

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203341Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Addendum to Cross-Discipline Team Leader Review

<b>Date</b>	August 7, 2012
<b>From</b>	Virginia Kwitkowski, MS, RN, ACNP-BC
<b>Subject</b>	Addendum to Cross-Discipline Team Leader Review
<b>NDA #</b>	203341
<b>Supplement#</b>	0
<b>Applicant</b>	Wyeth (a Pfizer company)
<b>Date of Submission</b>	November 17, 2012
<b>PDUFA Goal Date</b>	September 17, 2012
<b>Proprietary Name / Established (USAN) names</b>	Bosulif/ Bosutinib
<b>Dosage forms / Strength</b>	100 mg tablet 500 mg tablet
<b>Proposed Indication(s)</b>	For the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy
<b>Recommended:</b>	<i>Regular Approval</i>

Addendum to Section 2.0:

The Division requested a patient representative for Chronic Myelogenous Leukemia for a Divisional Assignment. Ms. Paige Brown was recommended by the AC staff. Ms Brown was consulted by the Division. A briefing package was issued to her for review.

The question posed to her was:

From a patient's perspective, is the **benefit:risk ratio** for Bosutinib acceptable for adult patients with Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) who demonstrate resistance or intolerance to prior therapy? This includes patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) CML in second or later lines settings.

Consultant Response:

**I've reviewed the package and the answer I would offer is that yes, the benefit : risk ratio is acceptable. My challenge, or my curiosity in these reviews, is always related to the refractory arms. I always suspect, though the data is not here, that intolerance is always subjective and that intolerance is often consistent in tki**

therapy. I am, of course

(b) (6)

Responses for refractory patients are an important measure to me, and there is evidence of positive response. I am always particularly excited when I see sustained responses in advanced or blast crisis CML, which this does show indication of. I struggle because I can't compare the ae's or responses to the other therapies with this data, and again there is a difference to me between intolerance and resistance, but when you have patients achieving and maintaining responses, it shows that the drug has value to some patients.

If you need a more formal statement or if you think I've misinterpreted something, please let me know. The bottom line is that I would use this therapy if others failed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIRGINIA E KWITKOWSKI  
08/31/2012

## Cross-Discipline Team Leader Review

<b>Date</b>	August 3, 2012
<b>From</b>	Virginia E. Kwitkowski, MS, RN, ACNP-BC
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 203341/0
<b>Supplement#</b>	
<b>Applicant</b>	Wyeth/ a Pfizer company
<b>Date of Submission</b>	November 17, 2011
<b>PDUFA Goal Date</b>	September 17, 2012
<b>Proprietary Name / Established (USAN) names</b>	<b>Bosulif/</b> bosutinib
<b>Dosage forms / Strength</b>	100 mg tablet 500 mg tablets
<b>Proposed Indication(s)</b>	For the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy
<b>Recommended:</b>	<i>Regular Approval</i>

## 1. Introduction

Bosutinib is a tyrosine kinase inhibitor that is a new molecular entity. Bosutinib is manufactured as immediate release oral tablets in 100 mg and 500 mg strengths.

Patients with chronic myelogenous leukemia who are relapsed, refractory, or intolerant of the approved tyrosine kinase inhibitors (imatinib, dasatinib, and nilotinib) have limited treatment options and a poor prognosis. The only curative treatment available for CML is allogeneic hematopoietic stem cell transplantation (HSCT). However, not all patients have available donors and due to comorbidities, may not be able to tolerate HSCT.

On November 17, 2011, Pfizer submitted a New Drug Application for Bosutinib. In this submission, they requested priority review designation because they believed that Bosutinib provides a major advance in the treatment of patients with Philadelphia Chromosome Positive Chronic Phase, Accelerated Phase, and Blast Phase CML. The Division concluded that this request was not justified because there are available therapies for patients who were relapsed/refractory/intolerant of imatinib. On January 26, 2012, the FDA issued a letter informing Wyeth that their application had been filed under a standard review classification and providing a user fee date of September 17, 2012.

The application contained only one efficacy trial (200-WW). This was considered acceptable to the Division because all of the previous applications for the second-line CML indication have contained a single trial. CML is a rare disease with approximately 5430 patients diagnosed in the U.S. per year<sup>1</sup>.

In support of the proposed indication, Pfizer submitted the results of Trial 200-WW, a Phase 1/2 single-arm trial enrolling a total of 570 patients. The largest number of patients enrolled had relapsed/refractory Chronic Myelogenous Leukemia (CML) in any one of three stages: Chronic Phase (CP), Accelerated Phase (AP), or Blast Phase (BP). The trial also enrolled a small number of patients with Philadelphia Chromosome-positive Acute Lymphocytic Leukemia (ALL). All patients had been treated previously with imatinib; some of the subjects were resistant to imatinib and others were intolerant of imatinib.

The trial consisted of two parts; a dose escalation part (Part 1) and an efficacy part (Part 2). The primary objectives of Part 1 were to determine the maximum tolerated dose (MTD), and to evaluate pharmacokinetics (PK) in patients with CP-CML. The primary objectives of Part 2 were to determine the rate of major cytogenetic response in subjects with imatinib-resistant chronic phase CML who had no prior Src, Abl, or Src-Abl kinase inhibitor exposure other than imatinib, and to determine the population PK parameters of this population.

Pfizer submitted data that included 24 months of follow-up.

The primary endpoint of Part 2 of Trial 200 was the MCyR at week 24 for second-line treatment of patients with CP-CML who were resistant to imatinib. The results for the primary endpoint were 35.5% (95% CI = 28.6, 42.8). The median duration of response was not reached.

The MCyR rate at 24 weeks for the overall evaluable Chronic Phase CML population was 33.8% (90 of 266 patients) [90% CI: 29, 38.9].

The MCyR rate at week 24 for second line treatment of patients with CP CML who were intolerant of imatinib was 30% (95% CI = 21.6, 39.5). This cohort did not reach the pre-specified MCyR rate of 53%. The median duration of response was not reached.

For the complete results, the reader is referred to Section 7 of this memo.

The Risk:Benefit assessment for Bosutinib is positive for patients with CML that have relapsed after or are intolerant to prior TKI therapy. Activity was demonstrated in patients who received prior imatinib with a toxicity profile that was similar (with few exceptions) to other approved TKIs for CML.

Prior regular approvals of tyrosine kinase inhibitors for CP-CML (dasatinib<sup>2</sup> and nilotinib<sup>3</sup>) were also based upon 24 months of follow-up data also using MCyR (Major Cytogenetic Response) as the primary endpoint.

I do not concur with the recommendation in Section 1.4 of Ms. McGinn's review for a "post-marketing requirement to continue long term follow-up of patients enrolled in clinical trials 200 and 3000 for a minimum of eight years and to submit the final completed study reports to the NDA." The reason for my disagreement is that the Applicant has demonstrated clinical benefit based upon acceptable MCyR rates of an acceptable duration and 24 months of follow-up in patients who have received prior TKI therapy for their CML. The Agency will

recommend a post-marketing commitment to follow the patients in the 200 trial for 5 years, as was specified in the protocol. This was discussed with Ms. McGinn and agreement reached after her review was finalized.

I concur with Ms. McGinn's recommendation for regular approval of Bosutinib for the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy.

Labeling negotiations are ongoing at the time of finalization of this review.

## 2. Background

Prior to 2001, CML was managed with agents like busulfan, hydroxyurea, interferon alpha, and allogeneic bone marrow or stem cell transplantation.

### Approval of Gleevec

The 2001 U.S. approval of imatinib (Gleevec®) revolutionized the treatment of CML in this country and provided the first tyrosine kinase inhibitor (TKI) for use in patients with newly diagnosed Chronic Phase (CP) CML based upon the results from the randomized phase 3 IRIS trial.

### Approval of Sprycel

On June 28, 2006, the FDA granted accelerated approval to dasatinib (Sprycel) for the treatment of adults with chronic myeloid leukemia [CP-CML, AP-CML, and BP-CML] with resistance or intolerance to prior therapy including imatinib. This approval was based upon at least 12 months follow-up of all patients. As a condition of accelerated approval, the Applicant was required to submit 24 month follow-up data from the original Phase 2 trial. On May 21, 2009 the FDA converted the accelerated approval to regular approval based upon 24 months of follow-up data submitted by the Applicant. On October 28, 2010, the FDA approved dasatinib, for the treatment of newly diagnosed adult patients with CML-CP, with a recommended dose of 100 mg/day.

### Approval of Tasigna

On October 29, 2007, FDA granted accelerated approval for nilotinib (Tasigna) "for chronic phase (CP) and accelerated phase (AP) Philadelphia positive chronic myelogenous leukemia (CML) in adult patients resistant to or intolerant to prior therapy that included Gleevec® (imatinib)". This approval was based upon at least 12 months follow-up of all patients. As a condition accelerated approval, the Applicant was required to submit 24 month follow-up data from the original Phase 2 trial.

On June 17, 2010, the accelerated approval was converted to regular approval based upon 24 months of follow-up data submitted by the Applicant. At the same time, nilotinib was granted accelerated approval by the FDA for the treatment of adult patients with newly diagnosed CP-CML based upon a randomized trial comparing nilotinib to imatinib in patients with newly diagnosed chronic phase CML. The recommended nilotinib dose for the newly diagnosed

patients is 300 mg by mouth twice daily. The recommended nilotinib dose for patients with CML that is resistant or intolerant to imatinib is 400 mg by mouth twice daily. Nilotinib also has regular approval for the treatment of accelerated phase CML in adult patients resistant to or intolerant to prior therapy that included imatinib.

### Summary of Evidence Needed for FDA Approval

The last two drugs approved for CP-CML (dasatinib<sup>2</sup> and nilotinib<sup>3</sup>), received accelerated approval based upon 12 months of data using MCyR (major cytogenetic response). Nilotinib was converted to regular approval based upon 24 months of data using the endpoint of MMR (major molecular response) at 1 year, with a supportive secondary endpoint of CCyR by 1 year (complete cytogenetic response). Dasatinib was converted to regular approval based upon 24 months of data and the primary endpoint of CCyR (complete cytogenetic response) within 1 year, with a supportive secondary endpoint of MMR (major molecular response).

Among patients with CP-CML who receive nilotinib or dasatinib in a second line setting (after imatinib), 40-50% of them do not achieve a major cytogenetic response (MCyR). Among patients with AP-CML who receive dasatinib, 64% do not achieve a major hematologic response (MHR). Among patients with AP-CML who receive nilotinib, 35% do not achieve a MHR.

In Blast Phase CML, the only second generation TKI approved is dasatinib and approximately 50% of these patients do not experience a MHR.

Today, the standard first treatment for CML in Chronic Phase is one of the three approved TKIs (imatinib, nilotinib, or dasatinib). If the disease does not respond to the first TKI, the patient may receive a second different TKI. At the present time, there are no approved TKI agents for patients with CP-CML in the third-line setting (those whose disease is refractory or intolerant to second-line TKI therapy). The National Comprehensive Cancer Network (NCCN) guidelines presently recommend investigational therapies or allogeneic HSCT after failure of 2 prior TKIs.

Because this application was not being presented to an Advisory Committee, the Division requested clearance of two leukemia specialists and one patient representative for consultation during the review. The Advisors and Consultants staff were consulted to begin clearance of the two leukemia experts on 4/17/12. The two leukemia experts were not able to be cleared for participation prior to the due date for primary or CDTL reviews. However, the patient representative, Elizabeth Paige Brown Strong, was cleared in adequate time for consultation with the Division. Her review is pending as of finalization of this memo. An addendum will be drafted to capture her recommendation once it is received.

## **3. CMC**

*The primary review was completed by Joyce Crich, PhD. The information in this section is from Dr. Crich's primary review. Dr. Crich was unable to provide a recommendation for approval from a CMC standpoint prior to finalization of her review. The final recommendation was pending the firm's agreement to revise the Postapproval Stability Commitment [refer ICH Q1A(R2) II(B)(8)] to monitor the stability of marketed drug products in the proposed commercial container closure system.*

*In the Division Director Memo authored by Sarah Miksinski, PhD, it is stated that ONDQA recommends approval of this NDA and that there are no outstanding CMC deficiencies for this NDA.*

*Dr. Miksinski recommends that the following language be placed into the action letter:*

***An expiration dating period of 24 months is granted for the drug product, when stored at 25°C (77°F) excursions permitted between 15°C to 30°C (59°F to 86°F).***

*The rest of the text in this section is directly from Dr. Crich's review.*

- General product quality considerations

#### Drug Substance

The drug substance bosutinib is a new molecular entity. Detailed information regarding the drug substance is provided in the NDA. Bosutinib monohydrate is manufactured by a

(b) (4)  
Detailed information regarding designation of the (b) (4) proposed starting materials, the commercial sources, acceptance criteria, and associated methods of analysis are provided.

A Quality by Design (QbD) approach was employed for the manufacturing process based on the principles of ICH Q8, Q9 and Q11, including quality target product profile (QTPP), identification of the potential critical quality attributes (CQAs), the process parameters (CPP, KPP) that have a potential impact on these CQAs, and operating spaces for each step of the drug substance manufacturing process by statistically designed multivariate experimental (DoEs) approaches, leading to the overall operating space and control strategy for the manufacturing process. The quality attributes of bosutinib monohydrate are defined in the drug substance specification based on a traditional approach. The key and critical process parameters for each manufacturing step are provided, as well as the regulatory commitment for the operating range.

Bosutinib monohydrate is a white to yellowish tan powder. It is classified as a BCS Class 4 compound (low soluble and low permeable material) with pH dependent solubility. It is non-hygroscopic. The selected polymorph form (b) (4) of bosutinib monohydrate for development and commercialization is the (b) (4)

The submitted stability data support the proposed retest period of (b) (4) when packaged in the proposed container system and stored at controlled room temperature.

#### Drug Product

Bosulif® (bosutinib) tablets are available in 100 mg and 500 mg dosage strengths. The tablets contain bosutinib monohydrate as the active pharmaceutical ingredient equivalent to 100 mg and 500 mg of bosutinib anhydrous together with microcrystalline cellulose, croscarmellose sodium, poloxamer, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow (for 100 mg tablet) and iron oxide red (for 500 mg tablet).

(b) (4)

#### Stability and Shelf Life

The applicant submitted the stability data from three primary batches for the 100 mg strength and 500 mg strength tablets up to 24 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug product in both strengths packaged in HDPE bottles and stored at controlled room temperature. Additionally, the submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

The NDA submission did not include any stability data for the proposed commercial container closure system which is different from the primary stability container closure system (e.g. configuration, fill volume, headspace, MVTR, and amount of desiccant). According to ONDQA's Initial Quality Assessment and Filling Review for this NDA dated 21-Dec-2011 in DARRTS, the issue of lacking stability data for the proposed commercial container closure system was determined as a review issue. During this review cycle, instead of providing any stability data for the proposed commercial container closure system after Agency's information request for such data, the applicant provided the calculations for moisture absorption capacity of desiccant canister and total available moisture within the commercial container closure system to justify the proposed shelf life in the proposed commercial container closure system. The provided justification appears to be reasonable, but it does not completely exclude possible impact on quality attributes linked to water content due to the potential difference in moisture level control. Although the risk of changing container closure system for solid dosage form is relatively small, the provided theoretical calculation of moisture exposure (MVTR vs desiccant capacity) is only a supporting data for moisture-barrier equivalence, and is not a replacement for stability study result from the proposed container closure system. According to ICH Q1A(R2) Section II(B)(4), Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing. Therefore, it is recommended that the Postapproval Stability Commitment be revised to include accelerated studies for 6 months along with the long-term studies through the

proposed shelf life for the first three production batches of bosutinib 100 mg and 500 mg tablets, to monitor the stability trend and to confirm the shelf life, based on ICH Q1A(R2) Section II(B)(8) (refer to the Letter of Information Request dated 18-Jul-2012). The approvability of the drug product bosutinib 100 mg and 500 mg strength tablets packaged in the proposed commercial container closure system is pending the applicant's response to this deficiency.

#### Release Specifications

All lots manufactured were successfully processed through to product and met the proposed release specification criteria. The manufacture experiences at the proposed manufacturing site and proposed manufacturing scale confirm the suitability of the proposed manufacturing process for bosutinib tablets (100 mg and 500 mg).

- Facilities review/inspection  
The Office of Compliance issued an overall "acceptable" recommendation dated 10-May-2012 for all facilities used for manufacturing and control of the drug substance and drug product.
- Product Quality Microbiology: The review was conducted by Robert J. Mello, Ph.D. His review concludes that the application is recommended for approval from microbiology product quality standpoint.

- Other notable issues:

The application cannot be recommended for approval from a chemistry, manufacturing, and controls (CMC) standpoint until the following deficiency is satisfactorily resolved:

*The post-approval stability commitment in Section P.8.2 is not adequate according to ICH Q1A(R2) Section II(B)(8).*

The approvability and the granted expiration dating period for the drug product is pending on the resolution of the deficiency.

- The recommendation and conclusion on the approvability for this NDA were made by incorporating QBD principle, risk management, and scientific rationale based on the stability data from the primary stability study container closure system, provided that if the firm agrees to revise the Postapproval Stability Commitment [refer ICH Q1A(R2) II(B)(8)] to monitor the stability of marketed drug products in the proposed commercial container closure system.

Note: The deficiency above noted by Dr. Crich was resolved and noted as such in Dr. Miksinski's memo.

## **4. Nonclinical Pharmacology/Toxicology**

The non-clinical pharmacology/toxicology review was conducted by Shwu-Luan Lee, Ph.D. (Team Leader, Haleh Saber, Ph.D.). Their review states that there are no pharmacology/toxicology issues which preclude approval of bosutinib (Bosulif®) for the proposed indication. Dr. Lee and Dr. Saber recommend approval of this NDA.

*The text in this section is taken directly from Dr. Lee's review.*

**Pharmacologic Class:** Kinase inhibitor

**Mechanism of action:** inhibitor of Src and Abl family of kinases

Bosutinib (SKI-606) inhibits Bcr-Abl and Src tyrosine kinases. In *in vitro* and/or *in vivo* systems bosutinib inhibited the cellular activities of several imatinib-resistant Bcr-Abl mutants including E255K, G250E, D276G and Y253F mutations. These mutations are commonly identified in CML patients who relapsed after or were resistant to imatinib treatment. Bosutinib exhibited much less effect against T315I mutation than the wildtype Abl.

Orally administered bosutinib was absorbed fairly rapidly ( $t_{max}$  of ~ 1.3-5.5 hr), with variable oral bioavailability (23% to 64%) in animal species. Bosutinib was highly bound to plasma proteins in all species tested (over 90%): mouse, rat, rabbit, dog, and human plasma. Metabolite M5 exhibited a similar protein binding. Following an oral dose of [<sup>14</sup>C]bosutinib in Sprague-Dawley rats, radioactivity was distributed in most tissues and organs, except for brain, indicating a limited ability of bosutinib and/or its metabolites to cross the blood-brain barrier in rats. Radioactivity was found in the placenta, fetus, as well as in the milk of lactating rats. The level of radioactivity in milk was up to 8-fold higher than that in maternal plasma, suggesting excretion of bosutinib and/or its metabolites into the milk of lactating rats. Radioactivity was present in the plasma of suckling pups 24 to 48 hours after lactating rats received a single oral dose of radioactive bosutinib. The level of radioactivity in pup plasma at 24 and 48 hr post-dose was at least 8-fold higher than that in the maternal plasma. In a separate distribution study, tissues rich in melanin, such as uveal tract, showed higher and longer radioactivity retention, indicating that the drug and/or its metabolites have affinity for binding to melanin. However, phototoxicity assessment was negative in pigmented Long Evans rats. After oral administration of [<sup>14</sup>C]bosutinib to mice, rats and dogs, bosutinib was the predominant radiolabeled component in plasma. The major circulating metabolites were M5 (11%) in mice, M9 (up to 17%-24%) in rats, and M5 (up to 20%)/M6 (up to 10%) in dogs. Similarly, bosutinib was the major component in patients' plasma. Of note, the prominent circulating metabolites in humans are M2 and M5 (~19% and 25% of the AUC of parent drug, respectively). The metabolite M2 is a human-specific metabolite. In human liver microsomes, bosutinib was predominantly metabolized by CYP3A4. Metabolite M2 was mainly metabolized via glucuronation by UGT enzymes. The primary route of elimination of bosutinib was via the feces in animals. Under the conditions tested, bosutinib did not inhibit or induce a panel of CYP enzymes. Based on studies conducted in caco-2 cells, P-glycoprotein transporter (P-gp) may be involved in bosutinib transport. There was a concentration dependent inhibition of P-gp mediated digoxin (a prototype P-gp substrate) efflux. While no gender effects were found in PK parameters in dogs, higher systemic exposures to bosutinib were

found in female rats after oral administration of bosutinib.

The safety pharmacology studies and general toxicology studies in rats and dogs identified GI tract, lymphoid tissues, adrenal, thyroid and mammary glands as the target organs/tissues. The major findings are as follows:

- Gastric-intestinal tract:

The most prominent effect of bosutinib in rats and dogs was dose-dependent GI toxicities. The toxicities were observed following a single or multiple oral administration of the drug, and were considered the cause of mortalities. Rats were more susceptible to GI toxicities than dogs. GI clinical signs included: liquid and mucoid feces with red pigment/blood. GI histopathology findings of mucosal/ goblet cell hyperplasia, hemorrhage, erosion and hyperkeratosis were dose-dependent and with a steep dose response relationship. Similar GI-related effects were noted in rabbits in the embryofetal developmental study.

- Hematopoietic/lymphoid system:

The hematology findings were primarily related to bosutinib-induced inflammation and bleeding. These findings included increased white counts (except for lymphocyte), increased platelet count, slight reduction in red cell mass, and increased fibrinogen.

- Liver:

Hepatobiliary findings were reported in rats treated at 70 mg/kg of bosutinib (2-week and 4-week studies) but were of low incidence or of low severity. These findings included centrilobular hyperplasia. There were no changes in liver enzymes.

- Cardiovascular system:

Bosutinib inhibited hERG channel currents at an IC<sub>50</sub> value of 0.3  $\mu$ M and may be considered a moderate potency blocker. In a single-dose safety pharmacology in Beagle dogs, an oral bosutinib dose of 10 mg/kg did not induce cardiovascular toxicity. This dose resulted in an exposure in animals that was less than 2-fold the exposure in patients at the recommended dose of 500 mg. In a separate safety pharmacology study in dogs, transient increases in blood pressure and a secondary reduction in heart rate were observed for 2 minutes after IV infusion of bosutinib. QTc prolongation was reported in patients treated with bosutinib.

### Mutagenicity

Bosutinib was not mutagenic in bacterial Ames test or clastogenic in a chromosome aberration test in human peripheral blood lymphocytes (HPBL). Bosutinib did not increase micronucleus formation in mice after oral doses up to 2000 mg/kg. Metabolite M2 was negative in two *in vitro* genotoxicity studies, the Ames test and the chromosome aberration assay in human peripheral blood lymphocytes (HPBL).

### Reproductive Toxicity

Reproductive and developmental toxicities of bosutinib were investigated in rats and rabbits. Bosutinib was administered orally to pregnant rats during the period of

organogenesis at doses of 1, 3 and 10 mg/kg/day. There was no maternal toxicity or adverse embryo-fetal developmental effects in rats treated with bosutinib up to 10 mg/kg/day (AUCs comparable to those reported in patients at the 500 mg/day dose). This study did not expose pregnant rats to enough bosutinib to fully evaluate adverse outcomes. In a fertility and early embryonic developmental study, decreased implantation and reduced number of viable embryos were observed at 30 mg/kg/day of bosutinib; approximately 1.4 times the human exposure at the clinical dose of 500 mg/day.

In a study conducted in rabbits, bosutinib was administered orally to pregnant animals during the period of organogenesis at doses of 3, 10 and 30 mg/kg/day. At the maternallytoxic dose of 30 mg/kg/day of bosutinib, there were fetal anomalies (fused sternbrae, and two fetuses had various visceral observations), and an approximate 6% decrease in fetal body weight. The exposure at 30 mg/kg/day resulted in exposures (total AUC) approximately 4 times those in humans at the 500 mg/day dose of bosutinib.

In a rat fertility study, drug-treated males were mated with untreated females, or untreated males were mated with drug-treated females. The dose of 70 mg/kg/day of bosutinib resulted in reduced fertility in males as demonstrated by 16% reduction in the number of pregnancies. There were no lesions in the male reproductive organs at this dose. This dose of 70 mg/kg/day resulted in exposure (total AUC) in male rats approximately equal to that in humans at the 500 mg/day dose of bosutinib. Fertility (number of pregnancies) was not affected when female rats were treated with bosutinib; although, decreased implantation and embryonic toxicities were evident at the dose of 30 mg/kg/day (see above). There were no effects on reproductive organs in general toxicology studies.

#### Carcinogenicity

The result of a 2-year carcinogenicity study in rats is under review.

## **5. Clinical Pharmacology/Biopharmaceutics**

The Clinical Pharmacology review was conducted by Elimika Pfuma, PharmD, PhD and her Team Leader was Bahru Habtemariam, PharmD. The Genomics review was also conducted by Elimika Pfuma, PharmD, PhD and her team leader was Rosane Charlab Orbach, PhD. The Pharmacometrics reviewer was Justin Earp, PhD, and his team leader was Christine Garnett, PharmD.

*The text in this section is taken directly from Dr. Pfuma's review.*

During the review cycle, an OCP Briefing was held on June 18, 2012.

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.

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<sup>+</sup> 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. No exposure-response relationships for effectiveness or safety were observed at the dose of 500 mg dose. 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.

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. 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 or inhibitor 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.

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.

1. Recommended Clinical Pharmacology PMRs: 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.

## 6. Clinical Microbiology

*Not applicable.*

## 7. Clinical/Statistical- Efficacy

### Pre-Submission Agency Interactions

The Agency met with the Applicant on several occasions during the development of Bosutinib for CML. The commercial IND was activated on 05/09/04.

On 08/10/07,

(b) (4)

In the comments to the Sponsor, the FDA recommended a blinded central review of cytogenetics for the primary endpoint of MCyR.

On 08/23/10, a pre-NDA meeting was held during which the design of the Phase 3 trial comparing Bosutinib to imatinib in first-line treatment of patients with CML was described.

On 09/28/10 a teleconference was held with the Sponsor to discuss the failed Phase 3 trial. The Sponsor was informed that secondary endpoints would not be considered because the primary endpoint was not met. The Agency indicated that 24-month follow-up data may be sufficient for regular approval in the second-line setting since this was the requirement for dasatinib and nilotinib to convert from accelerated to regular approval.

On 06/30/11, a pre-NDA meeting was held to discuss Wyeth's updated proposal for NDA submission given the failure of the Applicant's Phase 3 trial in patients with newly diagnosed CML. The proposed indication was discussed, "for treatment of patients with CP, AP, or BP CML who are resistant to or intolerant of prior therapy" based upon a single-arm trial. The meeting discussion included the expectation that Wyeth would submit a complete study report and all datasets for trial 3000 with the NDA.

### Issues with Submission:

The original submission review identified problems with the labels for the datasets. There were datasets that represented different data cutoff dates that were names identically. A

teleconference was held with FDA clinical and e-Sub team members and Wyeth to discuss these problems. The Applicant agreed to adjust the datasets for Study 200, Study 3000, and SCS in the NDA. The changes to the datasets were submitted on 12/21/2011 in Seq 002. The trial secondary endpoints varied between the protocol, the statistical analysis plan (SAP), and the Clinical Study Report. Also, in describing endpoints, the documents were not clear on which subgroup the analysis applied to. This made it difficult to make labeling decisions about what endpoints to include, as it was not clear what was actually intended by the Applicant. After internal discussion, it was decided to rely mainly upon the SAP and to model the labeling after the previously approved TKIs. This technique should enhance prescribers' abilities to judge the activity and usefulness from one drug to another.

The primary endpoint was consistent with endpoints that were previously used to support regular approval of dasatinib and nilotinib in the treatment of patients with CML who had received one prior therapy. The Agency has previously accepted MCyR with 24 months of follow-up data as evidence of clinical benefit in the second line CML indication.

**Table 1 Currently Available Therapy for CML**

Treatment	Indication	Dosing Regimen
<b>Imatinib</b>	• Adults with newly diagnosed Philadelphia positive (Ph+) chronic phase (CP) chronic myeloid leukemia (CML)	400 mg/day
	• Adults with Ph+ CP CML after failure of interferon-alpha therapy	
	• Children with newly diagnosed Ph+ CP CML	340 mg/m <sup>2</sup> /day
	• Patients with Ph+ CML in blast crisis, (BC) accelerated phase (AP), or in chronic phase after failure of interferon-alpha therapy	(NTE* 600 mg) 600 mg/day
<b>Dasatinib</b>	• Newly diagnosed adults with Ph+ CML in CP	100 mg/day
	• Adults with CP, AP, myeloid blast phase, lymphoid blast phase, Ph+ CML with resistance or intolerance to prior therapy including imatinib	140 mg/day
	• Adults with Ph+ acute lymphoblastic leukemia (ALL) with resistance or intolerance to prior therapy	140 mg/day
<b>Nilotinib</b>	• Newly diagnosed adult patients with Ph+ CML in CP	300 mg twice daily
	• CP and AP CML in adult patients resistant to or intolerant to prior therapy that included imatinib	400 mg twice daily

\*NTE = Not to exceed; HSCT = hematopoietic stem cell transplantation

The primary clinical review was conducted by Karen McGinn, MS, CRNP. The secondary clinical review was conducted by Virginia Kwitkowski, MS, RN, ACNP-BC. The statistical primary review was conducted by Kallapa Koti, PhD. The statistical secondary review was conducted by Mark Rothmann, PhD.

Trial 3160A4-200-WW (subsequently referred to as Trial 200-WW) was a single-arm, two-part, Phase 1/2, multi-national trial of 570 patients with Chronic Myelogenous Leukemia who had resistance or intolerance of imatinib. Eligible patients may have had additional therapies after imatinib. The study was conducted in North America, the European Union, Eastern

Europe, Africa, and Asia. The trial was conducted in accordance with ICH Guidelines for Good Clinical Practice. Inspections conducted by OSI indicated that the data were reliable.

The trial was conducted from 1/18/06-03/28/11 (the date of database snapshot for this application). The date of the Clinical Study Report reviewed is 10/14/11. Part 2 of the trial was ongoing at the time of submission.

During parts 1 and 2 of the study, 570 subjects received at least 1 dose of Bosutinib. Of these 570, 288 were patients with CP-CML who received second-line treatment with bosutinib, 118 were patients with CP-CML who received third-line or fourth line treatment with bosutinib, and 164 were patients with advanced leukemia (AP CML, BP CML, or Ph+ ALL) who had received prior imatinib or prior imatinib and 1 or more TKIs.

### **Efficacy Endpoints for Part 2 of Trial 200-WW:**

As previously discussed in Section 1 and earlier in this Section, it was not clear, which secondary endpoints were pre-specified because of variations between the SAP, trial protocol, and Clinical Study Report. The endpoints from the SAP were selected for presentation here [Source: Section 5.2.1 SAP; page 22]. No explanation was provided for these discrepancies in the submission.

The original trial design included only two cohorts: 1) imatinib-only exposed patients, and 2) patients with other TKI exposure in addition to imatinib. As other therapeutic options for patients with CML became available, the study was expanded to evaluate specific patient populations, and the design was revised to place chronic phase patients into one of five cohorts and advanced phase patients into one of four cohorts. Allocation to all cohorts was determined by drug history before enrollment and disease status at baseline.

The primary efficacy endpoint for Part 2 of the trial (which was not different between study documents) was “the MCyR rate at week 24 in imatinib resistant chronic phase CML patients who have no prior Src, Abl, or Src-Abl inhibitor exposure other than imatinib”. Subjects must have had a better response than at baseline to be counted as responders. Response status was assessed at screening, every 12 weeks during the first 2 years of treatment, every 6 months beginning in the third year of treatment, and at the final visit.

In order to “benchmark” Bosutinib against the other TKIs, the cumulative MCyR rates will be provided in this review as supportive or exploratory analyses.

### Secondary Endpoints:

The secondary efficacy endpoints will include the following variables for specified cohorts:

- MCyR rate for chronic phase patients
- CHR rate for all the advanced phase patients. A subject with a baseline CHR will be considered a responder if CHR is subsequently confirmed post-baseline
- OHR rate for all the advanced phase patients. A subject with a baseline OHR will be considered a responder if OHR is subsequently confirmed post-baseline
- Duration of MCyR for chronic phase patients

- Duration of confirmed CHR for chronic and advanced phase patients
- Time to MCyR for chronic phase patients
- Time to CHR for chronic and advanced phase patients
- Progression free survival rates at year 1 and year 2 for all enrolled patients
- Time to treatment failure for all enrolled patients
- Overall survival rates at year 1 and year 2 for all enrolled patients

The table below provides the trial cohorts in the protocol final version.

<b>Table 2-1: Overview of Study Cohorts by Protocol</b>				
<b>Phase</b>		<b>Drug History</b>		
		<b>Imatinib</b>	<b>Dasatinib</b>	<b>Nilotinib</b>
<b>Chronic</b>		Resistant or Intolerant (Cohort 1)**	No	No
		Resistant or Intolerant (Cohort 2)*****	Yes	Yes
		Resistant (Cohort 5)	No	No
		Intolerant (Cohort 6)	No	No
		Resistant or Intolerant (Cohort 7)	Resistant	No
		Resistant or Intolerant (Cohort 8)	Intolerant	No
		Resistant or Intolerant (Cohort 9)	No	Resistant
<b>Advanced Unexposed</b>				
<b>Advanced Unexposed</b>	Accelerated	Resistant or Intolerant (Cohort 31)	No	No
	Blast	Resistant or Intolerant (Cohort 32)	No	No
	Ph+ ALL	Resistant or Intolerant (Cohort 33)	No	No
<b>Advanced Exposed*</b>				
<b>Advanced Exposed*</b>	Accelerated	Resistant or Intolerant (Cohort 41)****	Yes	Yes
	Blast	Resistant or Intolerant (Cohort 42)****	Yes	Yes
	Ph+ ALL	Resistant or Intolerant (Cohort 43)****	Yes	Yes
<b>Accelerated</b>		Resistant (Cohort 11)***	No	No
<b>Blast</b>		Resistant (Cohort 12)***	No	No

Note: Original cohort 3 is mapped to cohorts 31, 32 and 33; cohort 4 is mapped to cohorts 41, 42 and 43.

\* Exposed to at least one other TKI: dasatinib, nilotinib or other

\*\* Cohort 1 is mapped to cohorts 5 and 6

\*\*\* Cohort 11 is part of cohort 31; Cohort 12 is part of cohort 32.

\*\*\*\* Yes for either Dasatinib or Nilotinib or both.

\*\*\*\*\* Yes for either Nilotinib intolerant or both Dasatinib and Nilotinib.

### **Efficacy Results:**

The efficacy analyses presented by the Sponsor were repeated and confirmed by Ms. McGinn. There were no disagreements with their efficacy results. The secondary efficacy results in this section will be presented based upon the Statistical Analysis plan but in an order that groups the analyses by logical patient/disease groups (Chronic, Accelerated, and Blast Phase CML). The primary population for efficacy was the evaluable population, which included all treated subjects with an adequate baseline assessment. This population definition is acceptable in a single-arm trial, because it provides the most accurate assessment of efficacy in the population under study.

The following efficacy results were taken directly from Ms. McGinn's review, with the exception of the TTP results which were taken from the Applicant's CSR. The results presented were confirmed via JMP analysis.

#### Primary Endpoint

The primary endpoint of Part 2 of Trial 200 was the **MCyR at week 24 for second-line treatment of patients with CP CML who were resistant to imatinib**. The results for the primary endpoint were 35.5% (95% CI = 28.6, 42.8). The nominal testing level for this endpoint at the final analysis was 0.33. The null hypothesis ([p0]=23%, alternative [p1]=33%) was rejected (1- sided p<0.001); therefore the primary objective of the protocol was met. The median duration of response was not reached.

#### Secondary Endpoints

- **MCyR rate for chronic phase patients**

The MCyR rate at 24 weeks for the overall evaluable Chronic Phase CML population was 33.8% (90 of 266 patients) [90% CI: 29, 38.9].

The MCyR rate at week 24 for second line treatment of patients with CP CML who were intolerant of imatinib was 30% (95% CI = 21.6, 39.5). This cohort did not reach the pre-specified MCyR rate of 53%. The median duration of response was not reached.

- **Duration of MCyR for chronic phase patients**

A total of 142 subjects (53.4%) attained a MCyR during the study, and 108 (76.1%) subjects had maintained the response as of the last assessment prior to the database snapshot. In the imatinib-resistant cohort, 73 (70.9%) subjects maintained the response as of the last assessment prior to the database snapshot and in the imatinib intolerant cohort, 35 (89.7%) have maintained the response.

The K-M estimate of maintaining MCyR at Year 1 and Year 2 was 68.4% (95% CI: [57.8, 76.9]) for both years in the imatinib-resistant cohort and 88.0% (95% CI: [71.1,

95.3]) for both years in the imatinib-intolerant cohort. The median duration has not been reached.

- **Time to MCyR for chronic phase patients**

The K-M median time to MCyR was 32.1 weeks (95% CI: [24.1, 48.0]) in the evaluable population. The K-M median time to a response was 36.0 weeks (95% CI: 24.1, 49.0) for imatinib-resistant subjects and 24.4 (95% CI: [12.3, 48.0]) for imatinib-intolerant subjects.

- **Duration of confirmed CHR for chronic and advanced phase patients**

Of the 244 (85%) patients with second-line CP-CML who attained a confirmed CHR or maintained their baseline CHR, 182 (74.6%) had maintained the response as of the last assessment before the data snapshot. The K-M estimates of retaining a CHR was 84.6% (95% CI: [79, 88.8]) at Year 1 and 72% (95% CI: [65.2, 77.8]) at Year 2. The median duration of CHR had not been reached.

In the AP-CML cohort, 24 subjects (34.8%) maintained or attained confirmed CHR and 66.7% of these subjects maintained the response as of the last assessment before the database snapshot; the K-M estimate of maintaining CHR was 76.7% (95% CI: 52.6, 89.7]) at both Year 1 and Year 2. The K-M median duration of CHR was not reached.

In the BP-CML cohort, 9 subjects (15.0%) maintained or attained confirmed CHR and 22.2% of these subjects maintained the response as of the last assessment before the database snapshot; the K-M estimate of maintaining a response was 12.5% (95% CI: [0.7, 42.3]) at both Year 1 and Year 2. The K-M median duration of CHR was 28.6 weeks (95% CI: [20.1, 40.0]).

- **Time to CHR for chronic and advanced phase patients**

In patients with second-line CP-CML, the K-M median time to confirmed (achieved or maintained) CHR in the evaluable population was 2.1 weeks (95% CI: [2, 2.6]).

In the AP-CML evaluable population, the K-M median time to a confirmed maintained or attained CHR was 36.7 weeks (95% CI: [24.0, 72.0]).

In the BP CML evaluable population, the K-M estimate of median time to a confirmed CHR has not been reached. If a subject entered the study with a CHR at baseline, the earliest a CHR (maintenance) could be achieved was on Day 7. If a CHR was present on Day 7 and confirmed at least 4 weeks later, it was considered to have occurred on Day 7.

- **CHR rate for all the advanced phase patients.** A subject with a baseline CHR will be considered a responder if CHR is subsequently confirmed post-baseline

In AP-CML patients, confirmed OHR, MHR, and CHR were maintained by 55.1% (95% CI: [42.6, 67.1]), 46.4% (95% CI: [34.3, 58.8]), and 34.8% (95% CI: [23.7, 47.2]) of subjects, respectively.

In BP CML subjects, confirmed OHR, MHR, and CHR were maintained or attained by 28.3% (95% CI: [17.5, 41.4]), 18.3% (95% CI: [9.5, 30.4]), and 15.0% (95% CI: [7.1, 26.6]) of subjects, respectively.

- **OHR rate for all the advanced phase patients.** A subject with a baseline OHR will be considered a responder if OHR is subsequently confirmed post-baseline

In AP CML subjects in the evaluable population, the OHR rate by Week 48 was 55.1% (90% CI: [44.5, 65.3]). In BP CML subjects in the evaluable population, the OHR rate by Week 48 was 28.3% (90% CI: [18.9, 39.4]). The analysis cohort did not include 7 AP CML subjects and 4 BP CML subjects who had an inadequate baseline efficacy assessment; hence the total number of AP CML subjects in the evaluable population was 69 and the total number of BP subjects in the evaluable population was 60.

- Progression free survival rates at year 1 and year 2 for all enrolled patients

The K-M estimates of PFS in the all-treated population of patients with CP-CML at Year 1 and Year 2 were 91.3% (95% CI: [86.8, 94.3]) and 80.6% (95% CI: [74.3, 85.4]), respectively (Table 8-22). The K-M median PFS has not been reached.

The K-M estimate of PFS in the AP-CML all-treated population was 64.9% (95% CI: [51.8, 75.3]) at Year 1 and 47.7% (95% CI: [33.2, 60.8]) at Year 2. The K-M median PFS was 22.1 months (95% CI: [14.6, not estimable]).

The K-M estimated PFS in the BP-CML all-treated population was 14.4% (95% CI: [6.0, 26.4]) at Year 1 and 11.5% (95% CI: [4.1, 23.2]) at Year 2. The K-M median PFS was 5.5 months (95% CI: [3.2, 8.3]).

CDTL Comment: PFS is not considered evaluable or substantial evidence for labeling when obtained from a single-arm trial. “Single-arm trials do not adequately characterize time-to-event endpoints such as survival, TTP, or PFS. Because of variability in the natural history of many forms of cancer, a randomized study is necessary to evaluate time-to-event endpoints”<sup>4</sup>

- Time to treatment failure for all enrolled patients

In the second-line CP-CML all-treated patients, the K-M median TTF was 24.8 months (95% CI: [18.2, 35.3]).

In the AP-CML all-treated population, the K-M median TTF was 10.6 months (95% CI: [5.5, 14.6]). In the BP CML all-treated population, the K-M median TTF was 3.1 months (95% CI: [2.5, 4.5]).

CDTL Comment: TTF is not considered evaluable or substantial evidence for labeling. “TTF is a composite endpoint that measures time from randomization to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. TTF is problematic for regulatory use because it does not adequately distinguish efficacy from these additional variables. A regulatory endpoint should be able to distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance.”<sup>4</sup>

- Overall survival rates at year 1 and year 2 for all enrolled patients

The K-M estimate of OS in the all-treated population with CP-CML at Year 1 was 96.8% (95% CI: [94.0, 98.3]) and 90.6% (95% CI: [86.5, 93.5]) at Year 2, with the K-M median OS yet to be reached.

OS for Advanced Phase CML

The K-M estimate of OS in the AP CML all-treated population was 76.0% (95% CI: [64.7, 84.2]) at Year 1 and 65.6% (95% CI: [53.4, 75.4]) at Year 2. The K-M median OS was not reached.

The K-M estimated OS in the BP CML all-treated population was 43.8% (95% CI: [31.3, 55.6]) at Year 1 and 35.4% (95% CI: [23.8, 47.3]) at Year 2. The K-M median OS was 11.1 months (95% CI: [8.9, 19.8]).

CDTL Comment: OS is not considered evaluable or substantial evidence for labeling when obtained from a single-arm trial. “Single-arm trials do not adequately characterize time-to-event endpoints such as survival, TTP, or PFS. Because of variability in the natural history of many forms of cancer, a randomized study is necessary to evaluate time-to-event endpoints”<sup>4</sup>.

- *Non-pre-specified* Cumulative MCyR in patients with second-line CP-CML:

In the second-line CP CML evaluable population, 142 subjects (53.4%; 95% CI: [47.2, 59.5]) achieved a (cumulative) MCyR, with 42.9% (95% CI: [36.8, 49.0]) attaining a CCyR.

## **Efficacy in Advanced Leukemia Subjects Receiving Fourth Line Treatment**

Sixteen (16) advanced leukemia subjects (10 AP-CML and 6 BP-CML) received bosutinib after having prior therapy with all 3 approved TKIs (imatinib, nilotinib, and dasatinib). Three (3) subjects had a response, defined as a hematologic (OHR), cytogenetic, or molecular response and of these, 2 remained on bosutinib as of the database snapshot.

### Statistical Review Issues

Dr. Koti's review confirmed the Applicant's findings as well. Please refer to his review for details of his findings. I do not concur with the following statements in Dr. Koti's review:

1. "Except the imatinib-resistant cohort analysis in Study 3160A4-200-WW, all other cohorts' analyses were either exploratory or indicated inefficacy or were based on small samples. Efficacy results from cohorts other than imatinib-resistant cohort should not be used to support labeling claims."
2. *In Section 5.1 Statistical Issues and Collective Evidence*, Dr Koti wrote: "In this reviewer's opinion, the collective evidence does not support the approval of this application as a whole."

Rationale for disagreement:

1. Dr. Rothmann's secondary review indicates that the two-stage Simon design used for the imatinib-intolerant cohort is not typically used to select an efficacious response rate result, but should be used for "go-no go" decision making. Therefore, in this single-arm trial, we found it adequate for labeling purposes. Refer to Dr. Rothmann's review for further details.
2. Previously approved TKIs for CML have contained data with the same primary and very similar secondary endpoints, with the same duration of follow-up. The clinical reviewer and CDTL agree that the data provided supports the approval of bosutinib for patents with CP-CML, AP-CML, and BP-CML that have received prior TKI therapy.

Conclusion from Dr. Rothmann's Review:

Based on the size of the response rates and the durability of the responses across CML cohorts, it "is" clear how a conclusion or recommendation can be made for approval and labeling claims for all cohorts except the Ph+ ALL cohort (which had a 0% MCyR rate at 24 weeks).

I recognize that for the CML cohorts the size of the response rates are not small and the responses appear to be durable and may be appropriately so for approval in the CML cohorts.

CDTL Note: I verbally confirmed on 08/03/12 with Dr. Rothmann that the word "is" was intended for the first conclusion sentence.

See Ms. McGinn's review Section 6.1.2 for discussion of demographic and disease characteristics of the patients who were enrolled in Trial 200. Overall, the clinical reviewer concurred with the statistical endpoint results.

The clinical team requests that the following PMC should be requested:

The Applicant agrees to continue follow-up of patients enrolled in Trial 200-WW for an additional two years past the March 28, 2011 cut-off date.

## 8. Safety

The safety review for the bosutinib application was conducted by Ms. McGinn. The findings were not entirely consistent with the Applicant's, primarily because of their use of investigator "attribution" which the Division does not support in applications with single-arm trials. According to the FDA Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review, "for the most part, attributions of causality by the investigators should be discounted, and adverse events should be assessed without regard to attribution."<sup>5</sup>

The safety database was adequate in size. The safety evaluation indicates that the adverse event profile for bosutinib is similar to that of the previously approved TKIs (imatinib, dasatinib, and nilotinib) with a few exceptions. Of note, diarrhea appears much more common with bosutinib use (85%) than with the other TKIs (approximately 25% for dasatinib and nilotinib).

The major focus of the safety review (contained in this section) is the data from the phase 2 trial, Trial 200. Reference will be made to PK, QT and drug-drug interaction studies where appropriate. The QT data has been reviewed by the IRT/QT team. Reference will also be made to Trial 3000, and to any signals from the ISS, which includes data from efficacy Trials 200 and 3000 as well as Trial 2203, a trial conducted in Japan.

Safety analyses in trial 200 included:

- Incidence and severity of Adverse Events (AEs) and serious adverse events (SAEs). Progression of underlying malignancy and hospitalization solely for progressive disease were not to be reported as AEs or SAEs.
- Laboratory test abnormalities
- Analysis of Deaths
- Review of Interdisciplinary Review Team's review of thorough QT trial in 70 healthy Volunteers

The Applicant integrated safety data from the 3 clinical trials conducted in patients with CML into a single safety database. Ms. McGinn's safety analysis presented safety data separately for the pivotal trial (Trial 200), and for the randomized controlled trial (Trial 3000). In addition, an integrated safety analysis of the three clinical trials in 870 patients with CML will be presented. The larger safety base did not demonstrate unexpected toxicities compared

with the findings in the pivotal trial. Across the trials the most commonly reported AEs were gastrointestinal toxicities, fatigue, alopecia, neutropenia, thrombocytopenia and rash.

The safety monitoring in the trial was adequate. Though there was not agreement with the Applicant's attributions for some SAEs and deaths, there were no safety signals for SAEs or deaths in the trials conducted with bosutinib.

Almost every patient in Trial 200 experienced treatment emergent adverse events (TEAEs). The most frequent AEs of any grade were diarrhea, abdominal pain, thrombocytopenia, rash, vomiting, fatigue, upper respiratory tract infection, pyrexia, cough, anemia and headache. See Figure 1 below from Ms. McGinn's review.

The datasets for Trials 3000 and 2404 were reviewed and were supportive of the toxicities that occurred during Trial 200. The most noticeable difference was that the incidence of diarrhea was 64% in Trial 3000 rather than 84% as observed in Trial 200.

**Figure 1****Table 30 Common Treatment Emergent Adverse Events in 10% or More Patients Taking Bosutinib for Ph+ CML**

	<b>CP CML Second Line N=288 n (%)</b>	<b>CP CML Third Line N=118 n (%)</b>	<b>Advanced Phase CML N=167 n (%)</b>
<b>Gastrointestinal Disorders</b>			
Diarrhea	244 (85)	103 (87)	118 (71)
Nausea	127 (42)	52 (44)	75 (45)
Vomiting	100 (35)	43 (36)	70 (42)
Abdominal Pain	144 (50)	46 (39)	48 (29)
<b>Blood and Lymphatic System Disorders</b>			
Thrombocytopenia	113 (39)	44 (37)	71 (43)
Neutropenia	34 (12)	18 (15)	27 (16)
Anemia	53 (18)	19 (16)	62 (37)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Rash	109 (38)	37 (31)	57 (34)
Pruritus	29 (10)	19 (16)	11 (7)
<b>General Disorders and Administration Site Disorders</b>			
Fatigue	92 (32)	30 (25)	44 (26)
Pyrexia	66 (23)	17 (14)	59 (35)
Edema	47 (16)	14 (12)	26 (16)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Upper Respiratory Infection	77 (27)	23 (19)	23 (14)
Cough	61 (21)	20 (17)	31 (19)
<b>Nervous System Disorders</b>			
Headache	50 (17)	29 (25)	31 (19)

Source: Karen McGinn's review

The most frequent Grade 3 and 4 TEAEs were thrombocytopenia, neutropenia, anemia, diarrhea, pneumonia, and rash. More patients with AP CML started treatment with pre-existing thrombocytopenia, neutropenia and anemia and experienced increased severity of these events during treatment with bosutinib. See Figure 2 below from Ms. McGinn's review.

Figure 2

Table 31 Grade 3 and 4 TEAEs in Patients Taking Bosutinib for Ph+ CML

	CP CML Second Line N=288 n (%)	CP CML Third Line N=118 n (%)	Advanced Phase CML N=167 n (%)
<b>Blood and Lymphatic System Disorders</b>			
Thrombocytopenia	68 (24)	29 (25)	60 (36)
Neutropenia	20 (7)	14 (12)	25 (15)
Anemia	21 (7)	7 (6)	39 (23)
<b>Gastrointestinal Disorders</b>			
Diarrhea	28 (10)	10 (8)	8 (5)
Nausea	4 (1)	1 (<1)	3 (2)
Vomiting	9 (3)	1 (<1)	6 (4)
Abdominal Pain	4 (1)	2 (2)	6 (4)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Rash	25 (9)	4 (3)	7 (4)
Pruritus	2 (<1)	1 (<1)	0
<b>General Disorders and Administration Site Disorders</b>			
Fatigue	4 (1)	1 (<1)	6 (4)
Pyrexia	2 (<1)	0	3 (2)
Edema	3 (1)	0	2 (1)
<b>Lower Respiratory Tract and Lung Infections</b>			
Pneumonia	9 (3)	0	16 (10)

The most significant laboratory findings during the trial were platelets decreased, hemoglobin decreased, neutrophils decreased, alanine aminotransferase increased, aspartate aminotransferase increased, and bilirubin increased. These laboratory findings support presentations in previous sections of this review regarding myelosuppression and liver toxicity.

The 120-day safety update was submitted March 8, 2012. The 120-day safety update provided no new safety signals.

## 9. Advisory Committee Meeting

An AC meeting was not needed. Bosutinib is the third drug in its class.

## 10. Pediatrics

According to 21 CFR Part 314.55(d) and draft FDA Guidance for Industry titled, “How to Comply with the Pediatric Research Equity Act”<sup>6</sup> issued in September 2005, a submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. On

24 February 2009, bosutinib was granted Orphan Drug status (designation number 08-2748) for the treatment of CML. The orphan designation covers the proposed indication in this application.

## 11. Other Relevant Regulatory Issues

In Section 1.4 of Ms. McGinn's review: This reviewer recommends that the Applicant have postmarket requirements to continue long term follow up of patients enrolled in clinical trials 200 and 3000 for a minimum of eight years and to submit the final completed study reports to the NDA.

As discussed in Section 1 of this memo, I do not concur with this recommendation.

### *Post-marketing Requirements*

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 and concurrence prior to trial initiation.

### *Post-marketing Commitments*

The Applicant agrees to continue follow-up of patients enrolled in Trial 200-WW for an additional two years past the March 28, 2011 cut-off date.

## 12. Labeling

*Other aspects of the review will address labeling in more detail. Only highlights of labeling discussions and areas of concern are to be addressed in this review.*

- Proprietary name: On 7/27/12, DMEPA issued their final review of the proposed proprietary name for bosutinib, "Bosulif". They concluded that the proposed proprietary name is acceptable.
- Physician labeling: Edited labeling containing all sections except for Section 14 (Clinical Studies) was sent to the Applicant on 7/30/12. Section 14 was sent to the Sponsor on 8/03/12. Major revisions were made to the Clinical Studies section (b) (4) Our edits presented the data in a manner that would be easily interpreted by prescribers. The Division awaits response to edited labeling at the time of finalization of this review.

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Regular approval for the indication:

“For the treatment of chronic, accelerated, or blast phase Ph + chronic myelogenous leukemia (CML) in adult patients with resistance or intolerance to prior therapy”

- Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<p><b>Summary of evidence:</b> Patients with chronic myeloid leukemia (CML) who are refractory to or intolerant of approved TKIs have a poor prognosis and limited treatment options. The usual course of CML is response to initial therapy followed by eventual relapse and retreatment with another TKI and eventual progression of disease and death; the only curative treatment is stem cell transplant (SCT), but not all patients have donors and many have comorbidities that preclude SCT.</p>	<p><b>Conclusions (implications for decision):</b> CP-CML is a life-threatening condition that will advance, if untreated to accelerated or blast phase within 3-5 years. Death typically results from complications of bone marrow failure such as bleeding or infectious complications.</p>
Unmet Medical Need	<p><b>Summary of evidence:</b> Approximately 40% of patients eventually discontinue imatinib due to drug resistance, intolerance, or transformation to advanced leukemia, highlighting the need for additional treatment options. Mutations within the BCR-ABL kinase domain have been found in both <i>in vitro</i> and clinical studies to confer resistance to dasatinib or nilotinib.</p>	<p><b>Conclusions (implications for decision):</b> Patients with CML eventually develop resistance to (possibly due to the development of new BCR-ABL mutations) or intolerance of the existing tyrosine kinase inhibitors. New TKIs are needed for the treatment of patients who have already received the approved TKIs.</p>
Clinical Benefit	<p><b>Summary of evidence:</b> Bosutinib was evaluated in a Phase 1/2 trial of 570 patients with CML (CP, AP and BP) or ALL. The trial data submitted contained follow-up information for 24 months. The majority of the patients enrolled had CML that was resistant or intolerant of imatinib (second-line). The trial also enrolled patients with 3<sup>rd</sup> and fourth line CML. Among the patients with second-line CML who were resistant to imatinib, 35.5% achieved the primary endpoint of Major Cytogenetic Response at week 24. This endpoint is more conservative than the previously used primary endpoints of cumulative MCyR. The non-pre-specified result for bosutinib of cumulative MCyR in patients with</p>	<p><b>Conclusions (implications for decision):</b> Bosutinib has established efficacy in a population of patients with CML in various phases (CP, AP, and BP). The efficacy results were comparable to the previously approved TKIs. The duration of follow-up data was the same as the Agency required for the conversion of accelerated approval to regular approval for dasatinib and nilotinib. The dose of 500mg appears to be tolerable and effective.</p>

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	second line CML was 53%, which is comparable to 63% reported in a similar population of patients for dasatinib and 51% for nilotinib.	
Risk	<b>Summary of evidence:</b> The most frequent AEs were diarrhea, abdominal pain, thrombocytopenia, rash, vomiting, fatigue, upper respiratory tract infection, pyrexia, cough, anemia and headache. No significant safety issues were identified by the SAE and death reviews. Safety evaluations are limited with a single arm trial. The trial size was considerable at 570 patients.	<b>Conclusions (implications for decision):</b> The safety profile of bosutinib appears to be similar to that of the other approved TKIs (imatinib, dasatinib, and nilotinib). A REMS was not needed for this approval. The toxicities associated with bosutinib are well known to oncologists who are familiar with the previously approved TKIs for CML.
Risk Management	<b>Summary of evidence:</b> There are no safety issues unique to bosutinib that require a REMS/ETASU.	<b>Conclusions (implications for decision):</b> No REMS/ETASU have been developed for bosutinib.

**Benefit-Risk Summary and Assessment**

The application provides for a positive Benefit-Risk assessment for bosutinib in patients with CML who are refractory to or intolerant of approved TKIs. The clinical efficacy was demonstrated with durable responses. The toxicity profile of bosutinib is similar to the other approved tyrosine kinase inhibitors.

- Recommendation for other Postmarketing Requirements and Commitments

One PMR is being requested

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.

One PMC is being requested

The Applicant agrees to continue follow-up of patients enrolled in Trial 200-WW for an additional two years past the March 28, 2011 cut-off date.

The clinical PMC is needed to update the product labeling with median durations of response, for which many subgroups were not mature at the time of the applicant submission.

## References

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3. Nilotinib Label: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/022068lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022068lbl.pdf) (Version 10/29/07).
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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf>.
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08/06/2012