± 23
	500	3	200 ± 12	3650 ± 425	6 (4-8)	21.7 ± 4.6	138 ± 17
	600	12	208 ± 73	3630 ± 1270[l]	6 (3-11)	25.9 ± 24.9[k]	185 ± 66[l]

[a]Median (min- max); [b]N=4; [c]N=53; [d]N=58; [e]N=9; [f]N=7; [g]N=9

2.2.10 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The single dose exposures appear to be comparable between healthy volunteers and cancer patients as shown in Section 2.2.9. Multiple doses were not used in healthy volunteer trials.

2.2.11 What are the characteristics of drug absorption?

The mean T_{max} of bosutinib ranged from 3.5 – 6 hours in cancer patients. Based on low solubility and permeability, bosutinib monohydrate can be classified as a BCS Class IV compound (see **Section 2.5.1** of the review for more discussion). The absolute bioavailability has not been established. BCS Class IV compounds generally have poor and highly variable bioavailability. Based on an *in vitro* study (RPT-71680) with Caco-2 cells, bosutinib is a substrate and an inhibitor of P-gp. In the food effect trial # 3160A4-1110-US, a high-fat meal increased bosutinib AUC 1.7-fold and C_{max} 1.8-fold compared with bosutinib administration under fasting conditions (**Table 19**).

2.2.12 What are the characteristics of drug distribution?

Plasma Protein Binding: Bosutinib is highly bound to plasma proteins *in vitro* (94 - 96%). Protein binding of bosutinib was not observed to be concentration dependant (100, 1 000 and 10 000 ng/mL). Bosutinib was found to bind to human serum albumin (HSA) 95.4 % and to α1-acid glycoprotein (AGP) 71.4%. In the dedicated hepatic impairment Trial # 3160A4-1111-EU, plasma protein binding was found to be similar in healthy volunteers and those with mild, moderate and severe hepatic impairment (>99% binding).

Blood to Plasma Ratio: *In vitro,* the whole blood to plasma ratio for bosutinib was approximately 1.2 at the concentration of 1 μM (0.53 μg/mL). In the human mass balance trial 3160A4-1112-US, the mean whole blood to plasma ratio could not be determined due to the low dose of radioactivity used.

Tissue Distribution: The apparent volume of distribution (Vd) based on single dose PK in cancer patients was 6 000 – 11 000 L, which may suggest that bosutinib is extensively distributed to peripheral tissues. However, the Vd may be overestimated if the bioavailability of bosutinib is low. An absolute bioavailability study has not been performed, but bosutinib likely has low bioavailability because it is a BCS Class IV compound.

Transporter Proteins: Based on an *in vitro* study (RPT-71680) with Caco-2 cells, bosutinib is a substrate of P-gp with concentration dependant permeability (1, 10 and 100 μM). This was confirmed in the *in vitro* study RPT-80268. Bosutinib is an inhibitor of P-gp with an IC_{50} of 2 μM, *in vitro*. The I/Ki (I based on steady-state C_{max} of 270 ng/mL at the 500 mg dose and Ki assumed to be $IC_{50}/2$) was approximately 0.5. Based on the I/Ki of >0.1, it has the potential to inhibit P-gp in humans. Other transporter proteins have not been evaluated.

2.2.13 Does the mass balance trial suggest renal or hepatic as the major route of elimination?

In the mass balance trial (3160A4-1112-US), six healthy male volunteers received 500 mg of oral ^{14}C-labeled bosutinib. Each volunteer was supposed to receive 0.1 μCi of ^{14}C-labeled bosutinib, but due to a pharmacy calculation error, the radioactivity dose was 0.01 μCi.

The urine samples were pooled from 0 – 24 hours and the fecal samples were pooled for 0 – 24 hours and from 24 – 144 hours for analysis. The pooling was done due to the low radioactivity dose administered. The total radioactivity recovered over 216 hours was 94.6±7.49 % (range of 82.6 – 104 %) of the total dose, with 91.3±8.39% (range 79.4 – 102.5%) recovered in feces and 3.29±1.4% (range 1.54 – 5.73) recovered in urine.

Since the absolute bioavailability of bosutinib was not assessed, it is not clear what proportion the administered dose recovered in feces was excreted following systemic absorption. Based on metabolic profiling of the samples from this mass balance trial (reported in RPT-79197), the parent drug bosutinib (up to 40%) and its metabolites M5 (up to 22 %) and M2 (up to 7.3%) were detected in feces. Bosutinib (72%) and M2 (7.5%) were detected in urine. Due to the low radioactivity dose, the relative distribution of the moieties based on radioactivity could not be assessed in the blood or plasma. However, the plasma PK parameters as assessed by LC/MS/MS were similar in this mass balance trial as those seen in trial 3160A4-1106-US (all three moieties were assessed in this trial). The mean AUC ratio of metabolites to parent drug was 0.196 for M2 and 0.251 for M5. The parent drug appears to be the major moiety in plasma.

2.2.14 What are the characteristics of drug metabolism?

Bosutinib is primarily metabolized by CYP3A4. The main circulating metabolites in human plasma are M2 (oxydechlorinated bosutinib) and M5 (N-desmethyl bosutinib). The mean AUC ratio of metabolites to parent drug was 0.196 for M2 and 0.251 for M5.

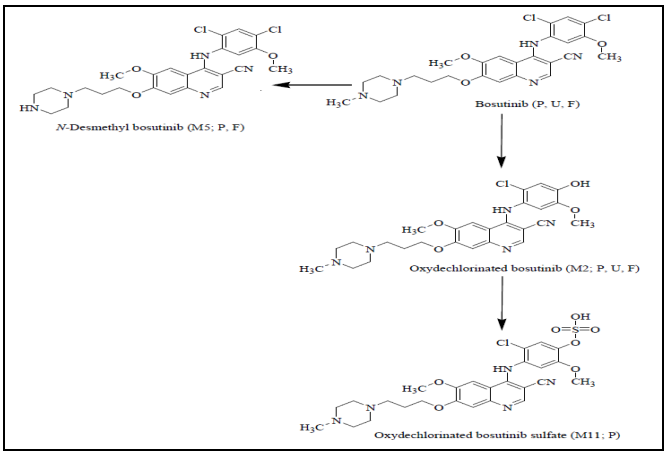
In vitro

Metabolic Profiling and Identification: Based on the metabolic profiling of samples from the

mass balance trial # 3160A4-1112-US (**RPT-79197),** M2 and M5 are the major metabolites of bosutinib in humans. Bosutinib, M2, M5 and M11 were detected in pooled plasma. Bosutinib, M5 and M2 were detected in pooled fecal samples, but only bosutinib and M2 were detected in pooled urine samples (**Figure 9**). In **Experiment # RPT-53085**, M2 and M5 were the major metabolites in human liver microsomes and M5 and M6 were the major metabolites formed in cryopreserved human hepatocytes.

In **experiment # RPT-53086**, only the CYP3A4 cDNA-expressed isozyme was capable of metabolizing bosutinib to five metabolites (M1, M2, M4, M5 and M6). M2, M5 and M6 were the most abundantly formed metabolites in the CYP3A4 cDNA expressed isozyme. Bosutinib metabolism was inhibited by ketoconazole (strong CYP3A4 inhibitor). CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2D6 and 2E1 did not have enzymatic activity and inhibitors of these enzymes did not inhibit bosutinib metabolism.

Figure 9: The Proposed Metabolic Pathways for Bosutinib Based on Metabolites Observed in Human Plasma, Urine and Feces in Trial # 3160A4-1112-US



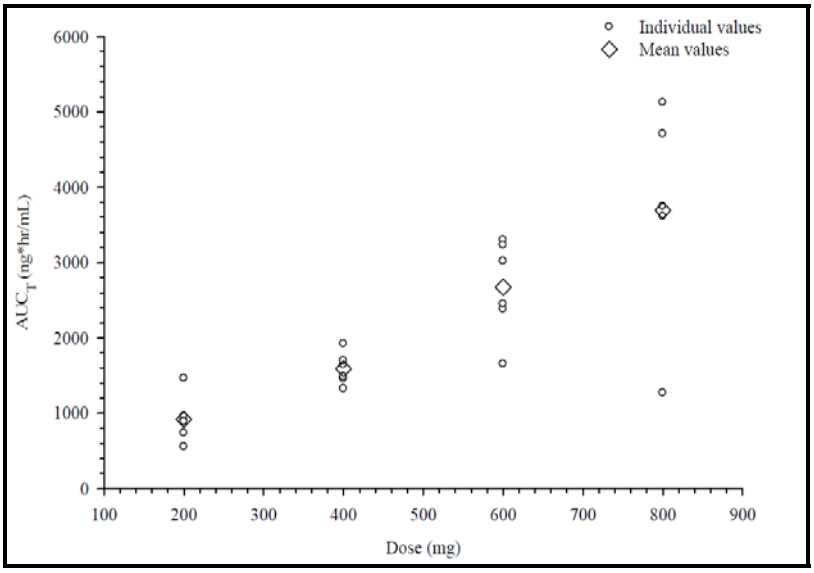
2.2.15 What are the characteristics of drug excretion?

The drug is mainly excreted by the fecal route (91%) with the urinary route accounting for 3% of the administered drug excretion. See Section 2.2.13.

2.2.16 Based on PK parameters, what is the degree of linearity or non-linearity?

It appears that exposure to bosutinib increases in a dose proportional fashion at doses ranging from 200 to 800 mg. The sponsor assessed dose proportionality using a power model and included the cohorts taking bosutinib with a high-fat meal in the dose escalation trial (3160A1-103-EU). In this trial only two doses were assessed under fasting conditions so dose proportionality could not be assessed under fasting conditions. The slope for the power model on a logarithmic scale for C_{max} was 1.1 with a 90% confidence interval of (0.80, 1.41) and AUC was 0.92 with a 90% confidence interval of (0.67, 1.18).

Figure 10: Bosutinib Individual and Mean AUC Values versus Dose after Administration of Single Ascending Oral Doses of Bosutinib to Healthy Subjects Under Fed Conditions (Trial # 3160A1-103-EU)



Source: Figure 3-3 from Page 65 in summary-clin-pharm.pdf

In addition, the reviewer used a linear fixed effects model in Phoenix WinNonLin to assess proportionality using data from trials 103-EU and 1114-EU. For the trial 103-EU data, the tests to reference ratios were within the 80 – 125% confidence interval limits for C_{max} and AUC (**Table 6**). For the data from trial 1114-EU, the test to reference ratios were within the 80 – 125% confidence interval limits for C_{max} and AUC for most dose levels, but the AUC ratio was 130 for the 600 mg (**Table 7**). However, taken together, the totality of data from both trials suggests the Cmax and AUC of bosutinib increase in proportion with the dose.

Table 6: Statistical Analysis of Dose-Normalized Pharmacokinetic Parameters Estimated for Single Doses of Bosutinib Ranging from 200 – 800 mg Taken with a High Fat Meal in Healthy Volunteers in Trial 3160A1-103-EU

PK Parameter	Dose	LS Mean (normalized to 200 mg)	Test/Ref Ratio (%)	90% CI
C_{max} (ng/mL)	200 (Ref)	41.29		
	400	42.85	103.79	(70.93, 151.87)
	600	44.39	107.51	(73.47, 157.32
	800	48.76	118.08	(79.21, 176.03)
AUC_{∞} (hr*ng/mL)	200 (Ref)	1041.98		
	400	874.74	83.95	(61.10, 115.35)
	600	962.67	92.39	(67.24, 126.95)
	800	919.12	88.21	(63.21, 123.10)

Table 7: Statistical Analysis of Dose-Normalized Pharmacokinetic Parameters Estimated After Single Doses of Bosutinib Ranging from 100 – 600 mg Taken with a High Fat Meal and Ketoconazole in Healthy Volunteers in Trial 3160A4-1114-EU

PK Parameter	Dose	LS Mean (normalized to 100 mg)	Test/Ref Ratio (%)	90% CI
C_{max} (ng/mL)	100 (Ref)	57.21		
	200	56.85	99.37	(67.88, 145.47)
	300	59.16	103.40	(70.63, 151.36)
	400	53.71	93.87	(64.13, 137.41)
	500	70.79	123.74	(84.53, 181.13)
	600	69.29	121.11	(82.73, 177.29)
AUC_{∞} (hr*ng/mL)	100 (Ref)	2887.32		
	200	3278.75	113.56	(83.14, 155.09)
	300	2809.87	97.32	(71.25, 132.92)
	400	2445.35	84.69	(62.01, 115.67)
	500	3188.25	110.42	(80.85, 150.81)
	600	3778.24	130.86	(95.81, 178.72)

2.2.17 How do the PK parameters change with time following chronic dosing?

Mean accumulation ratios of 2 - 3 were observed at steady-state compared to single dose exposures. The clearance appears to be the same after a single dose as with multiple doses. The PK variability was high for both single and multiple dose PK (see **Table 4** and **Table 5)**.

2.2.18 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

High PK variability was observed in both the healthy volunteer and patient trials (CV of 58 - 73% in the patient population PK model). High variability was observed in some of the healthy volunteer trials using an overnight fast before dosage administration. As such, some of the bosutinib variability may be attributed to the BCS Class IV classification. BCS Class IV drugs are generally considered to have poor and highly variable bioavailability. In the patient trials, bosutinib was taken with non-standardized meals. Since a high-fat meal increases exposures two-fold, the administration of bosutinib with non-standardized food may contribute to the high inter-patient variability.

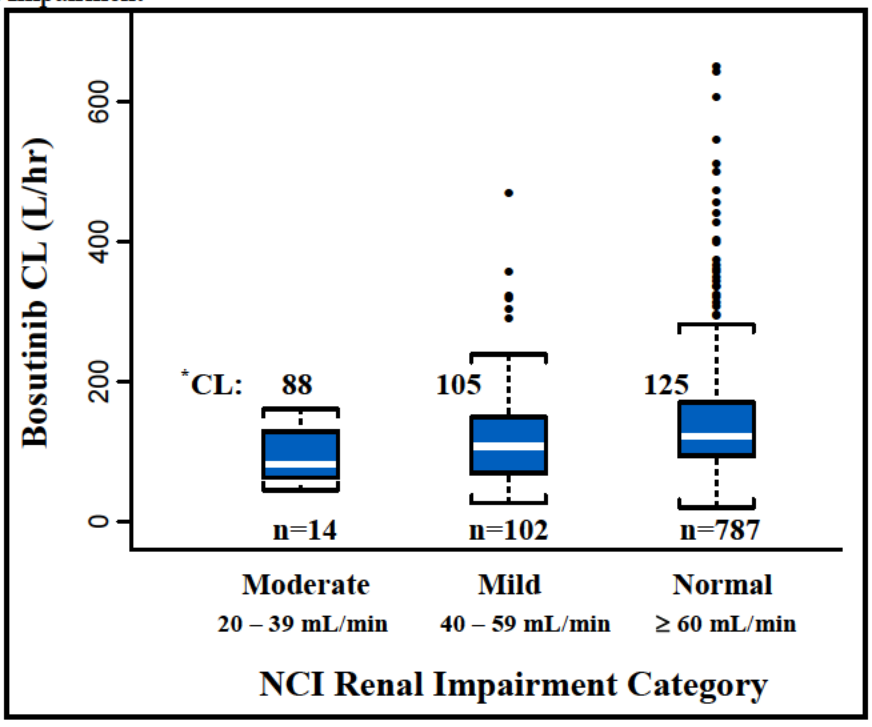
2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population pharmacokinetic (Pop PK) analyses showed that age, gender, albumin and race do not influence the PK of bosutinib. Weight and creatinine clearance may be potential covariates (**Figure 11, Figure 12 and Appendix 1**). The sponsor's final population PK model estimates of CL suggest that bosutinib clearance is reduced by approximately 30% in patients with moderate renal impairment (**Figure 11**). See **Appendix 1** for the pharmacometrics reviewer's assessment of the sponsor's population PK model.

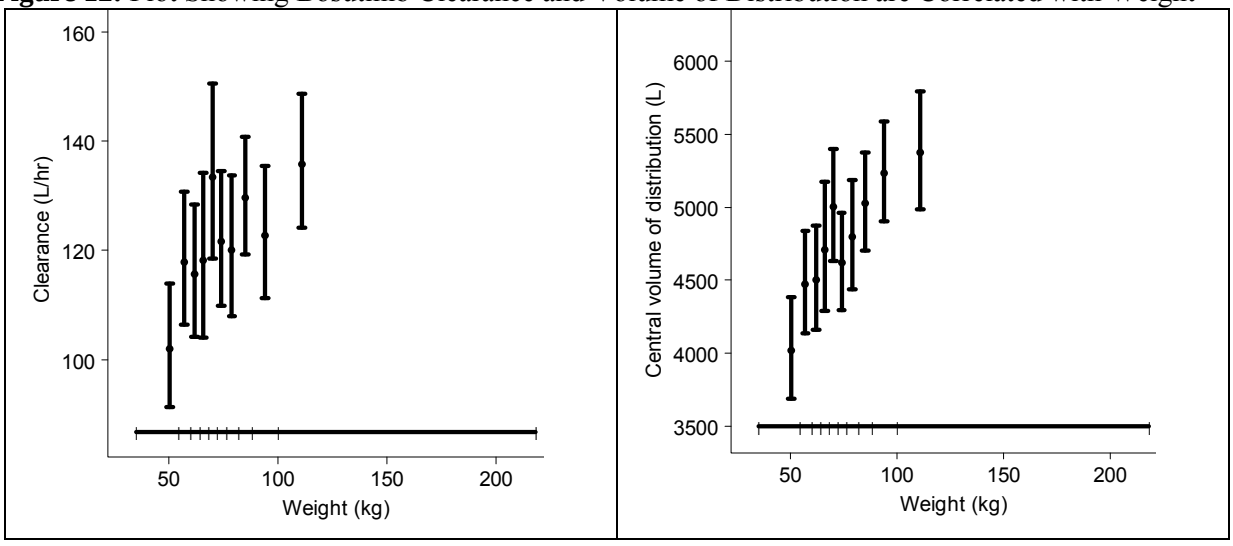
Relationship between Weight or CrCl and Exposure: Weight and creatinine clearance were considered to be potential covariates on the clearance of bosutinib. Weight appears to be correlated with bosutinib CL and Vd (**Figure 11 and Figure 12**). However, inclusion of this covariate in the population PK model did not reduce inter-subject variability on CL and Vd.

Figure 11: Plot Showing Bosutinib Clearance is Reduced Approximately 30% in CML Patients with Moderate Renal Impairment



*Boxplots are shown for model predicted CL values for individuals with moderate, mild, or normal renal impairment as defined by the NCI renal impairment classification. *Geometric mean CL values are shown on the plot adjacent each corresponding boxplot.*

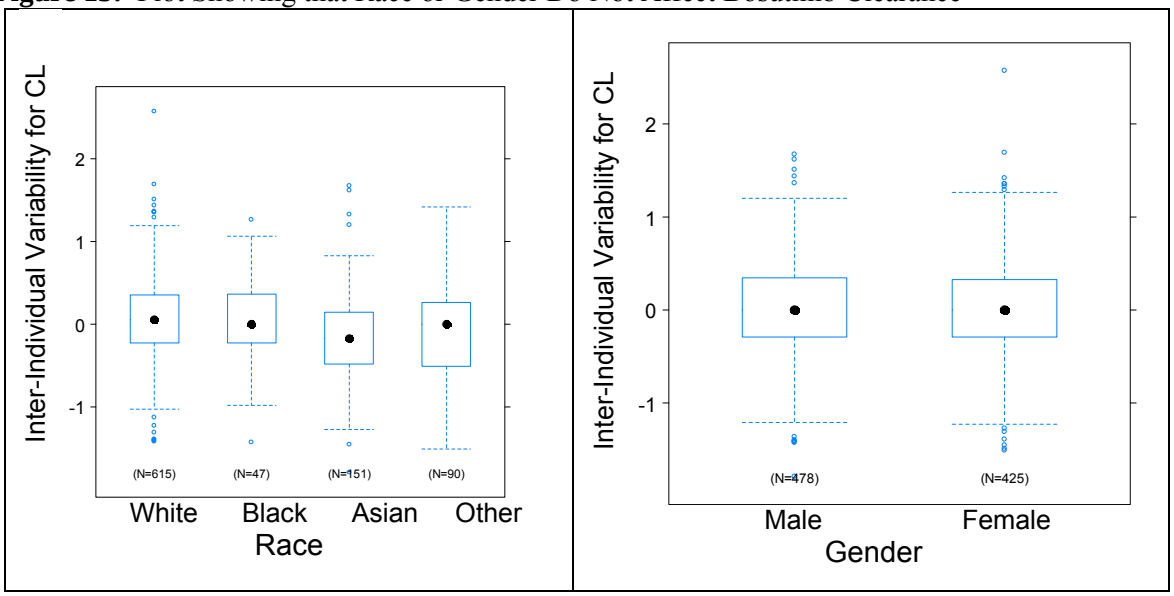
Figure 12: Plot Showing Bosutinib Clearance and Volume of Distribution are Correlated with Weight



Individual CL and Vd data from the sponsor's final population PK model were assigned to ten quantiles by weight. Data are shown as mean ± S.D.

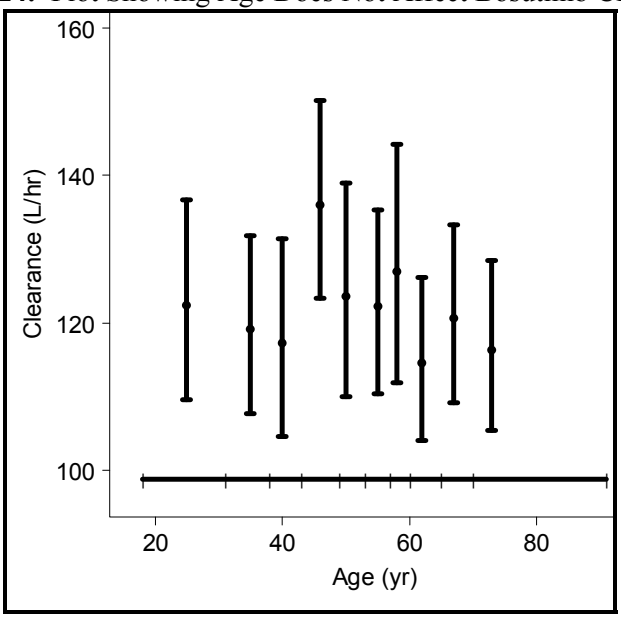
Relationship between Race, Gender or Age and Exposure: Race, gender and age do not appear to influence the clearance of bosutinib.

Figure 13: Plot Showing that Race or Gender Do Not Affect Bosutinib Clearance



Individual CL data from the sponsor's final population PK are shown by race category

Figure 14: Plot Showing Age Does Not Affect Bosutinib CL



Individual CL data from the sponsor's final population PK model were assigned to ten quantiles by weight. Data are shown as mean ± S.D.

Relationship between Renal Impairment and Exposure: Variability in the PK data did not permit a reliable assessment of the effect of creatinine clearance on the CL of bosutinib using population PK analysis. Bosutinib clearance is reduced approximately 30% in CML patients with moderate renal impairment (based on NCI criteria: CrCl of 20-39 mL/min) as shown in **Figure 11**. Based on the mass balance trial, 3% of bosutinib was detected in urine. The exact contribution of the renal route cannot be determined as the absolute bioavailability is not known. See page 57 in **Appendix 1** for further details on the evaluation of CRCL as a covariate on bosutinib CL.

Relationship between Hepatic Impairment and Exposure:

Trial 3160A4-1111-EU was an open-label, single dose trial that evaluated the pharmacokinetics and safety of bosutinib in volunteers with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (N=6 each) and in matched healthy adults (N=9). Each volunteer received a single 200 mg dose on day 1 given five minutes after completion of a standardized medium fat breakfast (20% fat and 550 calories). Blood samples were collected for up to 96 hours post-dose. Blood samples were collected for protein binding analyses at 3, 6 and 24 hours post-dose.

Bosutinib C_{max} and AUC increased by approximately 2-fold in those with Child Pugh A, B and C hepatic impairment as compared to the healthy volunteers. The median T_{max} was decreased and the mean elimination half-life increased in hepatic impairment (**Table 8**). Plasma protein binding was similar in healthy volunteers and in those with hepatic impairment (>99% binding).

The most frequently reported treatment emergent adverse events (TEAE) were prolonged QT interval (N=10, 37%), nausea (N=3, 11%) and vomiting (N=2, 7.4%). QTc interval was > 450

ms in 9 hepatically impaired patients (6 of the 9 patients in the Child-Pugh C group), although none of the patients had a QTc interval > 450 ms at baseline. Of these 9, five had increases > 30 msec (4 in Child-Pugh C), but no QTc prolongation > 60 msec was seen. The QT effects do not appear to be associated with exposures since the C_{max} and AUC of volunteers with QTc prolongation were not higher than those without QTc prolongation. In addition, in the Thorough QT trial, supra-therapeutic bosutinib exposures resulting from concomitant ketoconazole did not result in clinically meaningful changes in the QT interval. Therefore, the mild QTc prolongation signal observed in the hepatic impairment trial may not be clinically or mechanistically meaningful.

The applicant proposes a dose adjustment to 200 mg in patients with hepatic impairment. This dose adjustment appears to be reasonable based on the bosutinib exposure. These exposures will be in a similar range as those seen at the 500 mg in the pivotal BE trial 1120-US that also used a standard medium fat meal (30% fat).

Table 8: Summary of Bosutinib Pharmacokinetic Parameters Following a Single Oral Dose of Bosutinib 200 mg in Child-Pugh Class A, B and C and in Healthy Volunteers

PK Parameter	Healthy (N=9)	CP A (N=6)	CP B (N=6)	CP C (N=6)
C_{max} (ng/mL)	34.0 ± 10.5	86.7 ± 45.5	68.4 ± 24.2	58.8 ± 41.4
LSGM C_{max} (%)	N/A	242 (158 – 370)	199 (130 – 305)	152 (99 – 232)
T_{max} (hr)[a]	4.0 (1.0 - 8.0)	2.5 (0.5 - 4.0)	2.0 (1.0 - 4.0)	1.5 (1.0 - 3.0)
$T_{1/2}$	55.0 ± 15.8	85.7 ± 8.7	112.5 ± 37.9	111.1 ± 33.7
$AUC_{0-\infty}$ (ng*h/mL)	914 ± 334	1980 ± 450	1870 ± 688	1780 ± 778
LSGM $AUC_{0-\infty}$ (%)	N/A	225 (160 – 315)	200 (143 – 281)	191 (137 – 268)
Cl/F (L/h/kg)	3.0 ± 1.3	1.2 ± 0.4	1.5 ± 0.6	1.5 ± 0.4

Relationship between Mutations in the Drug Target and Response

Nearly 100 different Bcr-Abl mutations have been identified thus far. Bcr-Abl mutations have been observed in approximately 35 to 45% of CML patients with imatinib resistance, although the reported mutation frequency can vary based on the study and/or patient population. Some of the Bcr-Abl mutations have also been associated with resistance to dasatinib and nilotinib. In particular, the T315I mutation is considered resistant to all the currently approved Bcr-Abl inhibitors used to treat CML. Preliminary data from Trial 3160A4-200-WW suggest that CML patients with a T315I Bcr-Abl mutation also show less favorable responses to bosutinib. In addition, in preclinical studies submitted by the applicant bosutinib did not have activity in T315I and V299L Bcr-Abl mutant cells.

Bcr-Abl mutations in Trial 3160A4-200-WW:

Samples for Bcr-Abl mutational analysis were collected at screening and the end of treatment in both the pivotal 3160A4-200-WW and the supportive phase 3 trial 3160A4-3000-WW. However, mutation data from the supportive trial were not submitted due to low sample acquisition (< 10% of patients at baseline and < 20% at the end of treatment). Mutational analysis was performed by sequencing of the entire Bcr-Abl transcript. If bone marrow aspirate was not available, a peripheral blood sample was acceptable.

Baseline Bcr-Abl mutations:

Samples for Bcr-Abl mutation analysis were collected in 72% (412/570) of patients at baseline. Approximately 44 % (183/412) of patients had at least one mutation at baseline with up to 42 unique Bcr-Abl point mutations identified. In second-line CP CML, the most frequently detected mutations (9 patients each) were M351T, F359V and T315I. In third-line CP CML, F317L (N=8), T315I (N=7) and Y253H (N=6) were the most common. In the advanced leukemia (AP and BP), T315I was the most common (N=15, 12.8%). For the additional Bcr-Abl mutations detected in the trial, datasets were limited to mostly 1 - 2 patients per unique mutation. For example, the V299L mutation that is associated with dasatinib resistance was only identified in two patients in the third line setting.

The applicant conducted an exploratory analysis to assess response in patients with baseline Bcr-Abl mutations and indicated that response to bosutinib was seen regardless of the presence of mutations (**Table 9**). However, when the data is broken down by the most common mutations, responses in patients with T315I mutations appear lower compared with those in patients without mutations. The MCyR (primary endpoint) in second line CP was 22% (2/9) for patients harboring the T315I mutation compared to 54% (65/121) in those with no mutation. Similarly, the MCyR in the third line CP was 0% (0/6) for patients with the T315I mutation compared to 35% (15/43) in those with no mutation (**Table 9**).

Table 9: Response in Patients With and Without Bcr-Abl Mutations at Baseline

Baseline Mutation Status	Number of patients (%)	Confirmed CHR	MCyR
CP 2rd line			
Mutation Not Assessed	76/288 (26.4%)	59/76 (77.6%)	33/67 (49.3%)
No mutation	133/212 (62.7%)	120/133 (90.2%)	65/121 (53.7%)
At least 1 mutation	79/212 (37.3%)	65/78 (83.3%)	44/78 (56.4%)
T315I	9/212 (4.2%)	2/9 (22.2%)	2/9 (22.2%)
CP 3rd line			
Mutation Not Assessed	35/118 (29.7%)	25/33 (75.8%)	9/30 (30%)
No mutation	44/83 (53.0%)	34/44 (77.3%)	15/43 (34.9%)
At least 1 mutation	39/83 (47.0%)	26/39 (66.7%)	11/35 (31.4%)
T315I	7/83 (8.4%)	2/7 (28.6%)	0/6 (0%)
Advanced Phase		Confirmed CHR	OHR
Mutation Not Assessed	47/164 (28.7%)	6/43 (14%)	13/43 (30.2%)
No mutation	52/117 (44%)	19/49 (38.8%)	23/49(46.9%)
At least 1 mutation	65/117 (55.6%)	10/59 (16.9%)	21/59 (35.6%)
T315I	15/117 (12.8%)	0/13 (0%)	1/13 (7.69%)

Source: Compilation of sponsor's Tables 8-24, 9-20 and 10-20 from pages 111, 259 and 446 of csr79850-report-body.pdf

The applicant submitted Amendment 4 to the protocol on June 10, 2008 (*the trial dates from the start of the trial to the database cut-off for this submission were 01/18/06 – 03/28/11*) to exclude patients with documented history of T315I Bcr-Abl mutation from enrolling into the trial. As stated by the applicant, this exclusion criterion was added based on the lack of efficacy observed in patients with the Bcr-Abl T315I mutation. When the amendment was submitted 397 patients of a total of 570 were already enrolled. Of note the amendment did not preclude patients with

unknown mutation status to be enrolled. Four of the 31 patients positive for the T315I mutation at baseline were enrolled after the amendment.

Since this amendment was included in the Trial 3160A4-200-WW protocol, we recommend that the information regarding the amendment be included in Section 14.1 of the Bosulif® label (Clinical Studies).

Treatment Emergent Bcr-Abl Mutations: Samples for analysis of Bcr-Abl mutations were collected in 25% of patients during treatment in the pivotal trial. A new mutation (different from mutations detected at baseline) was detected in 28% of analyzed patients. T315I was the most frequent new mutation (7/15, 47%) in the second line CP population and V299L (4/9, 44%) was the most frequent in the third line CP population.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Pediatric patients

Safety and effectiveness have not been established in pediatric patients.

Renal impairment

Based on the lack of exposure-response relationships for efficacy and safety (Sections 2.2.4 and 2.2.5), within the studied dose range, dose adjustment for the 30% reduction in bosutinib clearance for patients with moderate renal impairment (based on NCI criteria: CrCl of 20-39 mL/min) are likely not necessary (Section 2.3.1). Bosutinib has not been studied in patients with CrCl < 20 ml/min.

Hepatic impairment

The applicant evaluated the relationship between hepatic impairment and exposure in Trial # 3160A4-1111-EU. Bosutinib C_{max} and AUC increased by approximately 2-fold in those with Child Pugh A, B and C hepatic impairment as compared to the healthy volunteers (Section 2.3.1). The applicant proposes a dose adjustment to 200 mg in patients with hepatic impairment. This dose adjustment appears reasonable based on bosutinib exposure.

2.3.3 What pregnancy and lactation use information is there in the application?

The safety and effectiveness of bosutinib have not been established in pregnancy and in lactating women.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for bosutinib were not assessed in a formal study.

Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

As a CYP substrate: CYP3A4 is the major isozyme responsible for the metabolism of bosutinib. The effect of a strong CYP3A4 inhibitor (ketoconazole) and an inducer (rifampin) on the PK bosutinib were evaluated in humans. The clinical trials are discussed in Section 2.4.3.

As a CYP inhibitor or inducer: Based on *in vitro* studies, bosutinib is unlikely an inhibitor or inducer of any of the major CYPs in humans at clinically relevant doses. Based on *in vitro* experiment # RPT-53488, bosutinib inhibited CYP 3A4, 2C19 and 2D6 with Ki values of 27, 27 and 10 μM, respectively. The I/Ki at the 500 mg dose is approximately 0.05 for CYP2D6 which is less than 0.1 and suggests that a clinically significant interaction is unlikely. Since CYP3A4 is expressed in the GI the R value for gut exposure was considered for the 500 mg dose and was approximately 1.1 [Rgut = 1+ ((500/250)/ (548) * 1000/27)], which is less than 11. CYP3A4 inhibition is unlikely in the gut or plasma. Based on *in vitro* experiment # RPT-79459, bosutinib did not exhibit mechanism based (NADPH dependant) inhibition of CYP 2C9, 2C19, 2D6 or 3A. Based on *in vitro* experiment # RPT-69677, bosutinib did not induce CYP 1A2, 2B6, 2C9, 2C19 or 3A4.

Based on pH dependant solubility: Bosutinib has pH dependant solubility, *in vitro*. The applicant evaluated the effect of a proton pump inhibitor (PPI) on bosutinib in humans as discussed in Section 2.4.6.

2.4.3 Is the drug a substrate of CYP enzymes *in vivo*?

Bosutinib is a CYP3A4 substrate, *in vitro*. Based on geometric mean ratios, up to a 5-fold increase in C_{max} and a 9-fold increase in AUC were observed when bosutinib was co-administered with ketoconazole as compared with bosutinib administered alone (**Table 10**). Rifampin decreased the Cmax of bosutinib by 86% and the AUC by 94% compared to that observed when bosutinib was dosed alone (**Table 10**). Therefore, the use of strong and moderate CYP3A4 inhibitors and inducers should be avoided. In addition, a PMR will be issued to require a trial with a moderate CYP3A4 inhibitor to identify an appropriate dose for concomitant administration.

The effect of multiple dose ketoconazole on single dose bosutinib was evaluated in Trial 3160A4-104-US (bosutinib 100 mg under fasting conditions). In addition, Trial 3160A4-1114-EU (bosutinib 100 - 600 mg given with a standardized high-fat meal) and the through QT Trial # 3160A4-105-US give additional information regarding the effect of ketoconazole on the PK of

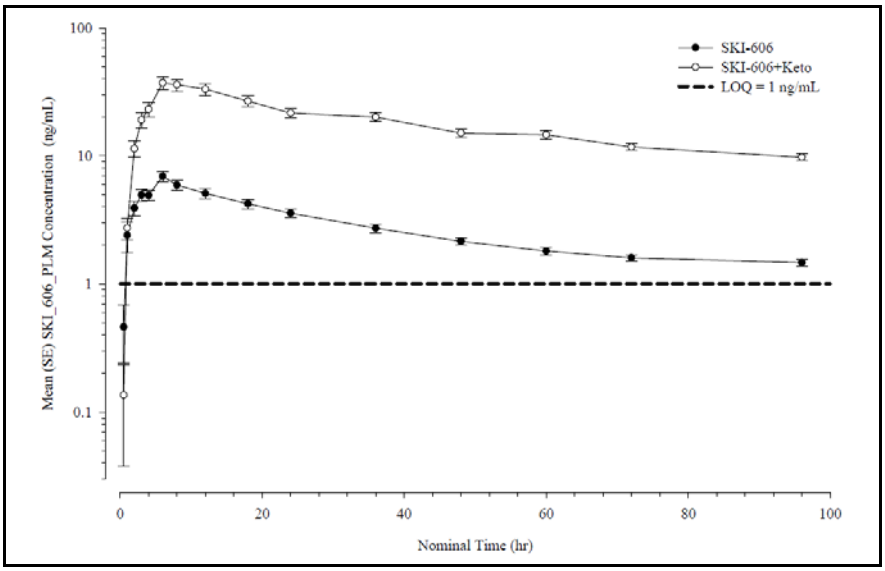
bosutinib. The effect of multiple dose rifampin on single dose bosutinib was evaluated in Trial 3160A4-1106-US (bosutinib 500 mg given with a standardized medium fat meal).

Table 10: Summary of Bosutinib Trials Evaluating the Effect of a Strong CYP3A4 Inhibitor and a Strong CYP3A4 Inducer

Trial	Dosing Regimen	Fold Change
Dedicated Ketoconazole DDI Trial 104-US (N=24)	Bosutinib 100 mg (over-night fast) ± Ketoconazole 400 mg dose	C_{max} - ↑ 5.2 fold AUC - ↑ 8.6 fold
Thorough QT Trial 105-US (N=60)	Part A: Single dose bosutinib 500 mg, placebo or moxifloxacin 400 mg Part B: Single dose bosutinib 500 mg or placebo with a medium-fat meal + ketoconazole 400 mg	C_{max} - ↑ 2.9 fold AUC - ↑ 6.5 fold
Ketoconazole DDI Trial 1114-EU (N=48)	Single dose bosutinib 100 – 600 mg on Day 2 with a high-fat meal ± ketoconazole 400 mg dose Days 1 - 5	C_{max} - ↑ 3.3 fold AUC - ↑ 7.3 fold (cross study comparison at 500 mg dose)
Dedicated Rifampin DDI Trial 1106-US (N=24)	Single dose bosutinib 500 mg Days 1 and 14 with a medium-fat meal ± Rifampin 600 mg Days 8-17	C_{max} - ↓ 7.3 fold AUC - ↓ 13 fold

Ketoconazole: **Trial 3160A4-104-US** was an open-label, randomized, 2-treatment period, 2-sequence crossover trial in 24 healthy volunteers (dedicated drug interaction trial). Bosutinib 100 mg oral capsule was dosed after an overnight fast of at least 10 hours on Day 1 of each period. Ketoconazole 400 mg oral tablets were dosed on Days -1 through 4. Based on the geometric mean, a 5.2-fold increase in C_{max} and an 8.6-fold increase in AUC were observed when bosutinib was co-administered with ketoconazole as compared with bosutinib administered alone. The mean bosutinib concentration time profile is shown in **Figure 15** and the PK is summarized in **Table 11**.

Figure 15: Mean Concentration versus Time Profile of Bosutinib in Plasma Following a Single 100 mg Oral Dose of Bosutinib Alone or in Combination with Ketoconazole (Keto) in Healthy Volunteers in Trial 3160A4-104-US



Source: Figure 7-1 from Page 29 in csr70105-report-body.pdf

Table 11: Summary of Bosutinib Pharmacokinetic Parameters Following a Single 100 mg Dose of Bosutinib Alone or in Combination with Ketoconazole in Healthy Volunteers in Trial 3160A4-104-US

PK Parameter	**Bosutinib Alone (N=24)**	**Bosutinib + Keto (N=24)**
C_{max} (ng/mL)	7.01 ± 3.17	38.36 ± 20.64
T_{max} (hr)[a]	6.00 (2.00 - 8.00)	6.00 (6.00 – 36.0)
$T_{1/2}$	46.19 ± 16.39	69.04 ± 29.05
AUCt (ng*h/mL)	233 ± 105	1694 ± 674
$AUC_{0-\infty}$ (ng*h/mL)	323 ± 138	2631 ± 791
Cl/F (L/h)	399 ± 272	42.41 ± 16.50
Pair-Wise Comparison Based on Least Square Geometric mean (LSGM)		
	C_{max} (ng/mL)	**$AUC_{0-\infty}$ (ng*h/mL)**
LSGM Ratio (90% CI)	5.2 (4.3 – 6.2)	8.6 (7.5 – 9.9)

Trial 3160A4-1114-EU was a randomized, double-blind, sponsor-unblinded, placebo-controlled, single-center, sequential-group trial performed in healthy adult volunteers assessing single bosutinib doses ranging from 100 – 600 mg co-administered with multiple doses of ketoconazole. Ketoconazole 400 mg was dosed using 200 mg oral tablets on Days -1 through 4. Bosutinib 100 mg oral capsules or placebo were used on Day 1 based on the group (100, 200, 300, 400, 500 and 600 mg) after a standardized high-fat breakfast on Day 1. When compared to exposures observed at a dose of 200 and 400 mg with a high-fat meal in trial 3160A1-103-EU a 6 fold increase in AUC was observed. This 6 fold increase can be attributed to the concomitant ketoconazole. The bosutinib PK is summarized in **Table 12**.

Table 12: Summary of Bosutinib Pharmacokinetic Parameters Following Single Ascending Oral Doses of Bosutinib in Combination with Ketoconazole in Healthy Volunteers in Trial 3160A4-1114-EU

	100 mg+ keto	200 mg+ keto	300 mg+ keto	400 mg+keto	500 mg+keto	600 mg + keto
N	6	6	6	6	6	6
C_{max} (ng/mL)	58.4 ± 13.3	120 ± 44.1	189 ± 69.8	242 ± 100	372 ± 107	426 ± 100
T_{max}[a] (h)	5.17 (3.00 - 6.00)	7.20 (3.00 - 12.17)	6.83 (1.00 - 12.00)	6.58 (5.83 - 8.00)	7.33 (5.88 - 8.03)	11.01 (6.02 - 23.93)
$t_{1/2}$ (h)	47.69 ± 5.41	52.45 ± 32.33	39.90 ± 5.43	41.98 ± 4.91	38.19 ± 4.81	41.62 ± 6.91
AUC_{0-24} (ng•h/mL)	876 ± 234	1950 ± 694	2850 ± 847	3730 ± 1460	5760 ± 1800	7080 ± 1640
AUC_{last} (ng•h/mL)	2740 ± 854	6390 ± 2110	8430 ± 1880	10300 ± 3730	16400 ± 5310	22200 ± 3630
AUC_{∞} (ng•h/mL)	2980 ± 802	6830 ± 2120	8600 ± 1860	10600 ± 3830	16800 ± 5510	23000 ± 4020
CL/F (L/h)	35.7 ± 9.83	31.8 ± 10.1	36.4 ± 8.59	45.6 ± 27.3	33.2 ± 13.1	26.8 ± 5.02
V_z/F (L)	2480 ± 773	2340 ± 1340	2150 ± 851	2800 ± 1790	1840 ± 881	1590 ± 276

Trial 3160A4-105-US was a single-dose, crossover, placebo and moxifloxacin controlled two part trial performed to assess the effect on QTc after administration of bosutinib (Section 2.2.6). Bosutinib was given as a single dose of five 100 mg capsules and the matching placebo was also given as 5 capsules with a standard medium fat meal (30% fat). Ketoconazole increased the C_{max} of bosutinib 2.9 fold and the AUC 6.5 fold (**Table 13**). The mean C_{max} decreased 4.9 fold for M2 and 4 fold for M5 when bosutinib was co-administered with ketoconazole, but the AUC was not significantly changed.

Table 13: Summary of Mean PK Parameters of Bosutinib after a Single Oral Dose of Bosutinib 500 mg Alone and in Combination With Multiple Oral Doses of Ketoconazole 400 mg in Healthy Volunteers Under Fed Conditions in Trial 3160A4-105-US

	Bosutinib Alone (N=56)	**Bosutinib + Ketoconazole (N=54)**
C_{max} (ng/mL)	114 ± 39.8	326 ± 77.2
T_{max} (hr)	5 (1.5 – 12)	8 (3 – 12)
T1/2 (hr)	22.3 ± 3.6	36.6 ± 9.6
AUC $_{0-\infty}$ (ng*hr/mL)	2330 ± 823	15200 ± 4480

Dr. Ping Zhao used Simcyp to simulate the effect of ketoconazole on bosutinib under fed conditions. The ketoconazole simulated Cmax and AUC ratios were similar to those observed in the thorough QT trial, but lower than those observed in the dedicated drug interaction trial 3160A4-104-US. Based on the simulation, moderate CYP3A4 inhibitors may increase the exposure of bosutinib 2 – 4 fold. Therefore, a PMR will be issued to identify the appropriate dose of bosutinib when used concomitantly with moderate inhibitors.

Table 14: Simcyp Simulations of the Effect of CYP3A inhibitors on Bosutinib PK

Inhibitor	Category	Cmax Ratio	AUC Ratio
Fluvoxetine	Weak	1.0	1.0
Fluvoxamine	Weak	1.0	1.0
Fluconazole	Moderate	1.6	2.0
Erythromycin	Moderate	2.5	3.8
Ketoconazole	Strong	3.6 (observed 2.9)	5.8 (observed 6.5)

Rifampin: **Trial 3160A4-1106-US** evaluated the effect of multiple oral doses of rifampin (Days 8 -17) on the PK profile of a single oral dose of bosutinib (Day 1 and 14) in healthy volunteers. The bosutinib dose was administered after a standardized medium-fat breakfast (30% fat) and rifampin 600 mg was dosed in a fasted state. Based on geometric mean, concomitant rifampin decreased the C_{max} and AUC of bosutinib by 86% and 94%, respectively, compared to bosutinib alone (**Table 15**).

Table 15: Summary of Bosutinib Pharmacokinetic Parameters Following a Single Oral Dose of Bosutinib Either Alone or in Combination with Rifampin in Healthy Volunteers in Trial 3160A4-1106-US

PK Parameter	Bosutinib Alone (N=24)	Bosutinib +Rifampin (N=24)
C_{max} (ng/mL)	112 ± 29.4	16.0 ± 6.69
T_{max} (hr)[a]	6.00 (2.00 - 12.00)	3.00 (1.00 - 6.00)
$T_{1/2}$	33.84 ± 7.65	20.37 ± 5.47
$AUC_{0-\infty}$ (ng*h/mL)	2740 ± 790	207 ± 45.9
Cl/F (L/h)	197 ± 57.3	2530 ± 555

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Based on *in vitro* studies, bosutinib is unlikely to inhibit or induce any major CYPs (Section 2.4.2). The inhibition or induction potential for CYPs has not been evaluated in humans.

2.4.5 Are other metabolic/transporter pathways important?

Bosutinib is a substrate and inhibitor of P-gp. Based on an *in vitro* study (RPT-71680) with Caco-2 cells, bosutinib is a substrate of P-gp with concentration dependant permeability (concentrations of 1, 10, and 100 μM assessed). It is an inhibitor of P-gp, with an IC_{50} of 2 μM *in vitro*. The I/Ki (using plasma C_{max} at the 500 mg dose) was approximately 0.5. No studies have been conducted with other transporter proteins.

2.4.6 Are there any other *in vivo* drug-drug interaction studies?

Bosutinib has pH dependant solubility *in vitro*. Bosutinib is highly soluble at or below pH 5 and the solubility reduces above pH 5. When a single 400 mg oral dose of bosutinib was co-administered with multiple oral doses of lansoprazole 60 mg, exposures to bosutinib decreased by 46% for C_{max} and by 26% for $AUC_{0-\infty}$ compared to when bosutinib was administered alone (Trial 3160A4-1108-US). The applicant recommended antacids should be considered as an alternative to proton pump inhibitors (PPIs) and administration times of bosutinib and antacids should be separated whenever possible.

The effect of pH on bosutinib was evaluated in an open-label, healthy volunteer trial (N=24). Single dose bosutinib 400 mg was dosed using 100 mg oral tablets either alone on Day 1 and with lansoprazole on Day 15. All doses were preceded by an overnight fast of at least 10 hours. A wash-out period of 14 days was used.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Bosutinib monohydrate can likely be classified as a BCS Class IV drug due to low solubility and low permeability characteristics (For more information refer to the Quality review by Dr Akm Khairuzzaman). It has not received official BCS classification/designation from the BCS Classification Committee within the FDA.

Solubility: Bosutinib has pH dependant solubility, *in vitro*. Bosutinib is soluble at or below pH 5 (based on solubility of 500 mg in 250 mL, 2 mg/mL) and the solubility reduces above pH 5 (**Table 16**).

Table 16: Solubility of Bosutinib in Different Aqueous Media at 37°C Across the pH Range of 1 - 8

Media	Solubility (mg/mL)
0.1 N Hydrochroloric Acid (pH 1.0)	11.03
0.01 N Hydrochroloric Acid (pH 2.0)	9.4
pH 4.5 USP Buffer	6.1
pH 5.0 USP Buffer	2.7
pH 6.8 USP Buffer	0.02
pH 8 USP Buffer	0.053

Permeability: Bosutinib is a substrate and inhibitor of p-gp, *in vitro* (See **Section 2.2.12**). Studies performed using Caco-2 cell monolayers indicated that bosutinib has low apparent permeability. Although the apparent permeability from the apical to the basolateral side is > 1 * 10^{-6} cm/sec, a low apparent permeability is expected due to efflux transporters. This is supported by the ratio of P_{app} (BA) to P_{app} (AB) which was > 1 as shown in **Table 17**.

Table 17: Permeability of Bosutinib in Caco-2 Monolayers Incubated for 2 Hours at 37°C

Bosutinib Conc (µM)	Treatment	Papp (AB) * 10^{-6} cm/sec (Mean ±SD)	Papp (BA) * 10^{-6} cm/sec (Mean ±SD)	Papp (BA)/ Papp (AB) Ratio
1	No Inhibitor	2.08 ± 0.24	14.0 ± 1.40	6.7
10	No Inhibitor	2.96 ± 0.25	14.3 ± 1.59	4.8
100	No Inhibitor	5.93 ± 0.18	6.87 ± 0.36	1.2
10	Verapamil	4.51 ± 0.43	7.94 ± 0.38	1.8
100	Verapamil	7.43 ± 0.93	6.23 ± 0.97	0.8

N=3 for Mean ±SD

2.5.2 What is the composition of the to-be-marketed formulation?

The commercial drug product is formulated as [redacted] (b) (4) 100 and 500 mg film coated tablets [redacted] (b) (4) The composition is summarized in **Table 18** below.

Table 18: Composition of Bosutinib 100 and 500 mg Film Coated Tablets

Ingredient	Quality Standard	% w/w (Uncoated Tablet)	Unit Dose *(mg/tablet)*	Unit Dose *(mg/tablet)*	Function
(b) (4)			**100 mg**	**500 mg**	
Bosutinib monohydrate	Pfizer [a]	(b) (4)	103.40 [b]	516.98 [c]	Active Ingredient
Microcrystalline cellulose	NF/Ph. Eur.				(b) (4)
Croscarmellose sodium	NF/Ph. Eur.				
Poloxamer	NF/Ph. Eur.				
Povidone	USP/Ph. Eur.				
(b) (4)					
Subtotal					
(b) (4)					
Total (Final Tablet)			**149.35**	**746.75**	

NA = Not applicable

Source: Module 2. description-and-composition.pdf

2.5.3 What moieties should be assessed in bioequivalence studies?

The parent compound, bosutinib, is the active moiety and should be assessed in bioequivalence studies. M2 and M5 are the major metabolites and the applicant has measured the exposures of these two metabolites in some of the trials. These metabolites are inactive.

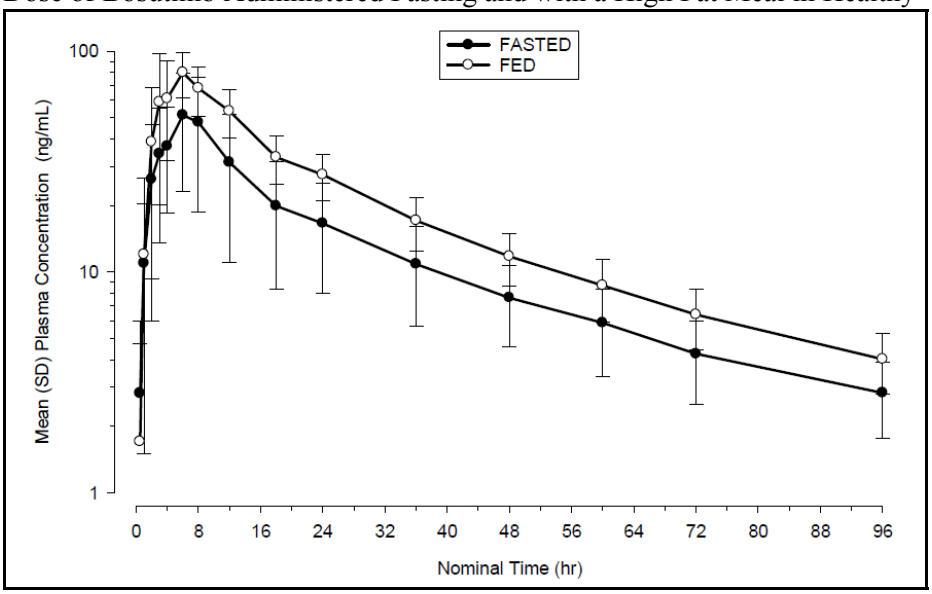
2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A high-fat meal increased bosutinib AUC 1.7-fold and C_{max} 1.8-fold compared with bosutinib administration under fasting conditions (**Table 19 and Figure 16**). The CV% was lower for bosutinib AUC when given with a high fat meal compared to when given under fasting conditions (22% verses 46%).

The effect of a high-fat meal on bosutinib exposures was assessed in an open-label, randomized, single-dose, 2-period crossover study in 24 healthy volunteers (Study # 3160A4-1110-US). A single 400 mg dose of bosutinib was administered under fasting conditions (A) versus five

minutes after the completion of an FDA recommended standard high-fat-meal (B) on Day 1 of each period. Bosutinib was given as a single dose of four 100 mg capsules using the phase 3 formulation (bioequivalent to the commercial tablets). Dosing in both periods was preceded by an overnight fast of at least 10 hours. PK samples were collected up to 96 hours post-dose.

Figure 16: Bosutinib Mean (±SD) Plasma Concentration-Time Profiles Following a Single Oral 400 mg Dose of Bosutinib Administered Fasting and with a High Fat Meal in Healthy Volunteers



Source: Figure 8-1 from Page 28 in csr78372-report-body.pdf

Table 19: Bosutinib Mean Pharmacokinetic Parameters Following a Single Oral Dose of 400 mg Bosutinib Administered Fasting or with a High Fat Meal in Healthy Volunteers

PK Parameter	**Fasting (N=24)**	**Fed (N=23)**
C_{max} (ng/mL)	55.9 ± 29.6	89.5 ± 24.1
T_{max} (hr)[a]	6.02 (3.02 - 8.02)	6.02 (2.02 - 8.02)
$T_{1/2}$	35.50 ± 11.24	31.93 ± 5.93
AUCt (ng*h/mL)	1160 ± 570	1860 ± 409
$AUC_{0-\infty}$ (ng*h/mL)	1310 ± 598	2060 ± 448
Cl/F (L/h)	369 ± 168	204 ± 45.2
Pair-Wise Comparison Based on Least Square Geometric mean (LSGM)		
	C_{max} (ng/mL)	**$AUC_{0-\infty}$ (ng*h/mL)**
LSGM Ratio (90% CI)	1.8 (1.4, 2.2)	1.7 (1.5, 1.9)

[a] Median (range)

Preliminary assessment of food effect with the earlier capsule formulation was performed in Study # 3160A1-103-EU (N=55). This was a single-dose, dose-escalation trial in healthy volunteers. A single oral dose of bosutinib 200 or 400 mg was given to volunteers after an overnight fast. In addition, single doses of 200, 400, 600 and 800 mg were administered 5 minutes after consuming an FDA standardized high-fat meal. Fifty five volunteers participated in this study.

A high-fat meal increased bosutinib AUC 2.3-fold and C_{max} 2.5-fold compared with bosutinib administration under fasting conditions at the 200 mg dose. A high-fat meal resulted in an AUC

increase of 1.5-fold and C_{max} increase of 1.4-fold at the 400 mg dose. The fold change seen at the 400 mg dose was similar to that seen in the food-effect study # 3160A4-1110-US.

Bosutinib was dosed with food in the pivotal and the supportive phase 3 trials. Bosutinib is proposed to be taken with food. The type of food is not specified in the proposed label and was not specified in the protocols for the pivotal and supportive efficacy trials. The variability seen is phase 3 may be similar to the variability that would be observed in patients post-approval.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Yes.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured appropriately in the clinical pharmacology and biopharmaceutics studies?

Yes. All the submitted clinical pharmacology related studies analyzed samples for bosutinib and most trials analyzed samples for the major metabolites M2 and M5. These metabolites are inactive.

2.6.2 Which metabolites have been selected for analysis and why?

Most trials analyzed samples for the major metabolites M2 and M5. The M2 and M5 metabolites are inactive.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Bosutinib is highly bound to human plasma proteins (94 – 99%). The total concentration of bosutinib in plasma was measured in the clinical trials. In Study # 3160A4-1111-EU, the plasma protein binding for bosutinib was similar in those with hepatic impairment and those with normal hepatic function. Therefore, the measurement of total concentrations in all trials is likely appropriate.

2.6.4 What bioanalytical methods are used to assess concentrations?

Bosutinib and its metabolites were measured using LC/MS/MS. The original bioanalytical method (Method LOG 2561-2908.0) developed and validated at the Wyeth Research (Collegeville, PA) only measured bosutinib concentrations. That method was updated at (Method TM.498) (b) (4) and the method was later broadened to an assay (Method TM.794) that included 2 metabolites, WAY-173607 (M5) and WAY-198760 (M2). Method TM.978 was a modification by (b) (4) that reduced the upper limit of detection for bosutinib and M5.

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The LC/MS/MS methods developed are discussed in section 2.6.4. The concentration ranges, correlation coefficients and inter assay precision and accuracy for the analytes are summarized for each method in **Table 20**.

Table 20: Summary of the LC/MS/MS Analytical Methods for Bosutinib and its Major Metabolites

Method	Analytes	Conc Range (ng/mL)	Correlation Coefficient	Inter-assay precision (CV%)	Inter-assay accuracy (CV%)
LOG 2561-2908.0	Bos	1 - 250	> 0.9919	5.7%	10%
TM.498	Bos	1 - 500	> 0.9984	5.1%	7.5%
TM.794	Bos	1 - 500	> 0.9979	4.6%	6.8%
	M2	0.5 - 200	> 0.9989	5%	3.2%
	M5	0.5 - 500	> 0.9967	6.2%	6.6%
TM.978	Bos	1 - 200	> 0.9973	NC	9%
	M2	0.5 - 200	> 0.9982	NC	4.7%
	M5	0.5 - 200	> 0.9978	NC	5.5%

NC – was not calculated due to insufficient number of replicates

Results for bosutinib, M2 and M5 were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. The mean bosutinib steady state C_{max} from multiple doses of 500 mg based on population PK was 255 ± 152 ng/mL. The mean C_{max} was < 200 ng/mL in the dose ranges analyzed in the single dose trials in healthy volunteers except the mean C_{max} was increased up to 420 ng/mL with the use of ketoconazole. In trial # 3160A4-1114-EU, where ketoconazole was used, the method with the upper limit of 500 ng/mL was used.

Replicates of QC samples were performed at low QC, medium QC and high QC concentrations that were within the calibration curve range. Mean inter-assay QC precision and accuracy were within 9.8 % and within 10.2% for bosutinib, within 5.6 % and within 9.4% for M5 and within 5.4% and within 8.7% for M2, respectively.

APPENDICES

3.1 Appendix 1 : Pharmacometrics Review

Summary of Findings

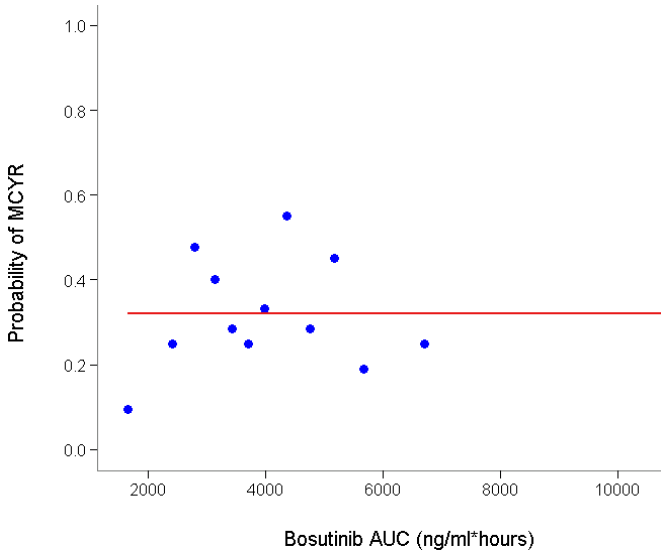
Key Review Questions

The purpose of this review is to address the following key questions.

Is there exposure-response for effectiveness?

No exposure-response relationship was observed for the primary endpoint of major cytogenetic response (MCYR) at 24 weeks (
Figure 17) in CML patients randomized to receive 500 mg bosutinib with dose interruptions/decreases for grade 3 adverse events. The efficacy analysis for Study 200 used patients that were imatinib resistant or imatinib intolerant and had evaluable PK data (266 subjects). The sponsor conducted a logistic regression analysis of the data and their final logistic model, indicates there is no increase in the probability of response with increasing exposure. Details of the logistic regression analysis and exposure metric calculation are discussed starting on pages 48 and 46.

Figure 17. Probability of major cytogenetic response at 24 weeks does not increase with increasing bosutinib exposure. Symbols represent the calculated probability for each exposure bin. The red line is the sponsor's model prediction.



(Source: Sponsor's Study Report PMAR-217, Figure 33.)

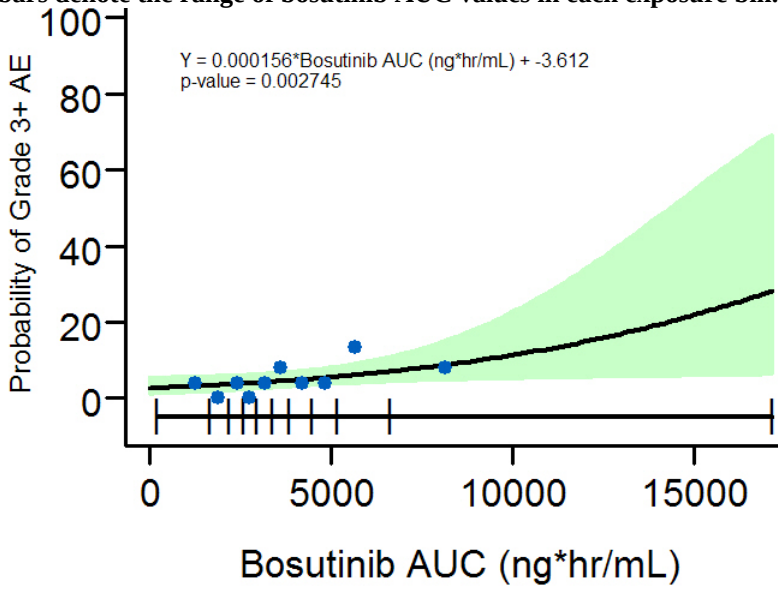
Are there exposure-response relationships for grade 3+ safety events that support reductions in 500 mg bosutinib dose?

No, while a population exposure-response relationship was observed for grade 3+ rash (Figure 18), predicted probability of the grade 3+ event at the mean AUC for the 400 and 500 mg doses (4087 ng•mL/hr and 5216 ng•mL/hr) do not suggest that reducing the starting dose (500 mg) would meaningful

reduce the rate of grade 3+ rash, on a population level. The current dosing regimen recommends dose interruption and reduction of the dose by 100 mg upon reinitiating therapy, for serious adverse events. Exposure-response relationships for rash were not evaluated on an individual level. No other significant relationships for grade 3+ safety events were identified. Details of this analysis and results are described below.

A logistic regression was applied to model the probability of having a grade 3 or higher adverse event (e.g. rash) versus bosutinib exposure (AUC) using data from both studies 200 and 3000. These clinical trials are described further starting on page 46.

Figure 18. Exposure-response for grade 3+ Rash. Text on the plot describes the logistic model equation and p-value for the coefficient on bosutinib exposure. Blue symbols are the probability of having grade 3+ rash by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. The solid line and green shaded area indicate the logistic model prediction and 90% confidence interval of the model prediction. Vertical bars denote the range of bosutinib AUC values in each exposure bin.



Grade 3+ diarrhea events did not increase with increasing bosutinib exposures (Figure 19). Whereas, the sponsor's analysis suggests there is an exposure-response relationship for grade 1+ diarrhea events (Figure 20). This may potentially be explained by the lower number of patients with grade 3+ events (n=68) compared with the grade 1+ events (n=567) creating more uncertainty in the analysis.

The primary differences between the reviewers and sponsor's analyses were.

- The reviewer's analysis evaluated grade 3 events or higher
- The reviewer's analysis calculated the individual bosutinib AUC values based on the time-averaged dose prior to the occurrence of the adverse event.
  $AUC_i = Dose_i/CL_i$
  where the subscript i refers to the individual, Dose refers to the time-average dose prior to the adverse event, and CL refers to bosutinib clearance.
  The sponsor's analysis used the mode dose for the individual regardless of when the adverse event occurred (see page 46).

Figure 19. No exposure-response relationship for grade 3+ diarrhea was observed. Blue symbols are the probability of having grade 3+ diarrhea by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

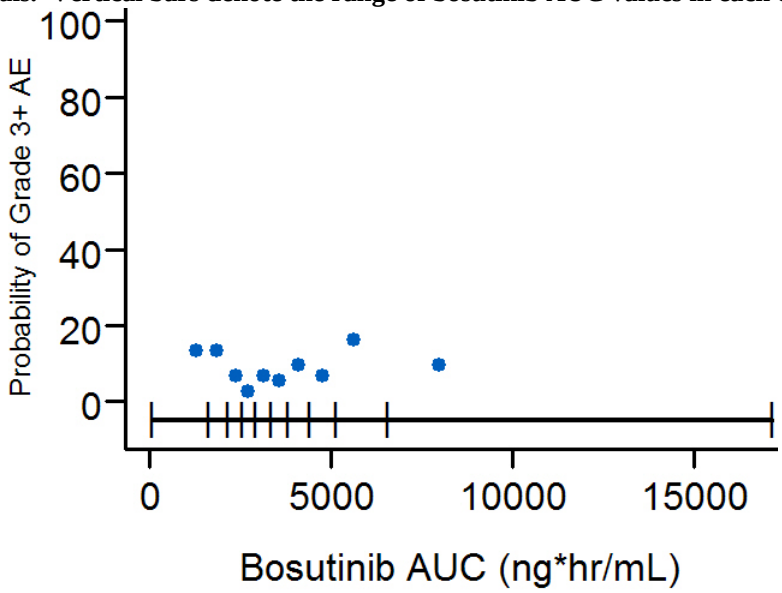
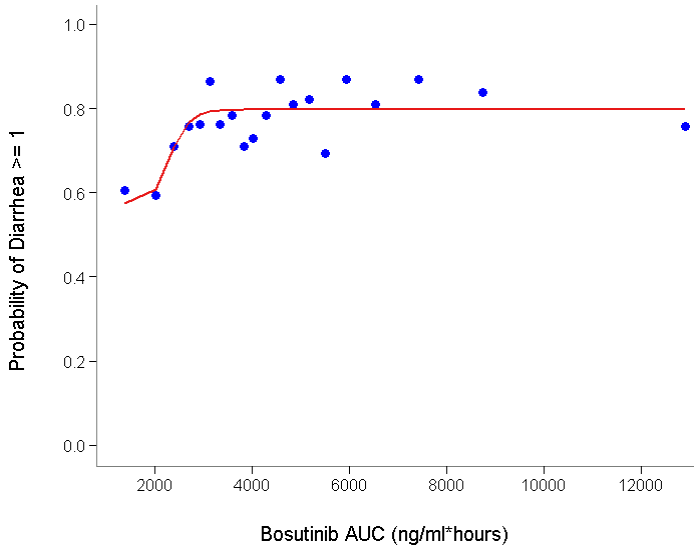


Figure 20. The sponsor's exposure-response analysis for diarrhea suggests an exposure-response relationship exists. Symbols are calculated probability of Diarrhea grade 1+ for each AUC bin for pooled data from Studies 200 and 3000. Solid lines are predictions of the best model fittings.



(Source: Sponsor's Study Report PMAR-217, Figure 5)

No exposure-response was observed for grade 3+ thrombocytopenia (Figure 21), neutropenia (Figure 21), nausea (Figure 22), vomiting (Figure 22), increases in aspartate aminotransferases (Figure 23), or increases in alanine aminotransferases (Figure 23). These results are consistent with the sponsor's results for grade 1+ events (see page 49).

Figure 21. No exposure-response relationships were observed for grade 3+ thrombocytopenia (left panel) or neutropenia (right panel). Blue symbols are the probability of having grade 3+ adverse event by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

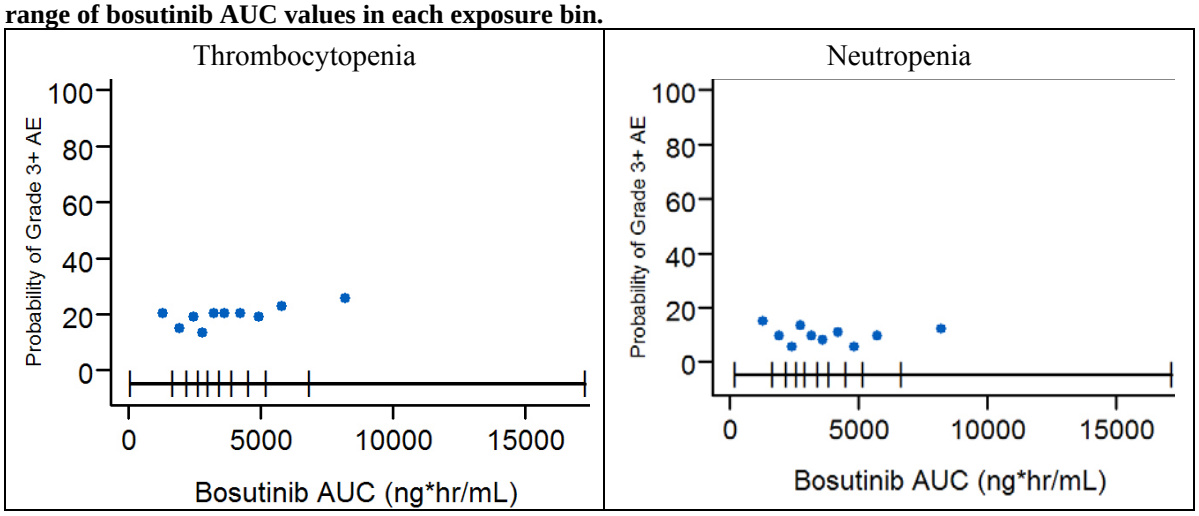


Figure 22. No exposure-response relationships were observed for grade 3+ nausea (left panel) or vomiting (right panel). Blue symbols are the probability of having grade 3+ adverse event by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.

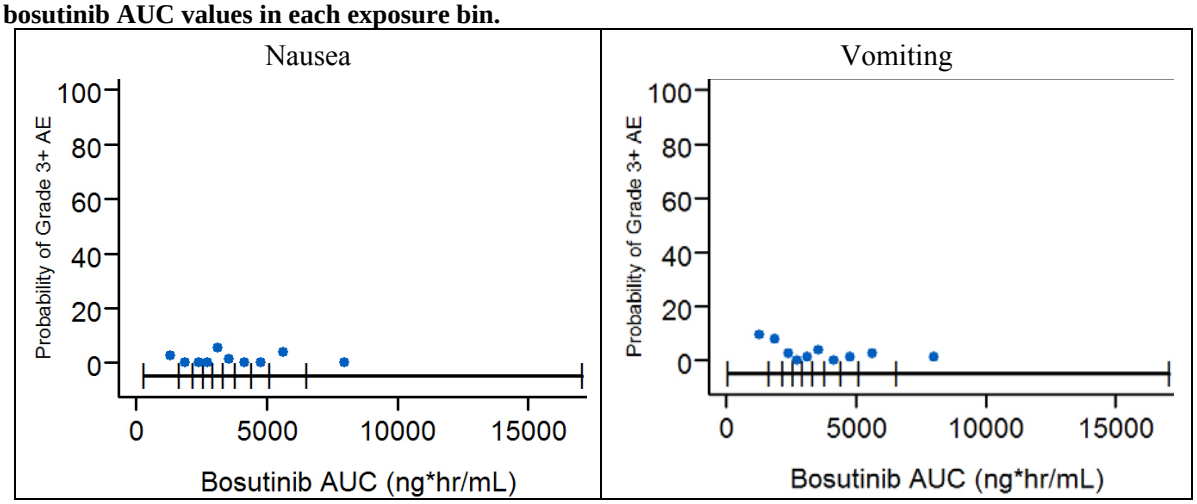
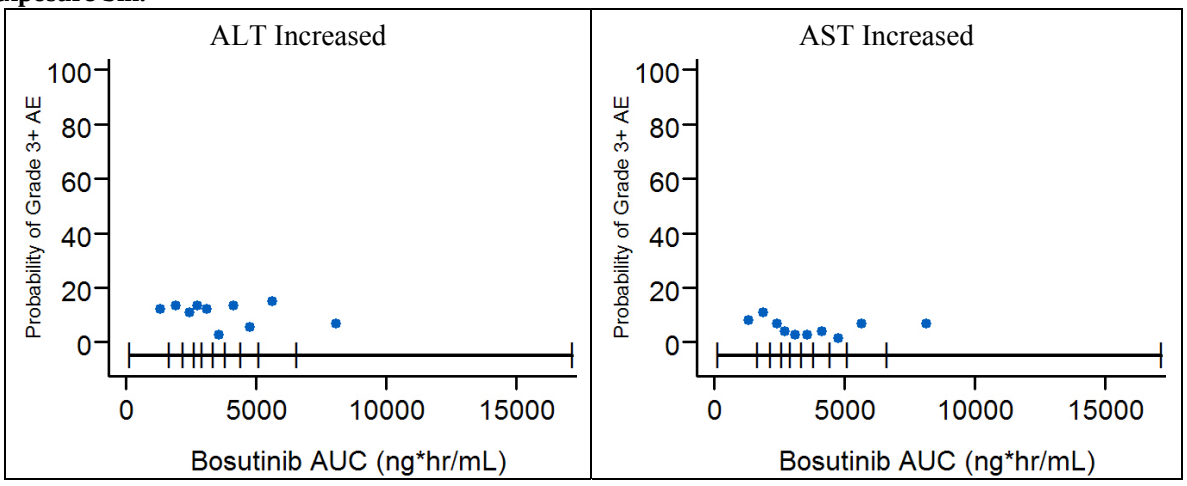


Figure 23. No exposure-response relationships were observed for grade 3+ increases in alanine aminotransferases (ALT, left panel) or aspartate aminotransferases (AST, right panel). Blue symbols are the probability of having grade 3+ adverse event by exposure bins. Ten exposure bins were assigned, each containing data from 75 individuals. Vertical bars denote the range of bosutinib AUC values in each exposure bin.



Do the exposure response relationships for efficacy and safety support the proposed dose adjustments for safety events?

Yes, the exposure-response for effectiveness plot (
Figure 17) supports reducing the dose for safety events. The mean AUC for the 400 and 500 mg doses are 4087 ng•mL/hr and 5216 ng•mL/hr, respectively. Based on
Figure 17, dose decreases to 400 mg for safety events are not expected to reduce the effectiveness of bosutinib.

Can the population PK data for creatinine clearance provide reasonable assessment of bosutinib clearance in patients with severe renal impairment or ESRD?

No. Variability in the PK data did not permit a reliable assessment of the effect of creatinine clearance on the CL of bosutinib. See page 57 for further details on the evaluation of CRCL as a covariate on bosutinib CL.

RECOMMENDATIONS

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed this application and finds it acceptable.

LABEL STATEMENTS

No labeling revisions are to be made based on this review.

PERTINENT REGULATORY BACKGROUND

Bosutinib is a new molecular entity of the tyrosine kinase inhibitor class. Pfizer is submitting this new

drug application seeking approval for the treatment of chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML) in patients with resistance or intolerance to prior therapy (2nd- and 3rd-line therapy).

RESULTS OF SPONSOR'S ANALYSIS

CLINICAL TRIALS

The sponsor used data from trial 3160A4-200-WW (Trial 200) to evaluate their exposure-response for effectiveness. Exposure response for safety was evaluated using data from both Trial 200 and trial 3160A4-3000-WW (Trial 3000). These studies are described in brief below.

Trial 200

This was a Phase 1/2 open-label, 2-part study in subjects with Ph+ leukemia. Part 1 was a dose escalation to determine the dose for Part 2. Part 2 was an efficacy study at the selected Phase 2 dose. The primary goal was to determine the safety, tolerability, MTD, PK, PD, and efficacy in subjects with chronic phase and advanced phase Ph+ leukemias. In part 1 fixed doses of 400 mg, 500 mg, and 600 mg bosutinib were studied. The dose of 500 mg was chosen for Part 2. A total of 288 patients were to receive bosutinib as 2nd-line therapy, 118 patients were to receive bosutinib as 3rd-line therapy, 164 patients were enrolled with advanced phase leukemias. Once-daily treatment would last until disease progression, unacceptable toxicity, or withdrawal of consent.

Trial 3000

This was a Phase 3 randomized, open-label trial to compare the efficacy (rate of complete cytogenetic response at 1 year) of 500 mg QD bosutinib versus 400 mg QD imatinib in subjects with chronic phase CML. A total of 250 and 252 patients were randomized to the bosutinib and imatinib treatment arms. Secondary aims were to compare major molecular response at 1 year, duration of complete cytogenetic response, complete hematologic response, time to transformation to advanced phase and blast phase; to assess the population PK; to assess the comparative safety of bosutinib versus imatinib. Once-daily treatment would last until completion of 8 years or early discontinuation due to treatment failure, unacceptable toxicity, death, or withdrawal of consent.

The sponsor used this trial to evaluate the efficacy and safety of bosutinib as first-line therapy in CML patients. As the population of patients in Trial 3000 is different from those that are seeking the indication in (imatinib resistant patients, 2nd- and 3rd- line therapy), efficacy data from this trial were not used in the evaluation of exposure-response for effectiveness. However, Trial 3000 data were used in the evaluation of the exposure-response relationships for adverse events.

POPULATION PK OF BOSUTINIB IN CML PATIENTS:

Pharmacokinetic data from three studies (3160A1-100-US, 3160A4-200-WW, and 3160A4-3000-WW) in patients with CML were combined to evaluate the population PK of bosutinib.

The sponsor described the PK of bosutinib in CML patients with a linear 2-compartment model with first-order absorption. Estimates of bosutinib PK parameters for the sponsor's final model are shown in Table 21.

Table 21. Bosutinib PK parameter estimates for the sponsor's final population PK model.

	Units	Parameter	se%	IIV (%)	se%	eta p-value	eta shrinkage
CL/F	L/h	120	5.33	59.89	11.62	0.432	12.4
V2/F	L	4917	2.48	47.69	10.21	0.014	18.6
Q/F	L/h	56.38	10.61				
V3/F	L	388300	27.97	211.4	15.51	3.523E-16	54.0
KA	1/h	0.6095	5.346	104.4	9.543	0.00240	24.7
LAG	h	0.8708	1.823				
DOSEonF		1.247	17.6				
Proportional error	ratio	0.297	7.65	Dose <= 100 mg			
Additive error	ng/ml	8.11	11.7	Dose > 100 mg			
Proportional error	ratio	0.320	2.59				
Correlation CL-V2		0.689	10.4				

(Source: Sponsor's Population PK Modeling Report, PMAR-00219, Table 9)

Inter-individual variability was large with CV% between 59% and 69% for observed and simulated concentrations (Table 22).

Table 22. Bosutinib concentrations at 2, 6, and 24 hr for 500 mg QD bosutinib.

		Bosutinib concentration (ng/ml)				
TAD	Data	mean	sd	CV	min	max
2h	Observed	125.0	74.1	59.3	2.17	593
	Simulated	147.7	96.5	65.4	0	1159
6 h	Observed	175.6	101.3	57.7	1.25	1200
	Simulated	162.2	102.8	63.4	0	1474
24 h	Observed	98.7	59.5	60.3	1.69	470
	Simulated	100.2	68.9	68.8	0	1112

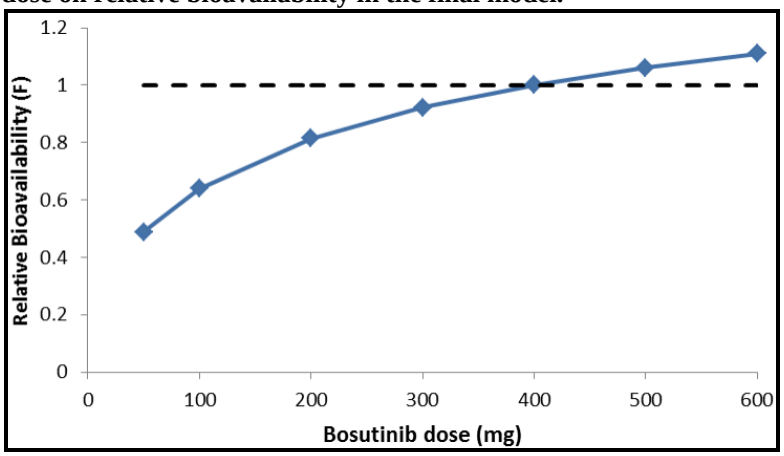
(Source: Sponsor's Study Report PMAR-219, Table 10)

None of the tested covariates (age, weight, BSA, BMI, sex, race, protocol, ECOG, creatinine clearance, total bilirubin, ALT, AST, and albumin) were included in the final PK Model. The effect of drug administration in the fed versus fasted state was not tested.

Bilirubin and creatinine clearance both had a statistically significant affect on the minimum value of the objective function, however they were not included in the final model because the sponsor felt these factors did not meet "the stated criteria for inclusion in the model as consistent with a parsimonious and clinically relevant model".
Relative bioavailability was dose-dependent in the PK model. Higher doses produced greater bioavailability. This dose-dependent effect is described in the model by a logit function to keep

bioavailability positive and centered on a value of 1 (for the 400 mg dose). The fitted relationship is shown in Figure 24.

Figure 24. Effect of dose on relative bioavailability in the final model.



The final population PK model was used to simulate individual estimates of bosutinib AUC, C_{max}, t_{max}, and C_{min} for exposure-response analyses with metrics of efficacy and safety.

> "The post-hoc PK parameters for the final PK model were estimated using the POSTHOC option of the $ESTIMATION step of NONMEM. These were merged with a database of the most frequent (mode) dose used in each patient and sample times from 0 to 24 h at 0.5 h intervals representing the inter-dose interval. The final model was used to estimate C_{max}, t_{max} and C_{min} from the simulated individual bosutinib concentration-time curves. AUC was estimated as $Dose_i/CL_i$, where the subscript i represents the individual values of mode dose and post-hoc clearance."

(Source: Sponsor's Study Report PMAR-217, page 17)

Reviewer's Comments: The sponsor's population PK model is acceptable for fitting the observed PK data and capturing each individual's PK parameters. However, the sponsor's final model does not account for the effect of weight or creatinine clearance on the central volume of distribution and clearance (see page 54). Therefore, using this model to extrapolate to a new population is not be appropriate. The availability of individual PK parameter values makes its use for characterization of individual bosutinib exposure reasonable.

EXPOSURE-RESPONSE ANALYSES FOR EFFICACY AND SAFETY

Methodology

The sponsor used both graphical and modeling analyses to evaluate exposure-response relationships. Observed probabilities of events were defined as the number of events/number of observations and were plotted for each exposure bin and plotted adjacent the best fit model. Exposure metrics (AUC, C_{max}, C_{min}) were grouped to give an approximately equal number of observations in each bin. The number of bins chosen was selected to give a minimum of 20 observations in each bin.

Both logistic and ordered-logistic regression models were used to characterize exposure-response relationships for efficacy and safety metrics. Five model structures (constant, linear, log-linear, E_{max} and sigmoidal E_{max}) were evaluated for each exposure metric and efficacy/safety metric based on the

minimum value of the objective function (MVOF). For each model the following logit function was used to describe probability (P) as a function of the log odds (LO):

$$P = \frac{e^{LO}}{\left(1 + e^{LO}\right)}$$

The log odds for each model are described by Equation 1 through Equation 5.

Equation 1. Constant Model

$$LO = Constant$$

Equation 2. Linear Model

$$LO = Constant + Slope \cdot AUC$$

Equation 3. Log-Linear Model

$$LO = Constant + Slope \cdot LOG\left(AUC\right)$$

Equation 4. E_{max} Model

$$LO = Constant + \frac{E_{Max} \cdot AUC}{AUC_{50} + AUC}$$

Equation 5. Sigmoid E_{max} Model

$$LO = Constant + \frac{E_{Max} \cdot AUC^{\gamma}}{AUC_{50}{}^{\gamma} + AUC^{\gamma}}$$

Reviewer's Comments:The sponsor's approach to evaluating exposure-response for ordinal and binary data is acceptable. The reviewer's analysis evaluates the grade 3/4 safety events since this is the grade of event that was used to recommend reducing the dose in Trial 200 and Trial 3000.

Analysis for Efficacy:

Based on
Figure 17, the sponsor concluded "there was no evidence of an exposure-response relationship for Major Cytogenetic Response at 24 weeks."

Reviewer's Comments:The sponsor's analysis of exposure response for effectiveness is reasonable. While a clear exposure-response relationship for major cytogenetic response at 24 weeks was not observed in the studied exposure range, the study met its primary efficacy endpoint. Thus, an exposure response may exist, and the flat response curve observed in
Figure 17 *potentially means that the exposures achieved were in the plateau of effect.*

Analysis for Safety:

The safety analysis used pooled data for the patients in Studies 200 and 3000 with evaluable PK data. Ordinal safety metrics (Table 23) were examined as listed below for the exposure metrics AUC, $C_{max,}$ and C_{min} (graphical analysis only for C_{min}).

Table 23. Summary of Safety Metrics

Ordinal

Adverse event	*Grade 0*	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total*
Diarrhea	172	332	184	60	1	749
Thrombocytopenia	533	38	30	94	54	749
Rash	518	135	58	36	2	749
Nausea	447	221	71	10	0	749
Vomiting	490	161	78	20	0	749
Alanine transaminase (ALT)	593	32	49	65	10	749
Aspartate transaminase (AST)	620	52	41	33	3	749
Neutropenia	630	11	23	56	29	749

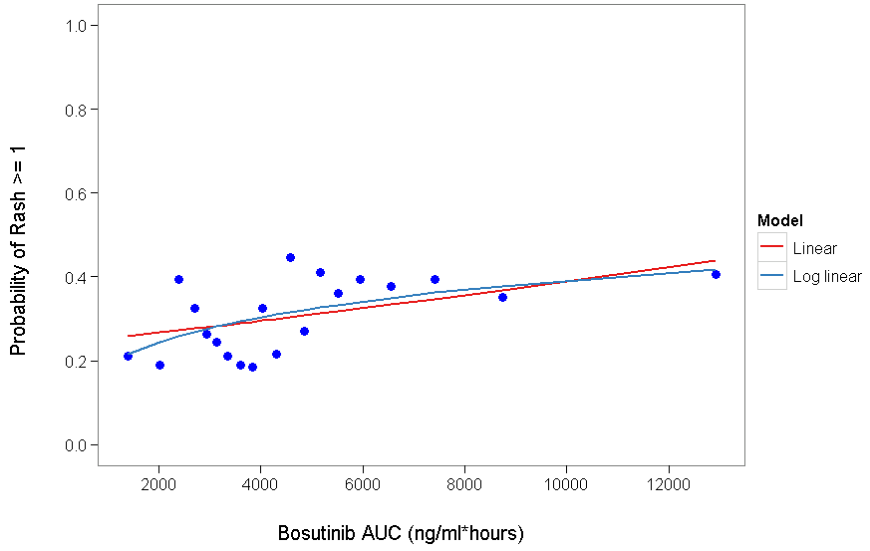
Continuous

Adverse event	*unit*	*mean*	*SD*	*min*	*max*	
Alanine transaminase (ALT)	U/L	159.6	698.9	0	16554	749
Aspartate transaminase (AST)	U/L	96.5	340.8	0	5760	749

(Source: Sponsor's Study Report PMAR-217, Table 2)

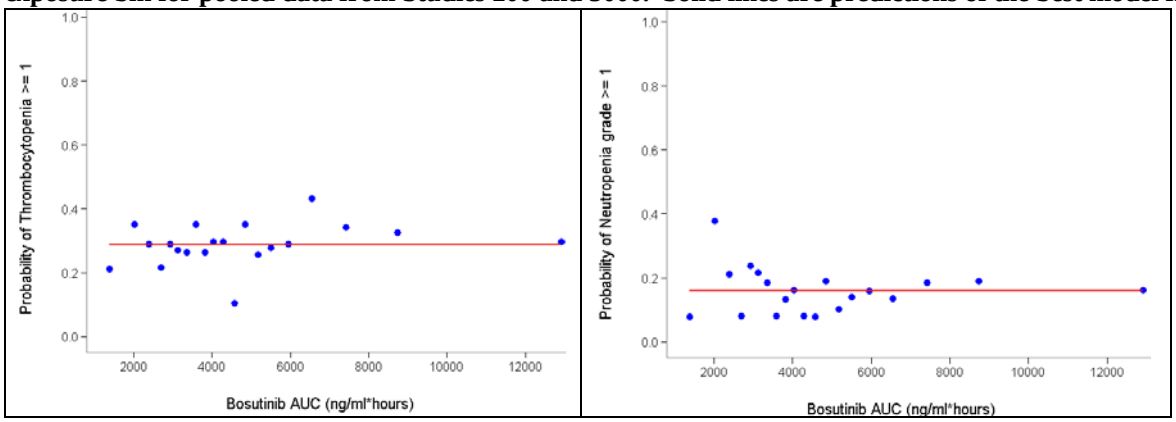
The incidence of an adverse event was defined as presence or absence of any adverse event, regardless of its CTC grade (i.e. grades >= 1). Using graphical analyses and logistic regressions the sponsor concluded exposure-response relationships for safety were found for diarrhea (Figure 20) and rash (Figure 25), but not for thrombocytopenia (
Figure 26, left panel), neutropenia (
Figure 26, right panel), nausea (Figure 27, left panel), and vomiting (Figure 27, right panel). Trends were identified for normalized AST and ALT values with increasing bosutinib AUC but were not considered to be clinically meaningful (**Figure 28**). No exposure response relationships were identified for the Grade of AST or ALT increase (**Figure 28**).

Figure 25. Exposure-response analyses for rash. Symbols are calculated probability of rash grade >= 1 for each AUC bin for pooled data from Studies 200 and 3000. Solid lines are predictions of the two best model fittings (log-linear and linear). The slopes of both lines are significantly different to zero (se% < 51.2).



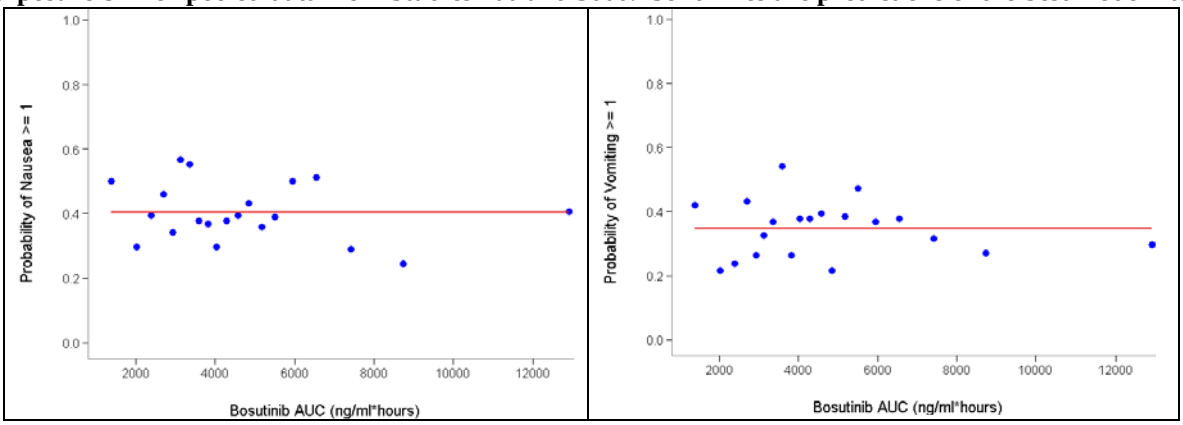
(Source: Sponsor's Study Report PMAR-217, Figure 11)

Figure 26. Exposure-response analyses for hematological adverse events, thrombocytopenia (left panel) and neutropenia (right panel). Symbols are calculated probability of the adverse event, grade >= 1, for each exposure bin for pooled data from Studies 200 and 3000. Solid lines are predictions of the best model fitting.



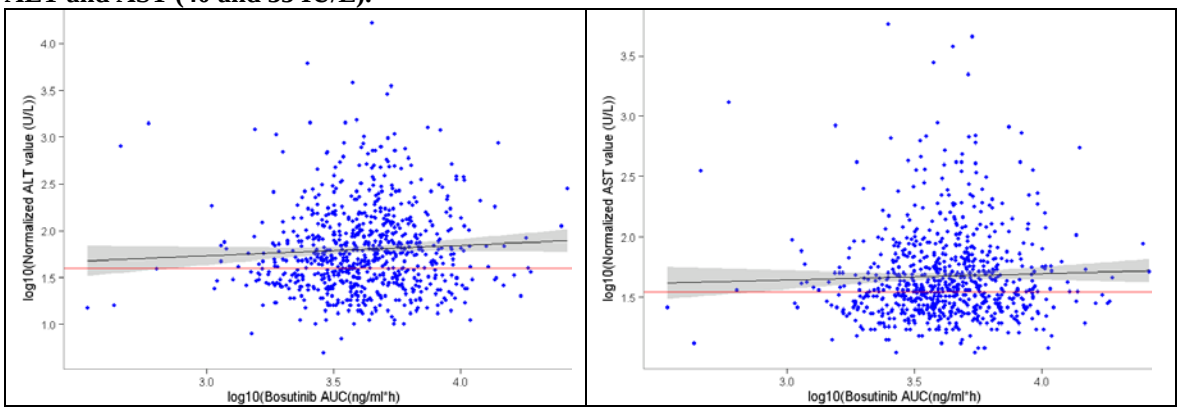
(Source: Sponsor's Study Report PMAR-217, Figures 8 & 32)

Figure 27. Exposure-response analyses for secondary gastrointestinal adverse events, nausea (left panel) and vomiting (right panel). Symbols are calculated probability of the adverse event, grade >= 1, for each exposure bin for pooled data from Studies 200 and 3000. Solid lines are predictions of the best model fitting.



(Source: Sponsor's Study Report PMAR-217, Figures 26 & 29)

Figure 28. Exposure-response analyses for normalized liver transaminase values, ALT (left panel) and AST (right panel). Symbols are observed data. Black line is line of best fit for linear regression with the confidence intervals for the line shown as a grey ribbon. Red line is the upper limit of the reference values for ALT and AST (40 and 35 IU/L).



(Source: Sponsor's Study Report PMAR-217, Figures 15 & 21)

Based on these safety analyses, the sponsor concluded:

- "An exposure-response relationship was identified for diarrhea severity which could be described by an E_{max} exposure-response relationship. The predicted probability of the incidence of diarrhea ranged from 0.575 for the lowest bosutinib AUC bin (1384 ng/ml*h) to 0.797 for the highest bosutinib AUC bin (12919 ng/ml*h)." **(See Figure 20)**
- "There was evidence to support a weak exposure-response relationship for the incidence of rash. The relationship between the probability of the incidence of rash and bosutinib AUC could be described by a log-linear model. The predicted probability of rash was 0.216 for the lowest AUC bin (1384 ng/mL•hr) and 0.419 at the highest AUC (12919 ng/mL•hr)." **(See Figure 25)**
- "There was no evidence to support an exposure-response relationship the incidence of thrombocytopenia adverse events. The data could be described by a constant probability model. The predicted probability of the incidence of thrombocytopenia was 0.288 regardless of bosutinib exposure." **(See**
- **Figure** 26**, Left Panel)**
- "There was no evidence to support an exposure-response relationship for the incidence of neutropenia. The data could be described by a constant probability model with an incidence of neutropenia of 0.158 regardless of bosutinib exposure." **(See**
- **Figure** 26**, Right Panel)**
- "There was no evidence to support an exposure-response relationship for nausea incidence. The data could be described by a constant probability model. The predicted probability of the incidence of nausea was 0.403 regardless of bosutinib exposure." **(See Figure 27, Left Panel)**
- "There was no evidence to support an exposure-response relationship for vomiting incidence. The data could be described by a constant probability model. The predicted probability of the incidence of vomiting was 0.346 regardless of bosutinib exposure." **(See Figure 27, Right Panel)**
- "There was no evidence to support an exposure-response relationship for the incidence of alanine transaminase (ALT) adverse events. The data could be described by a constant probability model. The overall probability of the incidence of an ALT adverse event was 0.208 regardless of bosutinib exposure." **(See**
- **Figure** 28**, Left Panel)**
- "There was no evidence to support an exposure-response relationship for the incidence or severity

of aspartate transaminase (AST) adverse events. The data could be described by a constant probability model. The overall probability of the incidence of an AST adverse event was 0.172 regardless of bosutinib exposure." **(See**

- **Figure** 28**, Right Panel)**

Reviewer's Comments:The sponsor's safety analysis uses a reasonable modeling approach. However, the logistic regression modeling does not address whether events that lead to dose decreases (grade 3 or higher) increase with increasing exposure. The reviewer's analysis (see page 59) uses a similar logistic regression analysis on grade 3 or higher adverse events for the same types of events shown above.
The sponsor's exposure-metric in the safety analysis does not consider dose interruptions/reductions due to adverse events. The metric simply uses the dose that the patient took the most of to calculate the AUC value. The reviewer's analysis calculated the AUC for each individual using the time-averaged dose prior to the occurrence of the adverse event of interest. See page 41 for the reviewer's analysis of the safety data.

Reviewer's Analysis

INTRODUCTION

The sponsor's analysis of exposure-response relationships for safety events evaluates the probability of having a grade 1 or higher (1+) adverse event. However, grade 3 or higher (3+) adverse events are relevant for dosing recommendations. This reviewers analysis is aimed at determining whether an exposure response relationship exists for the probability of having grade 3+ adverse events (thrombocytopenia, neutropenia, diarrhea, rash, increased liver transaminase levels).

OBJECTIVES

Analysis objectives are:

1. Review sponsor's population PK analysis to support model estimates for exposure-response analysis.
2. Conduct exposure-response for grade 3+ adverse events including thrombocytopenia, neutropenia, diarrhea, rash, and increased liver transaminase levels.
3. Evaluate whether range of creatinine CL values available to the population PK analysis and the model results are sufficient to waive a dedicated phase 1 study to evaluate the effects of severe renal impairment and ESRD on bosutinib PK.

METHODS

Data Sets

Data sets used are summarized in Table 24.

Table 24. Analysis Data Sets

Study Number	Name	Link to EDR

Software

NONMEM VI (Icon, Ellicott City, MD) was used to review the sponsor's Population pharmacokinetic analysis and test model covariates. The statistical software R (www.r-project.org) and S-plus (Tibco, Palo Alto, CA) were used to generate all plots.

Models

No original models were developed and applied as part of this review. Evaluation of the sponsor's final population PK model is discussed on page 57.

RESULTS

Population PK

Population PK Model

The sponsor's population PK model was reviewed to determine if the structural and covariate models for bosutinib were appropriate. The sponsor's final model was run on their datasets. Goodness-of-fit plots were generated to assess the structural model. Plots of between-subject variability versus covariates were used to determine if certain covariate effects should be included in the model.

The goodness of fit plots in Figure 29 indicate the sponsor's final PK model reasonably describes the central tendency of the bosutinib data. Shrinkage of the inter-individual variability of CL, in the final model, is 12.4%. Whereas for the central and peripheral volume of distribution parameters the values were 18.6% and 54.0%. Shrinkage was 24.7% for the first-order absorption rate-constant.

Figure 29. FDA-generated, goodness-of-fit plots for the sponsor's final bosutinib population PK model.

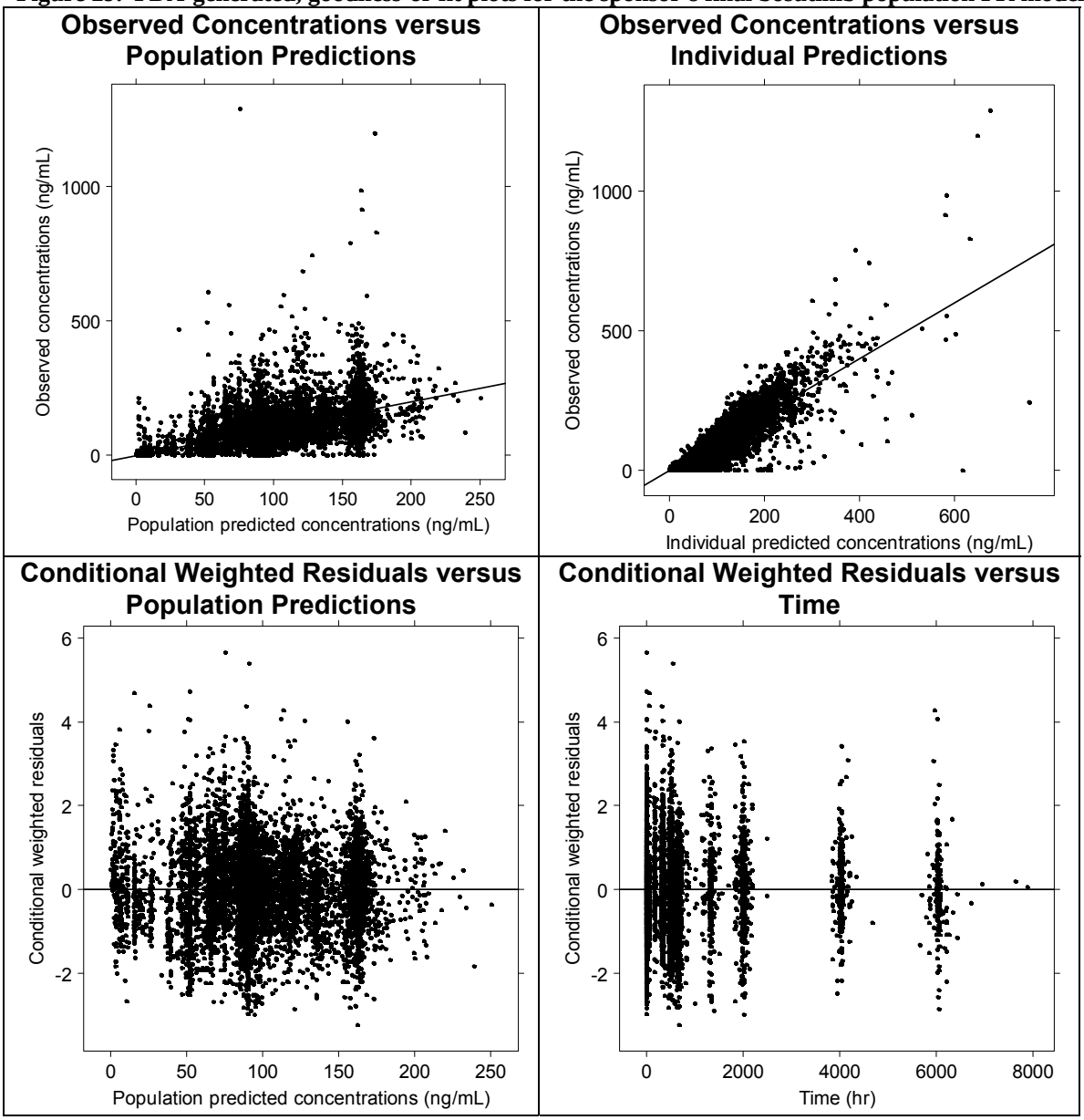


Figure 30 showed that age and albumin did not meaningfully alter the clearance of bosutinib. Whereas creatinine clearance and weight are potential covariates of CL.

Figure 30. Plots of inter-subject variability for bosutinib CL against potential continuous covariates.

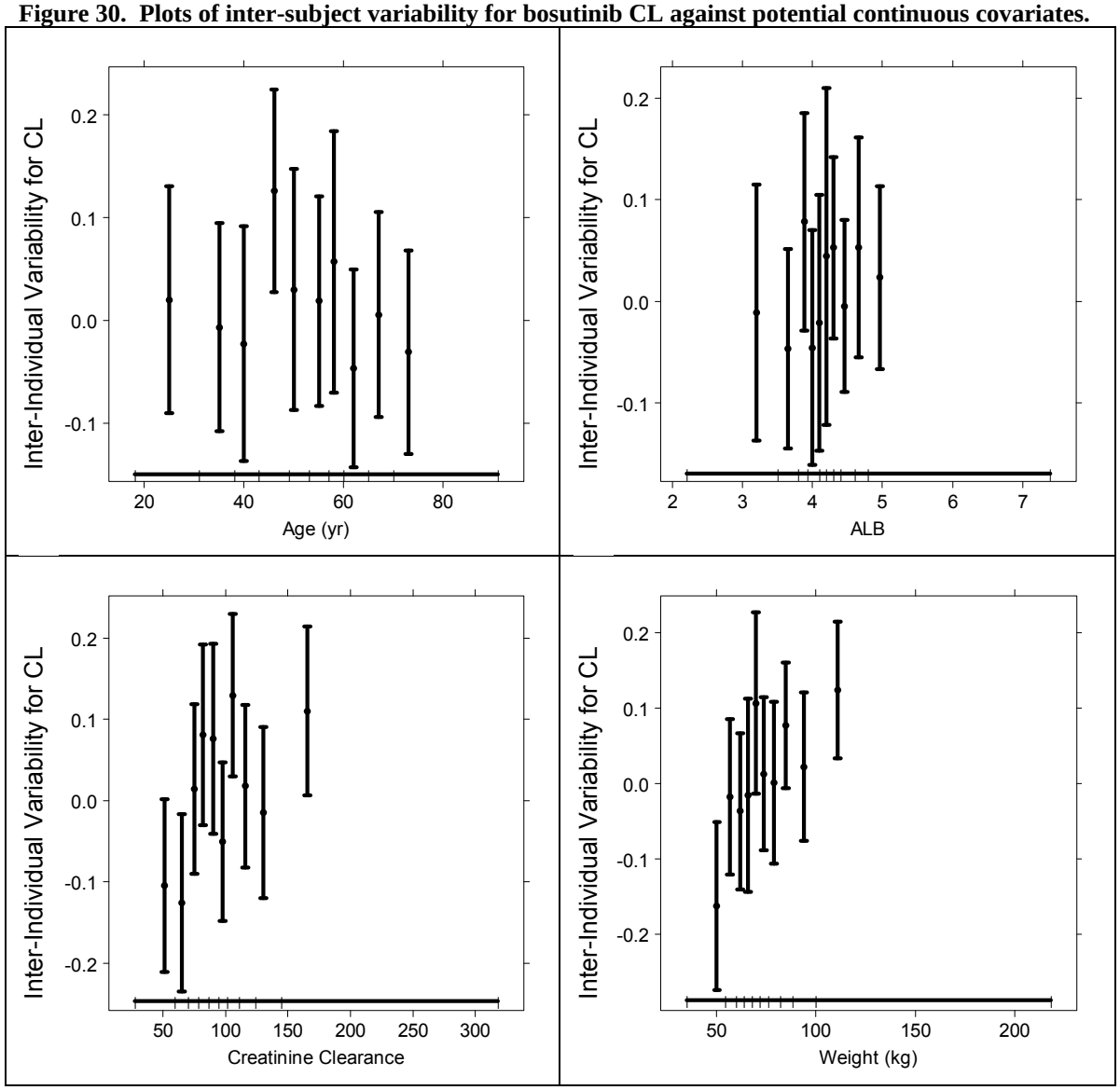
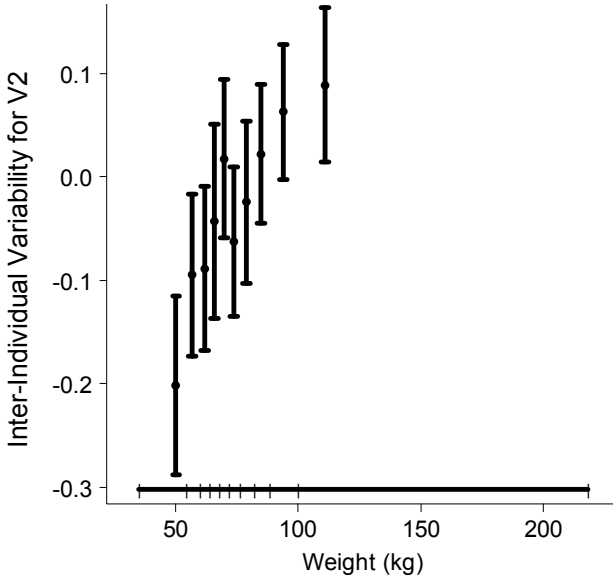


Figure 31 shows that weight is also a potential covariate on the bosutinib central volume of distribution (V2).

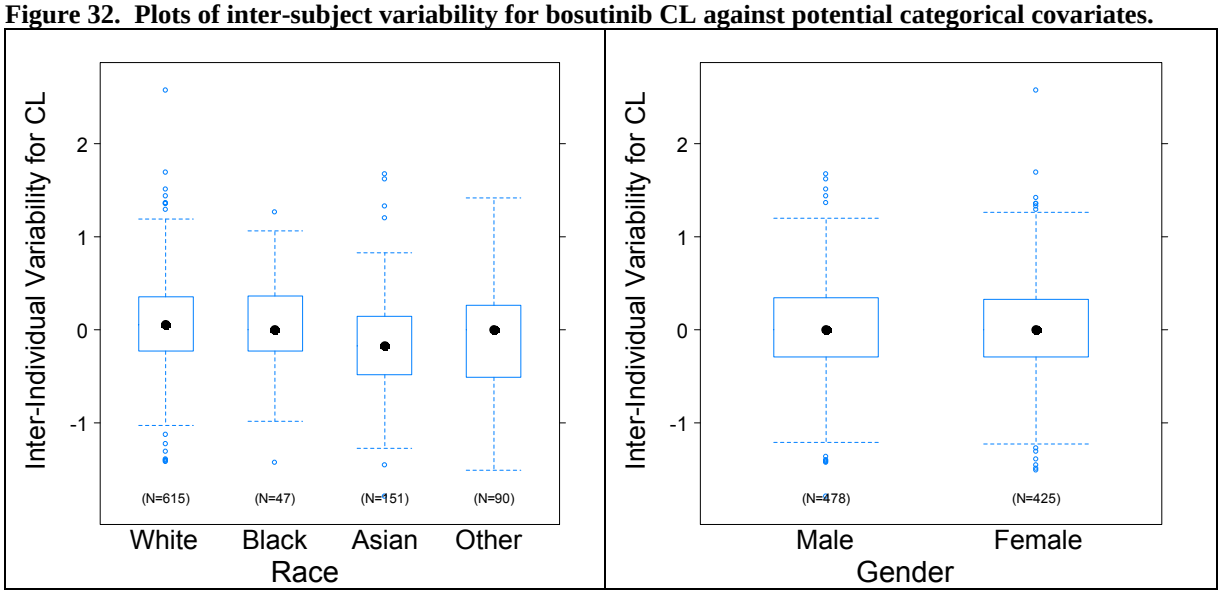
Figure 31. Distribution of inter-subject variability for bosutinib central volume of distribution (V2) is correlated with weight.



These plots raise the question: Why were weight and/or creatinine clearance excluded from the final population PK model as covariates of bosutinib clearance and volume of distribution? An attempt to address this question is described on page 57.

Figure 32 shows that race and gender did not impact the CL of bosutinib.

Figure 32. Plots of inter-subject variability for bosutinib CL against potential categorical covariates.



Effect of creatinine clearance on bosutinib exposure

The aim of this review with regards to the PK is to establish if the population PK analysis can be used to estimate the clearance in patients with severe renal impairment (creatinine clearance < 20 mL/min using the National Cancer Institute criteria).

Since 1) the population PK model did not include creatinine clearance (CRCL) as a covariate and 2) bosutinib clearance appeared to be potentially correlated with CRCL and/or body weight (Figure 30 and Figure 31), a forward-inclusion model building approach was performed to determine if creatinine clearance can be used to describe bosutinib clearance.

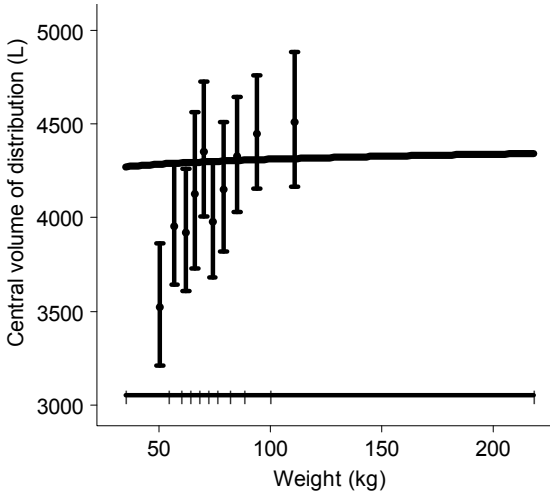
In the first stage of the model-building approach both creatinine clearance and weight were added into the sponsor's final model, one parameter at a time (Table 25). The drop in minimum value of the objective function (MVOF) and Figure 31 suggested that weight is a significant covariate on V2. While creatinine clearance as a covariate on clearance lowered the MVOF more than weight as a covariate on the V2, there was no reduction in the inter-individual variation on CL. Whereas, weight on V2 decreased the inter-subject variability of V2 by only 1.3%.

Table 25. Results of adjustments to the sponsor's final model. Only CRCL and weight (WT) were tested as covariates on either CL or central volume of distribution (V2).

		%CV for		Exponent for Covariate on	
Model Description	**MVOF**	**CL**	**V2**	**CL**	**V2**
Sponsor's Final Model	60786	59.9	47.6	---	---
plus CRCL on CL	60691	60.4	47.4	0.465	---
plus WT on CL	60786	60.1	47.6	0.0146	---
plus WT on V2	60758	59.3	46.3	---	0.377
plus WT on CL and WT on V2	60748	60.4	46.0	0.291	0.495
plus CRCL on CL and WT on V2	60640	45.3	50.7	0.281	0.009

In the second stage of covariate addition, weight was a covariate on V2 for each tested model. The objective function improved significantly for the addition of either weight or CRCL as covariates on CL (Table 25). However, inter-individual variability was not consistently improved for either CRCL or weight as covariates on CL. Further, when CRCL was included in the model, the covariate relationship for V2 and weight was not fitted properly (Figure 33) and the exponent (0.009) for the effect of weight on V2 did not appear reasonable as an allometric parameter.

Figure 33. The covariate relationship for bosutinib central volume of distribution (V2) was not properly estimated when CRCL was included as a covariate on clearance.



In conclusion, statistically significant improvements in the population PK model were observed with the addition of weight and/or CRCL. However, neither weight nor CRCL meaningfully reduced the inter-subject variability for bosutinib CL or Vd.. It is likely that the majority of the PK data were too sparse to evaluate covariate effects on both clearance and volume of distribution parameters

using a two-compartment model with first order absorption. Thus, it may not be appropriate to extrapolate effects of creatinine clearance on bosutinib clearance to those individuals with severe renal impairment.

Exposure-Response for Safety Events

See page 41 for the results of this analysis.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIMIKA PFUMA
07/27/2012

JUSTIN C EARP
07/31/2012

BAHRU A HABTEMARIAM
07/31/2012

ROSANE CHARLAB ORBACH
07/31/2012
Agree with Genomics part

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 203-341

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	203-341 (IND# 68268)	**Proposed Brand Name**	Bosulif®
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Bosutinib
Medical Division	Oncology	**Drug Class**	Tyrosine Kinase Inhibitor (TKI)
OCP Reviewer	Elimika Pfuma, Pharm.D., Ph.D.	**Proposed Indication**	The treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy.
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	100 and 500 mg immediate release tablets
Pharmacometrics Reviewer	Justin Earp, Ph.D.	**Dosing Regimen**	500 mg once daily with food
Pharmacometrics Team Leader	Christine Garnett, Pharm.D.		
Date of Submission	17-November-2011	**Route of Administration**	Oral
PDUFA Due Date	17-September-2011	**Sponsor**	Pfizer/Wyeth
		Priority Classification	Standard Review

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted (*numbers in smaller font were already counted in another section*)**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**6**		**Four methods for bosutinib and its major metabolites(RPT-56236, RPT-61652, RPT-73211 and RPT-73211) and a method each for moxifloxacin (RPT-57201) and ketoconazole (RPT-79423)**
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study # 3160A4-1112-US**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		**Study # WAY-173606**
Plasma protein binding:	**X**	**4**		***In vitro* plasma protein binding studies (Studies # RPT-54418, PF-05208763 and PF-05312061) and an *ex vivo* plasma protein binding study (Study # RPT-79220) using plasma from subjects in the hepatic impairment trial.**

Pharmacokinetics -	**X**	**15**		**Single dose – 11 studies in healthy volunteers and one hepatic impairment study.** **Multiple dose - Three studies in patients with advanced malignant solid tumors or chronic myelogenous leukemia (CML)**
Healthy Volunteers–				
single dose:	**X**	**12**		**Studies 3160A1-103-EU, 3160A4-104-US, 3160A4-1114-EU, 3160A4-1106-US, 3160A4-1108-US, 3160A4-1112-US, 3160A4-105-US, 3160A4-1109-US, 3160A4-1115-US, 3160A4-1120-US, 3160A4-1110-US and 3160A4-1111-EU.**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**Studies 3160A1-100-US, 3160A1-102-JA and 3160A4-200-WW.**
Dose proportionality -				
fasting / **non-fasting single dose**:	**X**	**1**		**Dose proportionality under fed conditions was assessed using a power model with data from Study# 3160A1-103-EU**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**4**		**Effect of strong CYP3A4 inhibitor and inducer: Studies 3160A4-104-US, 3160A4-1114-EU and 3160A4-1106-US. Effect of PH altering medications: Study 3160A4-1108-US**
In-vivo effects of primary drug:				
In-vitro:	**X**	**12**		**RPT-71680, RPT-80268, WAY-173606, PF-05208763, RPT-53085, RPT-53086, RPT-63186, PF-05898965, RPT-53488, RPT-79459, RPT-69677 and RPT-71680**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	**X**	**1**		**Study 3160A4-1111-EU in healthy volunteers with normal or mild, moderate and severe hepatic impairment**
PD - QT Study:	**X**	**1**		**QT study # 3160A4-105-US**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		**Exposure-response analyses for efficacy and safety using data from study 3160A4-200-WW (Pivotal trial; Phase2 study)**

Phase 3 clinical trial:	**X**	**1**		**Exposure-response analyses for safety studies 3160A4-3000-WW (Supportive Trial ; Phase 3)**
Population Analyses -				
Data rich:	**X**	**1**		**The population PK model assessing the effects of dose, food, formulation, sex, race, hepatic function, weight and age used PK data from the following eight phase 1 healthy volunteer studies: Studies 3160A1-103-EU, 3160A4-104-US, 3160A4-1114-EU, 3160A4-1106-US, 3160A4-1108-US, 3160A4-1112-US, 3160A4-105-US, 3160A4-1109-US, 3160A4-1120-US, 3160A4-1110-US and 3160A4-1111-EU.**
Data sparse:	**X**	**1**		**A population PK model in patients with cancer included data from Studies 3160A1-100-US, 3160A4-200-WW and 3160A4-3000-WW.**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Study # 3160A4-1109-US**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**2**		**Studies # 3160A4-1115-US and 3160A4-1120-US**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**Studies # 3160A4-1110-US and 3160A1-103-EU**
Bio-waiver request based on BCS				
BCS class	**X**	**1**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**44**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to	X			

	allow substantive review to begin?				
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X		
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No exposure–response information is in the proposed label
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Elimika Pfuma, Pharm.D., Ph.D.	08-December-11
Clinical Pharmacology Reviewer	Date
Julie Bullock, Pharm.D.	08-December-11
Clinical Pharmacology Team Leader	Date
Justin Earp, Ph.D	08-December-11
Pharmacometrics Reviewer	Date
Christine Garnett, Pharm.D.	08-December-11
Pharmacometrics Team Leader	Date

Clinical Pharmacology - NDA Filing Memo

NDA: 203-341 Original Submission **IND:** 68,268
Compound: Bosutinib 100 and 500 mg immediate release tablets
Sponsor: Wyeth/Pfizer
Filing Date: December 21, 2011
Clinical Pharmacology Reviewer: Elimika Pfuma, Pharm.D., Ph.D.
Pharmacometrics Reviewer: Justin Earp, Ph.D.

Mechanism of Action and Proposed Indication
Bosutinib is a tyrosine kinase inhibitor proposed for the treatment of chronic phase (CP), accelerated phase (AP) or blast phase (BP) Ph+ chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. In CML, bosutinib is believed to exert pharmacological action through the inhibition of abnormal Bcr-Abl kinase.

Sponsor's Phase 3 Dose Selection Rationale
The proposed dosing regimen is 500 mg daily taken with food. The MTD was determined to be 500 mg taken with food in a phase 1 dose escalation trial in patients with advanced malignant solid tumors (3160A1-100-US). In addition, a 500 mg dose taken with food was selected for evaluation in phase 3 from data in study 3160A4-200-WW (pivotal trial).

Pivotal Trial and Supportive Efficacy Trial

Study Number	Study Description	Treatment Groups	Study Endpoints
3160A4-200-WW (pivotal)	Phase 1/2 open-label 2- part study in subjects with Ph+ leukemia. Part 1: dose escalation in CP CML (N=18) Part 2: efficacy study at the selected Phase 2 dose - CP CML 2nd line (N=288) - CP CML 3rd line (N=118) - AP and BP Ph+ CML (N=164)	Part 1: Bosutinib 400, 500 and 600 mg Part 2: Bosutinib 500 mg	Part 1: MTD Part 2: CP CML 2nd/3rd line primary endpoint: Major cytogenetic response (MCyR) at 24 weeks AP and BP Ph+ CML primary endpoint: Overall hematologic response (OHR) by 48 weeks
3160A4-3000-WW (supportive)	Randomized, open-label, phase 3 study to compare the efficacy and safety of bosutinib to that of imatinib in subjects with newly diagnosed CP CML.	Bosutinib 500 mg QD (N=248) Imatinib 400 mg QD (N=251)	Rate of complete cytogenetic response (CCyR) at 1 year

In the pivotal trial (3160A4-200-WW) the MCyR at Week 24 was 35.5% in imatinib-resistant and 30% in imatinib-intolerant second-line CP CML patients. For third-line CP CML patients the MCyR at Week 24 was 26.9%. The overall hematologic response rate at 48 weeks was 55.1% in AP CML patients and 28.3% in BP CML patients. The supportive trial (3160A4-3000-WW) was a failed phase 3 trial where the adjusted odds ratio estimate of CCyR at 1 year in subjects on the bosutinib arm was 1.10 (95% CI: 0.74, 1.63).

Population PK
The sponsor submitted a population PK model assessing the effects of dose, food, formulation, sex, race, hepatic function, weight and age using PK data from eight phase 1 healthy volunteer trials. In addition the sponsor submitted a population PK model in patients with cancer including

data from Studies 3160A1-100-US, 3160A4-200-WW and 3160A4-3000-WW. Covariate analysis was performed for age, weight, BSA, BMI, sex, race, ECOG score, creatinine clearance, total bilirubin, ALT, AST and albumin.

Clinical Pharmacology and Biopharmaceutics Studies

Pharmacokinetic data are available from 15 trials conducted in healthy volunteers (HV) and patients including sparse PK in the pivotal trial.

Study Number	Study Description	Treatment Regimen	PK Sampling (population)
Comparative Bioavailability and Bioequivalence Studies			
3160A4-1109-US	Relative BA of 3 new formulation tablets and a reference capsule and an oral solution under fed conditions (N=40)	Single 500 mg dose of each formulation	Intensive (HV)
3160A4-1115-US	BE comparing the proposed commercial test formulation the phase 3 reference formulation under fasting conditions (N=30)	Single dose of each: 100 mg x 3 Commercial test 100 mg x 3 Phase 3 reference	Intensive (HV)
3160A4-1120-US	BE comparing the 500 mg proposed commercial test formulation to the Phase 3 reference formulation (N=31)	Single dose of each: 500 mg Commercial test 100 mg x 5 Phase 3 reference	Intensive (HV)
Pharmacokinetic and Initial Tolerability Studies			
3160A1-103-EU	Single dose PK and preliminary food effect (N=41)	Bosutin b 200 - 800 mg	Intensive (HV)
3160A4-1110-US	Food effect study (N=24)	Single doses of 400 mg (4 x 100 mg) under fed or fasting conditions	Intensive (HV)
3160A1-100-US	Dose-escalation study in patients with advanced malignant solid tumors with expansion cohorts (N=151)	Part 1 (dose-escalation): 50 to 600 mg daily (N=51) Part 2 (expansion): 400 mg QD (N=100)	Intensive and sparse (solid tumors)
3160A1-102-JA	Dose-escalation study in Japanese patients with advanced malignant solid tumors (N=25)	Daily doses taken with food ranging from 100 - 400 mg	Intensive (solid tumors)
3160A4-1112-US	Mass balance study (N=6)	A single 500 mg oral dose of bosutinib containing 0.01 µCi [^{14}C] bosutin b	Intensive (HV)
3160A4-105-US	Thorough QT study (N=60)	Part A: A single dose of bosutinib 500 mg, placebo or moxifloxacin 400 mg in a fed state. Part B: A single dose of bosutin b 500 mg or placebo with either given concomitantly with ketoconazole 400 mg in a fed state.	Intensive (HV)
Specific Populations			
3160A4-1111-EU	Hepatic Impairment Study (N=27). The study enrolled six subjects in each group of Child Pugh A, B and C and 9 matched healthy volunteers in the control group.	single 200 mg dose	Intensive (HV)
Drug Interaction Studies			
3160A4-104-US	Ketoconazole DDI (CYP3A4 Inhibitor) (N=24)	single dose of bosutinib 100 mg administered either alone or with ketoconazole (400 mg dose for 5 days) under fasting conditions	Intensive (HV)
3160A4-1114-EU	Ketoconazole DDI (CYP3A4 Inhibition) (N=48)	Single dose of bosutin b 100 - 600 mg co-administered with multiple doses of ketoconazole (400 mg tablets) under fed conditions	Intensive (HV)
3160A4-1106-US	Rifampin DDI (CYP3A4 Induction) (N=24)	A single dose of bosutinib 500 mg administered either alone or with rifampin (600 mg for 8 days).	Intensive (HV)
3160A4-1108-US	Lansoprazole DDI (pH altering proton-pump inhibitor) (N=24)	A single dose of 400 mg bosutin b alone or co-administered with multiple doses of 60 mg lansoprazole under fasting conditions	Intensive (HV)

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/s/

ELIMIKA PFUMA
01/30/2012

JULIE M BULLOCK
02/03/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-341	**Reviewer:** Akm Khairuzzaman, PhD	
Submission Date:	11/17/2011		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Wyeth Pharmaceutical, Inc (a wholly owned sudsidary of Pfizer, Inc.)		
Trade Name:	BOSULIF® Tablets	**Date Assigned:**	11/17/2011
Generic Name:	bosutinib monohydrate	**Date of Review:**	12/10/2011
Indication:	For the treatment of CP, AP, or BP Ph(+) CML in adult patients with resistance or intolerance to prior therapy	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Film coated tablets/100 mg and 500 mg		
Route of Administration	Oral		

SUBMISSION:

This is a 505(b)(1) New Drug Application for an immediate release film coated tablets containing 100 and 500 mg of bosutinib, indicated for the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. This submission has some Quality by Design elements employed during the drug product development.

BIOPHARMACEUTIC INFORMATION:

Bosutinib monohydrate has pH dependent solubility across the physiological pH range. At or below pH 5, bosutinib behaves as a high solubility compound. Above pH 5, its solubility reduces rapidly and therefore based on BCS, it is considered as a low solubility compound. The commercial drug product is formulated as a film coated tablets with commonly used compendial excipients such as Microcrystalline cellulose, Croscarmellose Sodium, Poloxamer, Povidone, Magnesium Stearate and film coating component, (b) (4) The formulations of the proposed 100 mg and 500 mg tablets (b) (4)

There is no polymorphism of the drug substance. The applicant has claimed that the drug substance particle size was found to have no impact on dissolution. Based on the results from BA study No. 3160A4-1109-US, the Applicant claims that the drug's absorption in the GI tract is not dissolution rate limited. Bioequivalence was established among different formulations of bosutinib such as fast release, slow release and oral solution. A list of target product profile was provided in the application, whereby disintegration and dissolution data were included.

From the risk assessment perspective, it was identified that the physicochemical properties of the drug substance have a potential impact on the tablet's disintegration and dissolution. (b) (4) The Applicant conducted several studies evaluating the variability in formulation composition and process (via some design of experiments, DoE) and their impact on the product quality from both, the *in vitro* and *in vivo* perspective. However, the evaluation of their criticality on quality will be made during the review cycles by the assigned reviewers.

A list of the in vivo bioequivalence studies that were conducted for the developmental formulations vs. the commercial formulation is provided in the application. The pharmacokinetic data from healthy volunteers showed that bosutinib has linear pharmacokinetics across the studied dose range of 100 mg to 800 mg. Since the bioavailability of the proposed 100 mg and 500 mg strengths were characterized, this application does not include a BA-waiver

request.

Regarding dissolution, the Applicant provided a brief summary for the dissolution method development. Various factors were evaluated during the method development, including; different types of apparatus, drug's solubility characteristics, effect of pH- ionic strengths – (b) (4) medium composition and bio-relevance, discriminating capabilities and other physical aspect of the test. This description is provided in the "Quality Overall Summary" under 2.3.P.2 section. However, the data on such development were not provided and therefore in absence of such data, the assessment on the acceptability of the proposed dissolution method is challenging to the reviewer.

The proposed dissolution method and acceptance criterion are as follow:

DISSOLUTION CONDITIONS	
Volume	900 mL
Apparatus	USP Apparatus II (Paddles)
Rotating Speed	50 rpm
Dissolution Medium	0.1 N HCl
Temperature	37°C ± 0.5°C

Q (b) (4) in 30 min

In this submission, the dissolution method for BOSULIF® Tablets is proposed to be used to control the quality of the drug product. The proposed method discriminates variations in the formulation and manufacturing process. However, this test is not intended to correlate to the in vivo performance of the product and the Applicant has no plans to establish an IVIVC for BOSULIF® Tablets.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criterion for BOSULIF® Tablets.

RECOMMENDATION:

The ONDQA-Biopharmaceutics team has reviewed NDA 203-341 for filing purposes. We found this NDA fileable from the Biopharmaceutics perspective. **However, the Applicant is advised to submit the following additional information:**

(1) Provide the specific details for the development of the dissolution method (ref section 2.3.P.2) along with the complete dissolution data collected during this development.
(2) Provide the multi time-point dissolution data for all the batches used in the PK and clinical studies listed in table 1, under section: 2.3.P.2, which are needed to evaluate the acceptability of your proposed dissolution acceptance criterion.

Akm Khairuzzaman, PhD
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, PhD
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AKM KHAIRUZZAMAN
12/13/2011
Fileable from Biopharmaceutics pont of view

ANGELICA DORANTES
12/13/2011

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-341	**Reviewer:** Akm Khairuzzaman, PhD	
Submission Date:	11/17/2011		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Wyeth Pharmaceutical, Inc (a wholly owned subsidiary of Pfizer, Inc.)		
Trade Name:	BOSULIF® Tablets	**Date Assigned:**	11/17/2011
Generic Name:	bosutinib monohydrate	**Date of Review:**	05/15/2011
Indication:	For the treatment of CP, AP, or BP Ph(+) CML in adult patients with resistance or intolerance to prior therapy	**Type of Submission:** Original New Drug Application	
Formulation/strengths	Film coated tablets/100 mg and 500 mg		
Route of Administration	Oral		

SYNOPSIS:

Submission: NDA 203-341 is a 505(b)(1) New Drug Application for an immediate release film coated tablets containing 100 and 500 mg of bosutinib, indicated for the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy. Bosutinib monohydrate has pH dependent solubility across the physiological pH range based on which it is considered as a low solubility compound (pKa is 4.7, as pH decreases, solubility increases and vice versa).

Review: The Biopharmaceutics review is focused on the evaluation and acceptability of the information supporting the proposed dissolution method and acceptance criteria.

The drug product is formulated using simple compendial excipients and manufactured following (b) (4) The Applicant provided a list of Target Product Profile (TPP) in the application in which dissolution was identified as a one of the target product profile.

During the course of development of this product (from Phase 1 through Phase 3), various different types of formulations were prepared and evaluated both in vitro and in vivo. In Phases 1 and 2, a capsule formulation were developed (b) (4) Additionally, different formulation (such as tablets with slow, fast and target dissolution profiles, capsule

formulation, solution formulation) were also prepared and tested *in vivo* (in healthy subjects under fed conditions) for their comparative plasma profiles. The statistical analysis indicated that the target release rate tablet formulation, the slow release rate formulation, the fast release rate tablet and the solution formulation had the same bioavailability as the reference capsule formulation despite their significant differences in dissolution behavior. Additionally, there were some changes [redacted] (b) (4) between the phase III tablet formulation and the commercial tablet formulations. Both formulations showed bioequivalence (300 mg strength, and 5x100 mg) in human subjects. All these *in vivo* data have provided to the reviewer a great confidence that the variability in dissolution may not have statistically significant impact on *in vivo* performance. It is to be noted that linear pharmacokinetics exist for this drug in the 200 mg to 800 mg range. There is no biowaver request in this application.

The Applicant conducted a very detailed risk assessment during the course of this product development. The effect of formulation components [redacted] (b) (4) and physical attributes of the finished product (such as tablet hardness) on dissolution and disintegration were thoroughly evaluated. The development of the dissolution method was also conducted very thoroughly and included factors such as; solubility and in vitro permeability of the drug, effect of dissolution apparatus, rotation speed, effect of media pH, ionic strength, [redacted] (b) (4) potential bio-relevant fed and fasted dissolution medium, and discriminating capability. The developed dissolution method was then tested for its robustness. The reviewer found all these studies sufficient to support the developed method.

Finally, the Applicant proposed a dissolution acceptance criterion of Q = [redacted] (b) (4) at 30 minutes. The reviewer found that this single point dissolution limit is acceptable since the Pharmacokinetic data showed that the in vivo absorption of bosutinib is controlled by permeability rather than dissolution of the tablet formulation and the tablets dissolute rapidly [redacted] (b) (4) released at 30 minutes). Moreover, the limit was established based on the release and stability data for batches of bosutinib tablets used in clinical studies.

RECOMMENDATION:

Based on the evaluation of the overall information, the following proposed dissolution method and acceptance criteria are acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Assay	Acceptance criterion
No. 2 (paddle)	50 rpm	900 mL	37°C± 0.5°C	0.1 N HCL	UV analysis at 266 nm	Q = [redacted] (b) (4) at 30 minutes

There are no deficiencies from the biopharmaceutics point of view. Therefore, This New Drug Application, NDA 203-341 for BOSULIF® Tablets **is recommended for approval** from the Biopharmaceutics point of view.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Angelica Dorantes, Ph.D.
Biopharmaceutics Supervisory Lead (acting), ONDQA

cc. NDA 203-341/DARRTS

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND: This is a 505(b)(1) New Drug Application for an immediate release film coated tablets containing 100 and 500 mg of bosutinib. The NDA was submitted on 11/17/2011. The drug product is formulated using compendial grade excipients following (b) (4) There are several in vivo studies in place with different formulations, a linear pharmacokinetics are also present in the dose range of 200 mg to 800 mg. Changes in formulation from phase 3 to commercial is supported by bioequivalence studies. There is no biowaver request in this application.

➔ **Solubility of the drug:**

Bosutinib monohydrate has pH dependent solubility across the physiological pH range. At or below pH 5, bosutinib behaves as a high solubility compound. Above pH 5, its solubility reduces rapidly and therefore based on BCS, it is considered as a low solubility compound. There is no polymorphism of the drug substance.

Table 1. Bosutinib Solubility in standard USP Buffers at 37°C

Media and pH	Solubility (mg/mL)
0.1N Hydrochloric Acid (pH 1.0)	11.03
0.01N Hydrochloric Acid (pH 2.0)	9.4
pH 4.5 USP Buffer	6.1
pH 5.0 USP Buffer	2.7
pH 6.8 USP Buffer	0.02
pH 8.0 USP Buffer	0.053

Based on the (b) (4) provided in the application, it appears that drug substance (b) (4) Additionally there is no test for polymorphic identification as a part of the drug substance specification and therefore Applicant should provide data to show if there is any significant solubility differences between these possible polymorphs.

➔ **Formulation composition of the drug product:**

The commercial drug product is formulated as a film coated tablets with commonly used compendial excipients such as Microcrystalline cellulose, Croscarmellose Sodium, Poloxamer, Povidone, Magnesium Stearate and film coating component, (b) (4). The formulations of the proposed 100 mg and 500 mg tablets (b) (4)

The drug product's formulation composition is as follows:

Table 2. Drug product formulation composition

Ingredient	Quality Standard	% w/w (Uncoated Tablet)	Unit Dose *(mg/tablet)*	Unit Dose *(mg/tablet)*	Function
Intra-granular			**100 mg**	**500 mg**	
Bosutinib monohydrate	Pfizer [a]	(b) (4)	103.40 [b]	516.98 [c]	Active Ingredient
Microcrystalline cellulose	NF/Ph. Eur.				
Croscarmellose sodium	NF/Ph. Eur.				
Poloxamer	NF/Ph. Eur.				
Povidone	USP/Ph. Eur.				
(b) (4)					
Subtotal					
(b) (4)					
Total (Final Tablet)			**149.35**	**746.75**	

NA = Not applicable

a. Pfizer in-house specifications for Bosutinib Monohydrate are listed in the Bosutinib Monohydrate Specification RB-36100, which is provided in Section 3.2.S.4.1 Specification for Drug Substance.

b. Equivalent to 100 mg of bosutinib per tablet based on an assay value of 100% for bosutinib monohydrate.

c. Equivalent to 500 mg of bosutinib per tablet based on an assay value of 100% for bosutinib monohydrate.

The actual input of the active ingredient for both strengths is adjusted based on its actual assay value of the bosutinib monohydrate used. A corresponding adjustment is made in the amount of (b) (4) (b) (4)

Reviewer's Note: (b) (4) *The Applicant conducted several studies evaluating the variability in formulation composition and process (via some design of experiments, DoE) and their impact on the product quality from both, the in vitro and in vivo perspective.*

➔ **Target Product Profile (TPP):**

The Applicant has defined the target product profile as follows:

Table 3. Target drug product profile

Attribute	Target
Drug Product performance	
Dosage Form	Film coated tablets for once a day dosing. Available in two strengths of : 1. 100 mg 2. 500 mg
Potency	100 mg and 500 mg of bosutinib
Pharmacokinetics	Bioequivalence to the Phase 1 & 2 capsule formulation
Appearance	Oval, biconvex, debossed and color coded for strength. *500 mg*- Red oval shaped film coated tablet debossed with an appropriate logo *100 mg*- Yellow oval shaped film coated tablet debossed with an appropriate logo
Disintegration	NMT 15 minutes
Dissolution	Meets all pharmacopoeia requirements for IR tablets
Content Uniformity	Meets all pharmacopoeia requirements
Drug product manufacturability	
(b) (4)	

NMT = Not more Than

Both **disintegration** and **dissolution** are considered as a target product profile. Using the above attributes the Applicant has conducted a risk assessment whereby it was identified that the physicochemical properties of the drug substance have a potential impact on the tablet's disintegration and dissolution.

EVALUATION of DISSOLUTION DATA

➔ **Effect of different formulations on in vitro and in vivo performance:**

In early stage of development (Phase 1), the Applicant conducted a clinical study using three different types of formulation such as capsule, target release tablets, slow release tablets, fast release tablets as follows:

Table 4. Composition of various formulation used in clinical trials

	Phase 1 & 2 capsules	Phase 1 & 2 capsules	Phase 1& 2 capsules	Phase 1 Fast release tablet	Phase 1 Slow release tablet	Phase 1, 2 & 3	Phase 1	Phase 1 & Proposed commercial tablet	Phase 1 & Proposed commercial tablet
Formula Identifier	**0932738V (Banded)**	**0931983V**	**0931981V**	**0932550A**	**0932551A**	**0932552C**	**0932546C**	**0932779C**	**0932771C**
									(b) (4)
Dosage form	Capsule	Capsule	Capsule	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Strength	100 mg	50 mg	100 mg	500 mg	500 mg	100 mg	500 mg	100 mg	500 mg
Bosutinib monohydrate[a]	100.0 mg	50.0 mg	100.0 mg	500.0 mg	500.0 mg	100.0 mg	500.0 mg	100.0 mg	500.0 mg
Poloxamer (b) (4)							(b) (4)		(b) (4)
Croscarmellose sodium									
Microcrystalline cellulose (b) (4)									
Povidone									
Magnesium stearate (b) (4)									
								-	(b) (4)
Total								149.3 mg	746.7 mg
									(b) (4)

The comparative dissolution behavior (using the proposed dissolution method: 0.1N HCl medium at 50 rpm speed, paddle) of these different formulations are as follows:

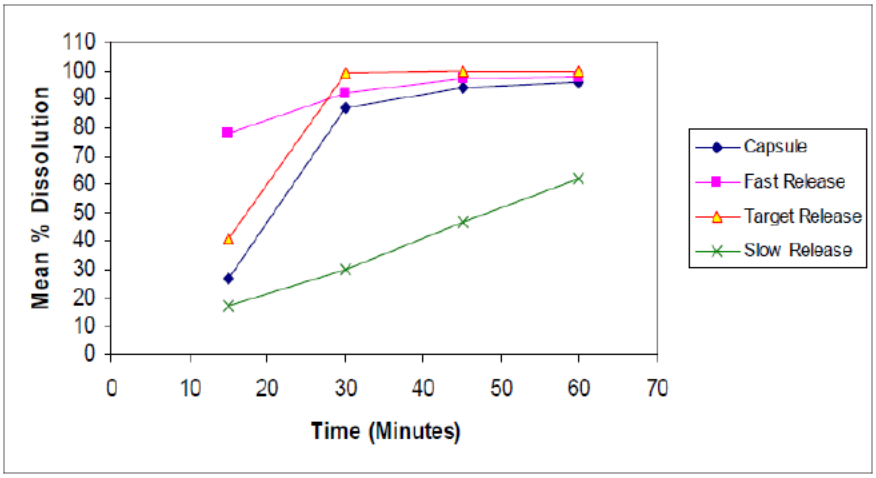

Figure 1. Dissolution Profile - Bosutinib Capsules, Fast Release Tablets, Target Release Tablets and Slow Release Tablets (Media – 0.1N HCl, 50 rpm Paddles)

Despite the significant differences in their in vitro dissolution behavior, the statistical analysis of the pharmacokinetic parameters (e.g. AUC and C_{max}) indicated that the all formulations had the same bioavailability as the reference capsule as follows.

Table 5. Statistical analysis of PK parameters of Bosutinib Capsules, Fast Release Tablets, Target Release Tablets and Slow Release Tablets

	P-Values from Log-Transformed Analysis of Variance		
	*C_{max}	*AUC_T	*AUC
	ANOVA Comparison: 500 mg FR (Test) vs. 5 X 100 mg caps (Reference)		
Ratio of Least Square Geometric Means (%)	105	103	102
90% Confidence Interval around Ratio	94-118	94-114	93-113
Statistical Power	93.5	98.3	98.6
	ANOVA Comparison: 500 mg soln (Test) vs. 5 X 100 mg caps (Reference)		
Ratio of Least Square Geometric Means (%)	102	102	101
90% Confidence Interval around Ratio	90-115	92-113	91-111
Statistical Power	91.2	97.4	97.8
	ANOVA Comparison: 500 mg SR (Test) vs. 5 X 100 mg caps (Reference)		
Ratio of Least Square Geometric Means (%)	99	98	97
90% Confidence Interval around Ratio	88-111	89-108	88-107
Statistical Power	93.2	98.2	98.5
	ANOVA Comparison: 500 mg TR (Test) vs. 5 X 100 mg caps (Reference)		
Ratio of Least Square Geometric Means (%)	103	102	100
90% Confidence Interval around Ratio	92-116	92-112	90-110
Statistical Power	93.0	98.1	98.4

Abbreviations: SD=standard deviation; caps=capsules; FR=fast release; soln=solution; SR=slow release; TR=target release; C_{max}=peak concentration; AUC_T=area under the concentration-time curve to the last measurable concentration at time T (C_T); AUC=total area under the concentration-time curve.
* These parameters were dose normalized before statistical analysis.

Additionally, the commercial formulation was changed from Phase 3 stage (b) (4) (b) (4) and a BE study was performed. The in vitro dissolution data and the BE results are presented in Figure 2 and Table 6, respectively.

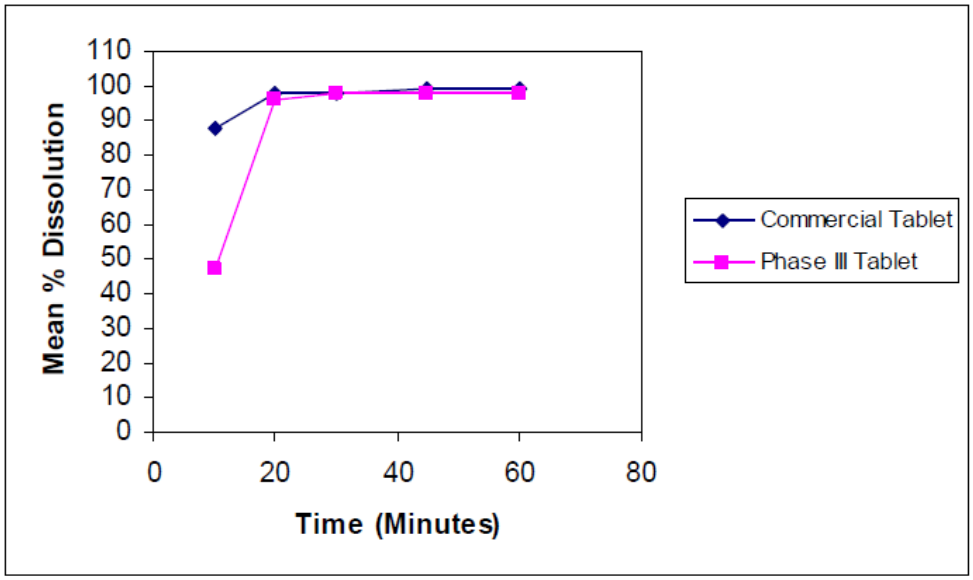

Figure 2. Dissolution Profile - Bosutinib Commercial Formulation and Phase 3 Formulations Dosed In Study 3160A4-1115-US (Media – 0.1N HCl, 50 rpm Paddles)

Table 6. The in vivo PK parameters

Commercial Bosutinib Test Formulation (1 × 500 mg, n = 29) Versus Phase 3 Reference Formulation Bosutinib (5 × 100 mg, n =30)			
	C_{max}	AUC_T	AUC
Ratio of LSGM (%)	110.11	103.93	103.50
90% CI around Ratio (%)	96.16-126.08	93.96-114.95	94.19-113.73
Intrasubject CV%	30.7	22.5	21.0
Data from subjects 1120-001-000009 and 1120-001-000021 from the period they vomited after taking the test formulation tablets were excluded.			

Reviewer's Evaluation: Acceptable

Although from the Phase 1 study, it can be concluded that the that the in-vitro performance of the formulations have no impact on the in-vivo performance, the 90% confidence interval of C_{max} ratio (96.16% to 126.08%) for the commercial formulation was outside the standard bioequivalence limits of 80.00 to 125.00% from that of the phase 3 formulation where the inactive ingredient, (b) (4)

It is to be noted that (b) (4) *was present in all three different formulations (e.g. fast, slow and target) at different level in the phase 1 in vivo study. The tablet's disintegration time was very high for the phase 3 formulation (18 min to 20 minutes) that used* (b) (4) *Therefore, the reviewer believes that such deviation from the conventional BE, was due to replacement of this excipient with* (b) (4) *thus promote rapid disintegration. These data support that variation in dissolution may not have clinically significant impact in vivo.*

The effect of other formulation components on dissolution such as the level of (b) (4) (b) (4) was also evaluated. A series of batches was manufactured which contained varying amounts of (b) (4) on drug product performance. It was observed that increasing the concentration of (b) (4) in the formulation led to a decrease in the dissolution release rate as follows:

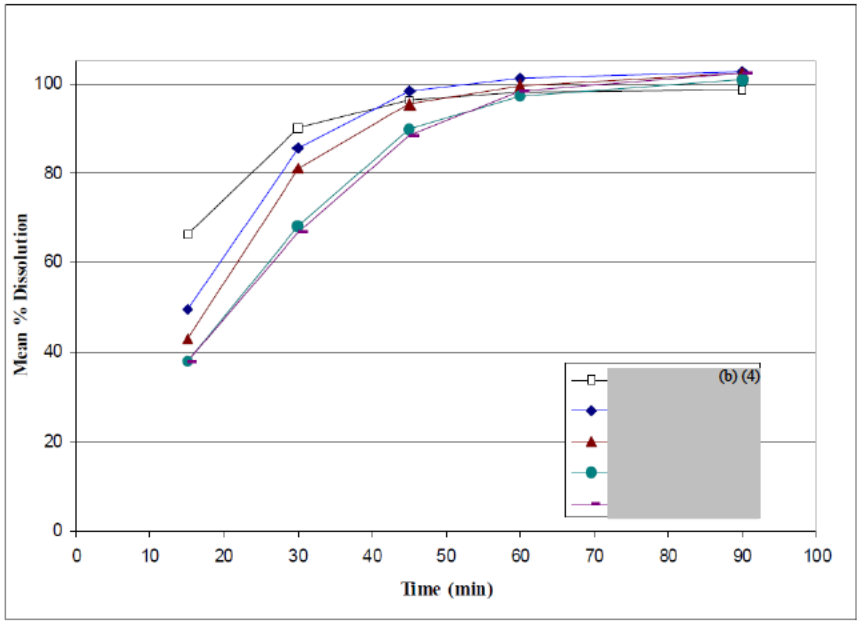

Figure 3. Effect of various level of (b) (4) concentration (in formulation) on dissolution in 0.1N HCl

(b) (4)

➔ ***Effect of various disintegrant in formulation:***

(b) (4)

Reviewer's comment: *All of the formulations containing* (b) (4) *showed significantly faster disintegration.*

➔ **Effect of drug substance particle size on dissolution:**

Three batches of bosutinib 500 mg tablets which were manufactured using drug substance with different particle size distributions (see following table) were compared for dissolution performance

Drug Product Batch Number	Drug Substance Batch Number	Drug Substance Particle Size Distribution (µm) (b) (4)
0904826	08-004	
0810461	RB7633	
0810462	08-002	

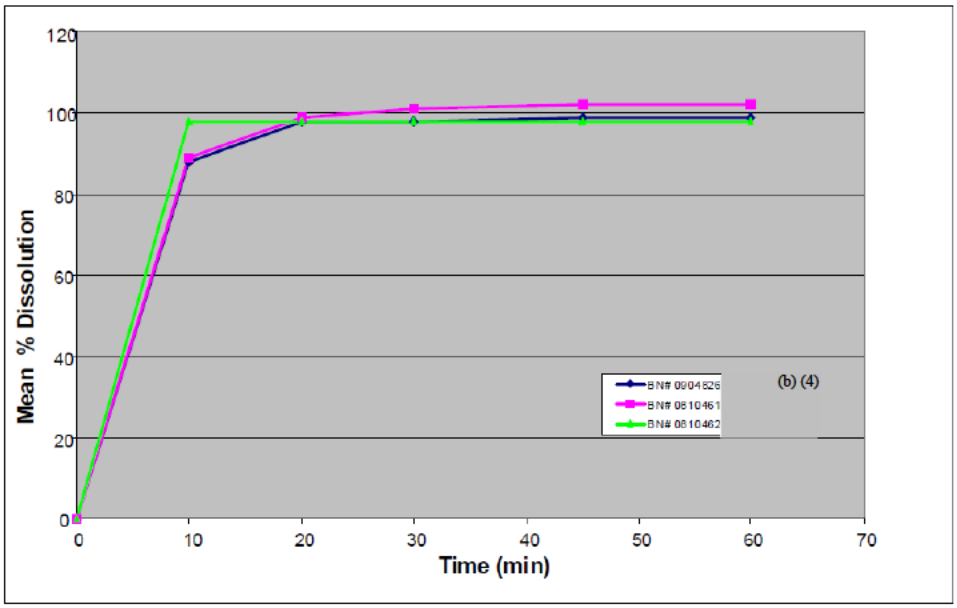

Figure 4. Effect of API particle size on drug product dissolution

The Applicant claimed that the drug substance particle size was found (b) (4) (b) (4) Also, based on the results from BA study No. 3160A4-1109-US, the Applicant claim that the drug's absorption in the GI tract is not dissolution rate limited. Bioequivalence was established among different formulations of bosutinib such as fast release, slow release and oral solution. A list of target product profile was provided in the application, whereby disintegration and dissolution data were included.

Reviewer's evaluation: Not Acceptable

The highest upper limit for the drug substance particle size used in the above study was (b) (4) (b) (4)). However, the Applicant has proposed a single point limit of (b) (4) which is not covered in the above study.

Question to the Applicant (Sent on March 23, 2012):

Provide data to justify that the single point particle size specification with (b) (4) has no effect on the drug product dissolution profile. It is noted that the drug substance batches used (08-044, RB7633 & 08-002) for the study of particle size effect on dissolution had a three-tier measurement and the highest value for the (b) (4) Therefore, either tighten the proposed particle size limit appropriately or provide additional dissolution data to justify the proposed limit.

Applicant's Response: On April 5th, 2012, applicant has responded with additional dissolution data that were generated on 100 mg and 500 mg tablets manufactured with drug substance batches produced during process validation with (b) (4). These dissolution data are as follows:

Tablet Strength	Batch Number	Drug Substance Batch	Drug substance Particle Size Distribution, (b) (4) (b) (4)	Dissolution % released at 20 min	Dissolution % released at 30 min
500 mg	0904826	08-004	(b) (4)	98	98
100 mg	0904918			100	100
500 mg	1109683	10-001		93	95
100 mg	1109635			95	98

Reviewer's final evaluation*: All of the drug product batches showed similar dissolution profiles that met the specification of Q* (b) (4) *released at 30 minutes. The drug substance with higher particle size (Lot # 10-001) and corresponding 100 mg and 500 mg tablet strengths (batch # 1109635 and 1109683,respectively) also met Q =* (b) (4) *released even at 20 minutes. Therefore, the review is in agreement that the limit set at NMT* (b) (4) *is justified.* ***Acceptable****.*

DISSOLUTION METHOD DEVELOPMENT

(b) (4)

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Finally, the Applicant has proposed the following final dissolution method and acceptance criterion are as follow:

DISSOLUTION CONDITIONS	
Volume	900 mL
Apparatus	USP Apparatus II (Paddles)
Rotating Speed	50 rpm
Dissolution Medium	0.1 N HCl
Temperature	37°C ± 0.5°C

Dissolution limit: Q (b) (4) in 30 min

Reviewer's Overall Evaluation: Acceptable.

Based on all the data from dissolution method development, the Reviewer is convinced that the proposed dissolution method has adequate discriminating capability. Additionally, based on the in vivo data, it appears that dissolution may not be the rate limiting step for bioavailability since significant variability in dissolution from different formulations (fast and slow) showed no statistically meaningful difference in their pharmacokinetic parameters.

(b) (4) *The Applicant has not proposed any test in their drug substance specification for polymorphic identification. There is no information available whether the* (b) (4) *have any significantly different solubility that may contribute different dissolution behavior or whether the dissolution method has any discriminating capability to distinguish these polymorphs. Therefore, the following deficiency is sent out to the Applicant:*

Question to the Applicant (Sent on March 23, 2012):

(b) (4) *include a test for polymorphic identification in the proposed drug substance specification. Furthermore, indicate if there is any potential for polymorphic conversion during the course of drug product manufacture and shelf life. If yes, clarify your approach to control and monitor such changes. In addition, provide solubility profiles for the drug substance polymorphic forms* (b) (4) (b) (4) *to describe their impact on dissolution.*

Applicant's response on April 5th, 2012: Applicant has reassured that the drug substance exists only in one polymorphic form which is (b) (4). Applicant has mentioned that all clinical and commercial batches of bosutinib drug substance were shown to conform to (b) (4) (b) (4) Stability data for drug substance monitored at 25 °C/60% RH for twelve months and at 40 °C/75% RH for six months further confirm conformance to monohydrate (b) (4) as tested by PXRD and water content testing. For release and stability assessment, water content testing (USP<921>) will be performed to verify water content in the final drug substance is consistent with the desired monohydrate form (theoretical - (b) (4)). Studies were conducted to assess the potential for form change during prolonged and representative hold times for (b) (4). The results of these studies indicate that no form conversion was detected for up to 30 hour hold

time for [redacted]. Form conversion was observed on hold times of 48 hours or longer. Therefore, it has been demonstrated that no form change occurs during the drug product manufacturing process provided the [redacted]

Reviewer's final evaluation: *The [redacted] stability of the polymorphic [redacted] in relation with water activity, the percent water that need to be retained for the maintenance of the monohydrate form ([redacted] studies conducted to evaluate the [redacted] and the test to be conducted for the batch release (USP <921>) need to be reviewed by the CMC reviewer. It is acceptable from biopharmaceutics point of view as long as there is a control in place during the drug product manufacture or as a part of the drug product specification such as water content testing (USP <921>).*

➔ **Additional confirmatory dissolution data at commercial stage:**

Formulation Change: Additional confirmatory dissolution studies were performed to evaluate the discriminatory power of the [redacted] method for the proposed commercial formulation. The Applicant performed experimental designs with following modifications to the Phase III formulation to produce the final proposed commercial formulation:

[redacted]

Outcome the study: Acceptable

The dissolution method was capable of distinguishing changes in the ratio of [redacted]

Different media [redacted]: Additional studies on dissolution medium were conducted as follows:

[redacted]

Data from these studies provided by the Applicant are as follows:

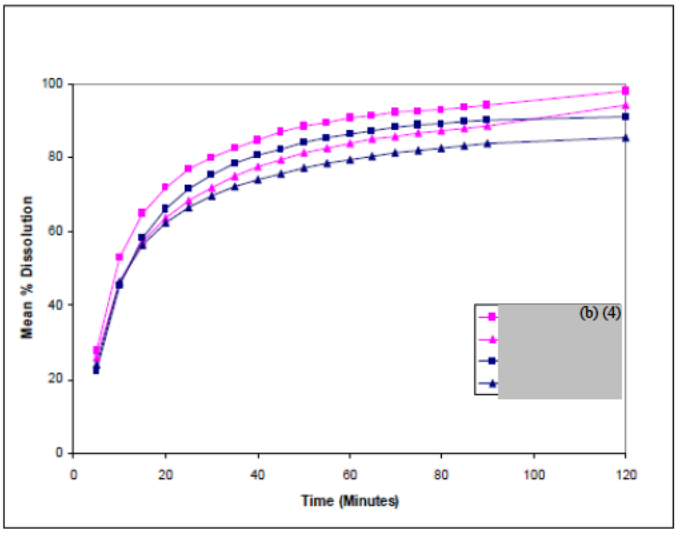

Figure 14. Effect of (b) (4) Type and Levels on the Dissolution of Bosutinib Commercial Formulation

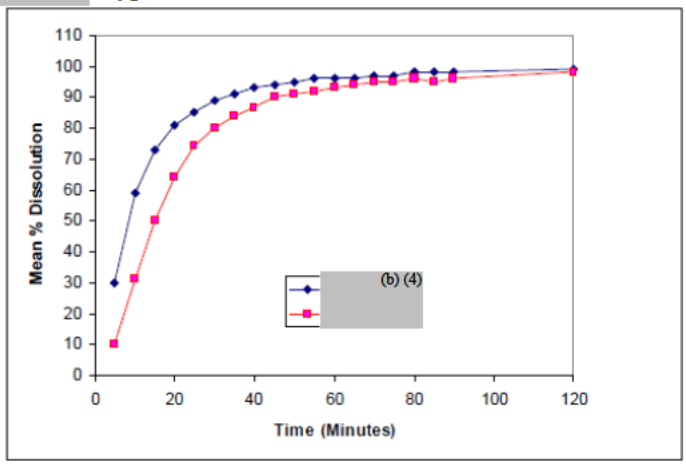

Figure 15. Dissolution of Bosutinib Commercial Formulation Tablets With Different Ratios of (b) (4) (b) (4) Components in pH5.0 Acetate Buffer with 0.5% CTAB.

Outcome the study: **Acceptable**.
Acetate buffer pH 5.0 with 0.5% CTAB with 50 rpm paddles demonstrated similar discriminating power (b) (4) [redacted] The Reviewer concluded that the dissolution method should remain same as follows:

USP II apparatus at 50 rpm; Medium – 900 mL of 0.1N HCL held at 37 °C ± 0.5°C,

REVIEWER CONCLUSIONS:

- Both **disintegration** and **dissolution** are considered as a target product profile.
- Pharmacokinetic data showed that the *in vivo* absorption of bosutinib is controlled by permeability rather than dissolution. Different formulations (fast, slow and target) were tested in humans for comparative bioavailability. Regardless of their significant differences in dissolution behavior, no statistically meaningful differences were observed in the pharmacokinetics parameters.
- The proposed dissolution method (USP II apparatus, medium – 900 mL of 0.1N HCL held at 37 °C ± 0.5°C, 50 rpm) as a quality control tool, ensures the robust and reproducible product performance and therefore is acceptable.
- A single point dissolution acceptance criterion of Q = (b) (4) at 30 minutes was proposed by the Applicant, and it is acceptable to the reviewer, because the limit was established based on the release and stability dissolution data from batches of bosutinib tablets used in clinical studies.

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/s/

AKM KHAIRUZZAMAN
05/15/2012
Recommended for approval from Biopharmaceutics point of view.

ANGELICA DORANTES
05/15/2012