CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number	203341
Priority or Standard	Standard
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Division / Office	Division of Hematology Products/Office of Hematology and Oncology Products
Reviewer Name	Karen McGinn, MSN, CRNP
Review Completion Date	July 20, 2012
Established Name	Bosutinib
Trade Name	Bosulif
Therapeutic Class	Tyrosine Kinase Inhibitors
Applicant	Wyeth Pharmaceuticals
Formulation	100 mg and 500 mg tablets
Dosing Regimen	500 mg orally once daily
Indication	Patients with Relapsed or Refractory Chronic, Accelerated or Blast Phase Chronic Myeloid Leukemia
Intended Population	Adults

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

Abbreviation	Definition
Abl	Abelson kinase
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	accelerated phase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	total area under the concentration-time curve
Bcr	breakpoint cluster region
Bcr-Abl	protein resulting from the transcription of the Philadelphia chromosome following 9:22 chromosomal translocation
BCR-ABL	fusion gene transcript for Bcr-Abl protein
BP	blast phase
CBC	complete blood count
CCyR	complete cytogenetic response
CHF	congestive heart failure
CHR	complete hematologic response
CI	confidence interval
CK	creatine kinase
Cmax	peak concentration
CML	chronic myelogenous leukemia
CMR	complete molecular response
CNS	central nervous system
CP	chronic phase
CRF	case report form
Crkl	Crk-like protein
CSR	clinical study report
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACS	fluorescence activated cell scanning
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GVHD	graft versus host disease
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQOL	Health-related Quality-of-life
ICF	informed consent form

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MHR	major hematologic response
MI	myocardial infarction
MiHR	minor hematologic response
MMR	major molecular response
MTD	maximum tolerated dose
MUGA	multiple gated acquisition scan
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEL	no evidence of leukemia
OHR	overall hematologic response
OS	overall survival
PCR	polymerase chain reaction
p-CrkL	phospho-CrkL
PCyR	partial cytogenetic response
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PFS	progression free survival
Ph+	Philadelphia chromosome-positive
PK	pharmacokinetics
PS	performance status
QTc	corrected QT interval
QTcF	QT interval corrected using the Fredericia formula
RCP	return to chronic phase
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SRC	proto-oncogene tyrosine-protein kinase
t½	terminal-phase elimination half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
tmax	time of peak concentration
ULN	upper limit of normal
WHO	World Health Organization

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends regular approval of Bosulif (bosutinib) for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance to, or intolerance of prior therapy. The Applicant has provided clinical evidence of activity for bosutinib in patients with CML in second and later lines of treatment and an acceptable risk profile. The pivotal trial was a Phase 2, single arm trial which required all subjects to have previously been treated with imatinib. The trial enrolled 288 patients with Chronic Phase (CP) CML in second line treatment with bosutinib. Of the 288 patients, 200 were resistant to imatinib, and 88 were intolerant of imatinib. The primary endpoint of the trial was major cytogenetic response (MCyR) at 24 weeks in patients with CP CML who were resistant to imatinib. The trial also enrolled patients with CP CML who had been exposed to more than one tyrosine kinase inhibitor (TKI) and patients in advanced phases of CML which includes accelerated phase (AP) and blast phase (BP) and enrolled a small cohort of patients with Ph+ acute lymphoblastic leukemia (ALL). Key secondary endpoints were MCyR at 24 weeks in patients with CP CML who were intolerant of imatinib in second line treatment with bosutinib; MCyR by 24 weeks in patients with third line CP CML, and objective hematologic response (OHR) by 48 weeks in patients with AP CML, BP CML and Ph+ ALL.

The MCyR rate for patients with CP CML who were imatinib resistant and were in second line treatment with bosutinib at 24 weeks was 35.5% (95% CI: 29, 42). The Kaplan-Meier estimate of maintaining MCyR at Year 1 and Year 2 was 68.4% (95% CI: 58, 77) for both years in the imatinib-resistant cohort.

The MCyR rate for patients with CP CML who were imatinib intolerant and were in second line treatment with bosutiniib at 24 weeks was 30% (95% CI: 20, 40). The Kaplan-Meier estimate of maintaining MCyR at Year 1 and Year 2 was 88% (95% CI: 71, 95) for both years in the imatinib-intolerant cohort.

The MCyR rate for patients with CP CML who were in third line treatment with bosutinib following prior treatment with imatinib and dasatinib or imatinib and nilotinib by week 24 was 27% (95% CI: 19, 36). The Kaplan-Meier estimate of maintaining MCyR was 63.9% (95% CI: [44, 78) at Year 1 and 59% (95% CI: 39, 75) at Year 2.

The confirmed OHR rate by week 48 in patients with AP CML and prior therapy with more than one TKI (AP multi TKI) was 43% (95%CI: 26, 63) with a median duration of 42 weeks. Confirmed CHR rate in the same cohort was 27% (95% CI: 11, 42) with a median duration of 74 weeks. The confirmed OHR rate by week 48 in patients with AP CML and prior imatinib

only was 64% (95% CI: 47, 79) with a median duration of 53 weeks. The confirmed CHR rate by week 48 in the same cohort was 41% (95% CI: 26, 56) with a median duration of 69 weeks.

The confirmed OHR rate by week 48 in patients with BP CML and prior therapy with more than one TKI (BP multi TKI) was 19% (95% CI: 6, 38) with a median duration of 31 weeks. Confirmed CHR in the same cohort was 4% (95% CI: 0, 20) with a duration of 28 weeks. The confirmed OHR rate by week 48 in patients with BP CML and prior imatinib only was 36% (95% CI: 20, 55) with a median duration of 29 weeks. Confirmed CHR rate in the same cohort was 24% (95% CI: 10, 39) with a median duration of 26 weeks.

Only 2 of 24 patients with Ph+ ALL responded, and the Applicant discontinued enrollment of this cohort after the first interim analysis. Because the population of patients with Ph+ ALL was small in this trial, and because there were few responders in this cohort, the Sponsor did not seek an indication and the results will not be reflected in labeling.

1.2 Risk Benefit Assessment

This risk benefit assessment of bosutinib considers the following factors: 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; the clinical activity of bosutinib must be weighed against the toxicities of therapy; and the limitations of a single arm trial must be considered.

The Applicant has demonstrated clinical activity of bosutinib in the treatment of patients with relapsed and refractory chronic, accelerated and blast phases of chronic myeloid leukemia (CML). Responses in patients in all phases of CML were durable, and as expected, patients in chronic phase CML had higher response rates and more durable responses than patients in accelerated and blast phases. Also as expected, patients in second line treatment with bosutinib had better response rates than those in third line treatment. However the trial data is not yet mature; and median duration of response in most cohorts had not been reached.

The toxicity profile of bosutinib is similar to the other approved tyrosine kinase inhibitors with a few exceptions. More than eighty per cent of patients treated with bosutinib experienced diarrhea, but this toxicity was manageable, was usually low grade, and did not account for many discontinuations. The incidence of diarrhea with bosutinib was worse than what has been seen in trials of other TKIs in patients with CML.

Prolongation of the QT interval has been observed in patients treated with nilotinib, but this toxicity was not observed with patients taking bosutiniib. In addition, a thorough QT study was

conducted by the Applicant and reviewed by the Independent Review Team of the Office of New Drugs.

Myelosuppresion was expected and manifested as thrombocytopenia, neutropenia, anemia, and neutropenia in rates similar to what were observed in the pivotal trials for the other TKIs. Fluid retention was expected by the Applicant to be less frequent than with the previously approved TKIs, because bosutinib did not inhibit the PDGF receptor in preclinical studies. Fluid retention did manifest in patients treated with bosutinib. Events of peripheral edema and pleural and pericardial effusions were reported. However, an additional serious toxicity, congestive heart failure, was not reported with bosutinib.

Hepatotoxicity has been observed with imatinib, dasatinib and nilotinib, and all three agents have Warnings and Precautions for hepatotoxicity in their labels. Bosutinib also causes elevations of liver enzymes, but there have been no cases of drug induced liver injury in the CML trials. However, there was one patient with drug induced liver injury enrolled in Trial 2207-WW, a trial that enrolled patients with metastatic breast cancer who received a combination of bosutinib and letrozole. The hepatotoxicity started within the first week of treatment and resolved after discontinuation of bosutinib.

Tumor lysis syndrome has occurred in patients taking nilotinib, but has not been observed with bosutinib. Hemorrhage has occurred in patients taking imatinib and dasatinib and to a lesser degree in patients taking bosutinib. Because the pivotal trial is a single arm trial with a small number of subjects (570), the safety profile of bosutinib is limited. The Applicant submitted the safety database from a failed Phase 3 trial (Trial 3000-WW) as supportive evidence. The trial was a randomized, controlled trial which compared 248 patients randomized to receive bosutinib with 251 patients randomized to receive imatinib as first line treatment for CML. The safety profile in the Phase 3 trial was similar to that of the Phase 2 trial.

In addition, the Applicant submitted data from a Phase 2 trial in Japan in 52 patients with CML (Trial 2203-JA). The total safety database for patients with CML receiving treatment with bosutinib is comprised of 870 patients. The safety profile in the Japanese trial was similar to that of the pivotal trial.

In summary, bosutinib offers another treatment option for patients with CML who have limited options, and has an acceptable safety profile. Bosutinib has demonstrated activity in patients with CP, AP and BP CML that is resistant to or intolerant of previous TKI therapy.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommended postmarket risk evaluation and mitigation strategies for bosutinib.

1.4 Recommendations for Postmarket Requirements and Commitments

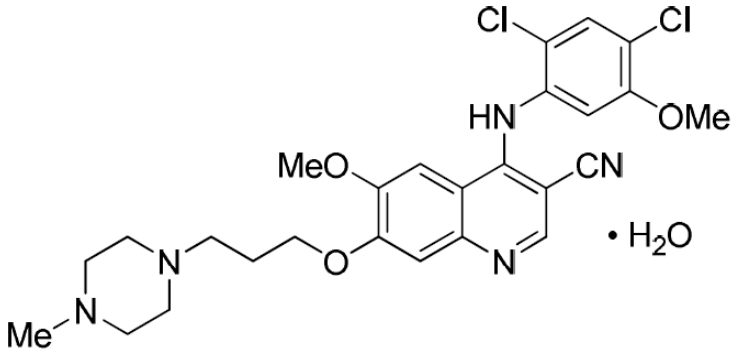
This reviewer recommends that the Applicant have postmarket requirements to continue long term follow up of patients enrolled in clinical trials 200 and 3000 for a minimum of eight years and to submit the final completed study reports to the NDA.

2 Introduction and Regulatory Background

2.1 Product Information

Bosutinib monohydrate is a new molecular entity with the chemical name 3-Quinoline-carbonitrile, 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-piperazinyl) propoxy]-, hydrate (1:1). See Figure 1. Bosutinib is manufactured into 100 mg and 500 mg tablets. The 100 mg tablets are yellow, oval-shaped, immediate release film coated tablets with appropriate debossing; Bosutinib film coated tablets, 500 mg are red, oval-shaped, immediate release film coated tablets with appropriate debossing.

Figure 1 Chemical structure of bosutinib monohydrate (Applicant Figure)



The drug product composition is presented in Table 1.

Table 1 Drug Product Composition (Applicant Table)

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**	

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently there are three tyrosine kinase inhibitors approved for the treatment of patients with CML. All three have demonstrated efficacy in inducing remissions; however the only curative treatment for patients with CML is allogeneic hematopoietic stem cell transplantation. Many patients are ineligible for transplantation due to other co-morbidities or advanced age, and many patients do not have a suitable donor. See Table 2.

Other drugs that have been approved for patients with CML but do not have as favorable a benefit/risk profile as the TKIs are the following: Busulfan, cyclophosphamide, interferon alpha, cytarabine and mechorethamine.

Table 2 Tables of Currently Available Treatments for CML (Reviewer Table)

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

*NTE = Not to exceed; HSCT = hematopoetic stem cell transplantation

2.3 Availability of Proposed Active Ingredient in the United States

Bosutinib is a new molecular entity and is presently not marketed in the United States nor in any other country.

2.4 Important Safety Issues with Consideration to Related Drugs

Bosutinib is the fourth drug in the class known as tyrosine kinase inhibitors (TKIs) which are used in the treatment of patients with CML. The three currently marketed TKIs used to treat CML have the following Warnings and Precautions in their labels:

Imatinib
- Pregnancy
- Fluid retention and edema
- Gastrointestinal irritation
- Hemorrhage
- Hematologic toxicity manifesting as anemia, neutropenia and thrombocytopenia
- Hepatotoxicity

Dasatinib

- Myelosuppression manifesting primarily as thrombocytopenia and neutropenia
- Bleeding events associated with severe thrombocytopenia
- Fluid retention, sometimes severe, including ascites, edema and pleural and pericardial effusion
- QT prolongation
- Congestive heart failure, left ventricular dysfunction and myocardial infarction
- Pulmonary arterial hypertension
- Pregnancy

Nilotinib

Boxed warning: Prolongs the QT interval—monitor for hypokalemia or hypomagnesemia and correct deficiencies. Sudden deaths have been reported. Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors

- Myelosuppression
- QT prolongation
- Sudden deaths
- Elevated serum lipase
- Liver function abnormality
- Electrolyte abnormalities
- Hepatic impairment
- Tumor lysis syndrome
- Drug interactions
- Food effects
- Pregnancy

The safety review of this application will direct particular attention to the above toxicities that have been identified with the other TKIs.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

May 9, 2004--IND 68268 activated for a new tyrosine kinase inhibitor, SKI-606 for patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML)

August 10, (b) (4) FDA also recommended a blinded central review of cytogenetics for the primary endpoint of MCyR.

August 23, 2010-- Pre-NDA meeting at which Phase 3 trial design comparing bosutinib versus imatinib in first-line treatment of CP CML was described.

September 28, **2010**--Teleconference with sponsor to discuss results from Phase 3 trial; trial failed its primary endpoint (superiority design, CCR rate at one year), and the Agency informed the sponsor that secondary endpoints would not be considered as primary endpoint was not met. In discussion about the Phase 1/2 single-arm Trial 200, the Agency indicated that 24-month follow-up data may be sufficient for full approval in the second line setting since this was the requirement for both dasatinib and nilotinib to convert from accelerated to regular approval.

May 30, 2011—Submission of interim report of failed Phase 3 randomized, controlled trial which compared bosutinib to imatinib in the treatment of patients newly diagnosed with CML. The primary efficacy endpoint was complete cytogenetic response (CCyR) by one year after starting treatment; there was no significant difference between the two arms. This Phase 3 trial will be discussed in the safety section of this review.

June 30, 2011—Pre-NDA meeting to discuss Wyeth's updated proposal for NDA submission given the failure of the Applicant's Phase3, randomized trial to meet its primary endpoint in patients with newly diagnosed CML. The proposed indication is for treatment of patients with CP, AP or BP CML who are resistant to or intolerant of prior therapy based on a single-arm trial. The meeting discussion included the expectation that Wyeth would submit a complete study report and all data sets for trial 3000 with the NDA>

2.6 Other Relevant Background Information

CML is a myeloproliferative disorder that presents in three phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP). Since the advent of the first tyrosine kinase inhibitor, imatinib, the 8 year overall survival rate in patients in chronic phase, has increased from 6% (1975) to 86% (after 2001). Progression to AP signals a more aggressive course, and progression to blast phase translates to a median survival of less than one year.
An estimated 5430 patients will be diagnosed with CML in the United States in 2012.*
Approximately 95% of patients with CML harbor the characteristic cytogenetic abnormality of chromosome 22, known as the Philadelphia chromosome. It results from a reciprocal translocation of chromosomes 9 and 22, a process that produces the *Bcr-abl* fusion gene. The *Bcr-abl* fusion gene codes for the constitutively active tyrosine kinase *Bcr-abl* oncoprotein, which is linked to both the oncogenesis and maintenance of CML. This same *Bcr-abl* fusion gene exists in a small subset of patients with acute lymphoblastic leukemia (ALL).

* SEER Cancer Statistics, based on November 2011 SEER data and posted to SEER website, 2012

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was entirely electronic. The original submission used the same titles for three sets of datasets obtained at different time points which presented potential review issues. However, the Applicant responded promptly to requests by the Division of Hematology Products for a clearer presentation of the data, and the resulting format was easier to review.

3.2 Compliance with Good Clinical Practices

The protocol, the investigator's brochure, and the informed consent form (ICF) for the pivotal clinical trial were submitted to an institutional review board (IRB) or an independent ethics committee (IEC) for review and written approval. Subsequent amendments to the protocol and revisions to the ICF were submitted for IRB or IEC review and written approval. The trial was conducted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. All investigators provided written commitments to comply with GCP standards and the protocol. Written informed consent was obtained from all subjects before their enrollment. The identity of the subjects remained confidential.

Protocol Violations
There were major protocol violations in 11 (4%) of the CP CMP second-line population of patients. Ten of these were inclusion criteria violations and one was an exclusion criterion violation. None of these violations seemed to have compromised patient safety during the trial nor inflated efficacy parameters during analysis of the trial.

There were major protocol violations in 5 (4%) of the CP CMP third-line population of patients. Two of these were inclusion criteria violations, two were exclusion criteria violations and one was a prohibited medication during bosutinib treatment violation. None of these violations seemed to have compromised patient safety during the trial nor inflated efficacy parameters during analysis of the trial.
There were major protocol violations in 14 (8%) of the AP CML population of patients. Seven of these were inclusion criteria violations, two were exclusion criteria violations and five were prohibited medications during bosutinib treatment violations. None of these violations appear to have compromised patient safety during the trial nor inflated efficacy parameters during analysis of the trial. See Table 3.

Table 3 Protocol Violations in Trial 200 (Reviewer Table)

Subject	Type of Violation	Comment
107-000421	Inclusion Criterion	Inadequate sample for cytogenetics
041-001004	Inclusion Criterion	Inadequate sample for cytogenetics
005-003113	Inclusion Criterion	No Ph+ chromosome detected
008-000669	Inclusion Criterion	Taking imatinib until 3 days before start of trial
017-000439	Inclusion Criterion	Taking imatinib until 3 days before start of trial
040-000990	Inclusion Criterion	Low platelet count (66,000)
041-001004	Inclusion Criterion	Not intolerant of or resistant to imatinib
095-002276	Inclusion Criterion	Low platelet count (47,000)
041-001003	Inclusion Criterion	INR not done
041-001004	Inclusion Criterion	INR not done
001-000004	Exclusion Criterion	Inadequate recovery time post surgery
003-000109	Inclusion Criterion	Not resistant to or intolerant of imatinib
117-002832	Inclusion Criterion	Part of chemistry not done
017-000425	Exclusion Criterion	Ph+ but Bcr-Abl negative
012-000242	Exclusion Criterion	Extramedullary disease only
020-000514	Prohibited medication	Cyclosporine
071-002058	Inclusion Criterion	Inadequate sample for cytogenetics
071-002064	Inclusion Criterion	Inadequate sample for cytogenetics
008-000667	Inclusion Criterion	Taking nilotinib until 3 days before start of trial
017-000427	Inclusion Criterion	Taking imatinib until start of trial
008-000677	Inclusion Criterion	Taking imatinib until 3 days before start of trial
017-000423	Inclusion Criterion	Abnormal INR (1.44)
045-001046	Inclusion Criterion	Abnormal INR (1.26)
008-000671	Exclusion Criterion	Inadequate recovery time post surgery
045-002116	Exclusion Criterion	Coagulation panel, part of chemistry and differential not done
016-000361	Prohibited medication	Fluconazole
017-000427	Prohibited medication	Fluconazole
045-001046	Prohibited medication	Fluconazole
054-001329	Prohibited medication	Fluconazole
095-002272	Prohibited medication	Amitriptyline

Division of Scientific Integrity

Division of Scientific Integrity (DSI) conducted inspections at the two investigational sites in the U.S. with the highest enrollments, M.D. Anderson and Emory University. Preliminary results indicate that the data are acceptable. The Site at Emory University received a VAI—No Response Requested for failure to obtain continuing IRB approval. For the complete report see the review of Anthony Orencia, M.D. See Table 4 for a summary of the findings.

Table 4 Division of Scientific Integrity Findings Regarding Data Integrity

Name of CI City, State	Protocol/Study Site	Insp. Date	Final Classification*
Jorge Cortes, M.D. Houston, TX	3160A4-200-WW Site #001	May 9 to 18, 2012	Preliminary: NAI
Hanna Khoury, M.D. Atlanta, GA	3160A4-200-WW Site #017	March 22 to April 2, 2012	VAI—No Response Requested
Wyeth Pharmaceuticals, Inc. Groton, CT	Sponsor Sites #001 and #017	April 24 to 30, 2012	Preliminary: NAI

*Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations from regulations. Data unreliable/Critical findings may affect data integrity. Preliminary= The Establishment Inspection Report (EIR) has not been received and findings are based on preliminary communication with the field.

Reviewer Comment: *The nature of the deficiencies was deemed unlikely to significantly impact data reliability. The trial appeared to have been conducted adequately, and the data generated may be used in support of the indication.*

3.3 Financial Disclosures

During this reviewer's early analysis of the financial disclosures prior to the filing meeting, the following statements were accurate:

- The Applicant submitted financial disclosure information from 99.4% of principal investigators and sub-investigators on Trial 200 and 100% of principal and sub-investigators on Trial 3000.
- Disclosable financial interests were recorded by 2 out of 501 (<1%) investigators in Trial 200, and 3 out of 764 investigators in Trial 3000.

The Applicant submitted updated financial disclosure information on April 17, 2012.

- Table 5 summarizes the investigators with disclosable financial interests in the bosutinib development program.

Table 5 Disclosable Financial Interests in Trials 200 and 3000 (Reviewer Table)

Trial	Site	Investigator Name	Patient Enrollment	Disclosure
200	(b) (6)		(b) (4)	$ 91,035.99
200				$335,200.00
3000				$ 41,568.98
3000				$335,200.00
3000				$ 54,337.45

Reviewer Comment: *The financial disclosures cast some uncertainty about possible bias in the two trials due to one sub-investigator with significant disclosable interests whose site* (b) (6) *enrolled the* (b) (4) *of the total number of patients in Trial 200.*

The following factors mitigate this uncertainty:

- *The primary endpoints were all laboratory endpoints and were objective measures of response*
- *A sensitivity analysis of the cytogenetic and hematologic responses in patients enrolled at this site were similar to those in the overall trial population.*

The results of Trial 200 appear reliable.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review of NDA 203341 was conducted by the Office of New Drugs Quality Assurance (ONDQA). For a detailed presentation of biopharmaceutics, see the review of Akm Khairuzzaman, Ph.D. For a detailed presentation of product quality, see the review of Joyce Crich, Ph.D.

4.2 Clinical Microbiology

The drug product microbiology review was conducted by the Office of Pharmaceutical Science, New Drug Microbiology Staff. For a detailed presentation, see review of Robert Mello, Ph.D.

4.3 Preclinical Pharmacology/Toxicology

The preclinical pharmacology/toxicology review was conducted by the Division of Hematology and Oncology Toxicology (DHOT).

Bosutinib was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames Test), the *in vitro* test using human peripheral blood lymphocytes and the micronucleus test in orally treated male mice.

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 dose of bosutinib, Fertility (number of pregnancies) was not affected when female rats were treated with bosutinib. However, there were increased embryonic resorptions at ≥10 mg/kg/day of bosutinib (40% of the human exposure), and decreased implantations and reduced number of viable embryos at 30 mg/kg/day of bosutinib (1.4 times the human exposure).

For a detailed presentation see the review of Shwu Luan Lee, Ph.D.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Bosutinib belongs to a pharmacologic class of drugs called TKIs. It inhibits the abnormal Bcr-Abl kinase that promotes CML as well as the Src-family of kinases including Src, Lyn and Hck. Bosutinib causes minimal inhibition of PDGF receptor and c-Kit.

Please see the review of bosutinib by Elimika Pfuma, Pharm.D., Ph.D. for a detailed presentation of mechanism of action.

4.4.2 Pharmacodynamics

PK and pharmacodynamic studies were performed in which flow cytometry was used to monitor inhibition of Bcr-Abl tyrosine kinase activity in the peripheral blood of CP CML patients treated with bosutinib. The goal of this work was to estimate the suppression of kinase activity in subject cohorts defined by disease type (CP CML or Ph+ ALL), stage of disease, prior therapies, and different doses of bosutinib. A protocol-specified secondary objective of Part 1 (dose escalation phase) of the study was to obtain data on the ability of bosutinib to inhibit Bcr-Abl kinase activity at various dose levels. Part 1 comprised 18 imatinib-resistant subjects (17 with CP CML and 1 with AP CML) who received the following doses: 400 mg (n=3), 500 mg (n=3) and 600 mg (n=12). Whole blood was drawn immediately prior to and 6 hours after bosutinib dosing on days 1, 8 and 15, for a total of 6 measurements, with the first blood draw providing the baseline measurement. Phosphorylation of CrkL(Y207), a well-known Bcr-Abl target, was monitored in whole blood cells, as well as in the CD3+ (T cell), CD19+ (B cell), and CD34+ (blast cell) compartments. All work was performed at (b) (4)

(b) (4), following approval of an assay validation document prior to the evaluation of clinical samples. p-CrkL signals were consistently highest in the whole blood assays, whereas the other compartments did not stain consistently for p-CrkL, and showed no staining in some samples. Thus, by necessity, the pharmacodynamic analysis was focused on the p-CrkL signal in the whole blood compartment.

A total of 287 patients (Part 1 and Part 2) provided a baseline sample that was successfully evaluated by flow cytometry, and between 50 and 220 samples were measured at each of the 5 time points during treatment. The results were tabulated for each subject, and also summarized for each cohort (where cohorts are defined based on bosutinib dose in Part 1, and based on disease stage and prior therapies in Part 2).
At the cohort level, no consistent trends suggesting decreased p-CrkL levels in response to bosutinib were noted relative to the corresponding mean baseline signal. In addition, virtually all datasets were accompanied by high CVs. Therefore, the team further evaluated the dataset by reviewing p-CrkL signals over time for individual subjects. For most subjects, the lack of discernable trends in p-CrkL levels over time reinforced the conclusions from the cohorts; these analyses also indicated points where fluorescence activated cell scanning (FACS) data were not successfully generated.

Reviewer Comment: *Because the trial did not elucidate any trends regarding p-Crkl levels in response to bosutinib, and FACS data were not successfully generated, the pharmaco-dynamics of bosutinib are not fully characterized at this time.*

Please see the review of Elimika Pfuma, Pharm.D, Ph.D. for a detailed presentation of Pharmacodynamics.

4.4.3 Pharmacokinetics

Absorption: Bosutinib has linear PK in the dose range of 200 – 800 mg. The median T_{max} ranges from 3 to 6 hours and a 2 – 3 mean accumulation ratio is observed at steady-state. The absolute bioavailability of bosutinib has not been assessed. A high-fat meal caused a 2-fold increase in exposure. However, food also increased tolerability to bosutinib, therefore bosutinib was co-administered with food in patient trials thereafter.

Distribution
After administration of a single dose of BOSULIF (500mg) with food to healthy subjects, bosutinib had a mean apparent volume of distribution (standard deviation) of 7,700 L (±2,940 L), suggesting that bosutinib is extensively distributed to extra-vascular tissue.
Bosutinib was highly bound to human plasma proteins *in vitro* (94%) and *ex vivo* in healthy subjects (96%), and binding was not concentration-dependent.

Metabolism and Drug-Drug Interactions: Bosutinib is primarily metabolized by CYP3A4. It is a P-gp substrate and inhibitor, *in vitro*. Ketoconazole (strong CYP3A4 inhibitor) increased bosutinib C_{max} 2.9- to 5-fold and AUC 6.5- to 8.9-fold. Rifampin (strong CYP3A4 inducer)

decreased the C_{max} by 86% and the AUC by 94%. Therefore, we recommend that the use of strong and moderate CYP3A4 inhibitors and inducers should be avoided. A 2-fold increase in exposures was observed in patients with hepatic impairment. The applicant proposes a dose adjustment to 200 mg in patients with hepatic impairment.

Elimination: The mean elimination half-life of bosutinib after a single dose in patients ranged from 19 to 30 hours. Based on an oral mass balance study, only 3% of radioactivity was recovered in urine.

Please see the reviews of Elimika Pfuma, Pharm. D., Ph.D. and Justin Earp, Ph.D. for detailed presentations of Clinical Pharmacology.

4 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

In addition to three clinical trials in patients with CML, the Applicant submitted data from 18 additional trials: 4 bioavailability and bioequivalent trials, 5 hepatic and drug interaction trials, 4 PK trials, 1 QT trial and 4 efficacy trials in patients with breast cancer. This review is based primarily on Trial 200. Trials 2203 and 3000 were analyzed primarily for safety. See Table 6.

Table 6 Tables of Clinical Trials (Reviewer Table)

Trial	Trial Design	Treatment Groups (N)	Endpoint
200	Phase 1/2 open-label, 2-part trial in subjects with Ph+ leukemia	• CP CML Second line (288) and Third line (118) • AP CML (144); Ph+ ALL (24)	MCyR @ week 24 CHR by week 48
3000	Phase 3 RCT in subjects with newly diagnosed CP-CML to compare bosutinib to imatinib	• CP CML treated with bosutinib (248) • CP CML treated with imatinib (251)	CCyR @ 1 year CCyR @ 1 year
2203	Phase 1/2 open-label trial in subjects with Ph+ leukemia	• Phase 1 (17) • Phase 2 (35)	MTD MCyR and CHR

MCyR = Major Cytogenetic Response; CCyR = Complete Cytogenetic Response

MTD = Maximally Tolerated Dose; CHR = Complete Hematologic Response

5.2 Review Strategy

The clinical review for this NDA was conducted by Karen McGinn, M.S.N., C.R.N.P., Senior Clinical Analyst, Division of Hematology Products, Office of Hematology and Oncology Products.
This clinical review included the following:

- A survey of current literature on diagnosis, classification and treatment of CML using standard textbooks, reviews, references submitted by the sponsor and publications listed in PubMed;
- Review of the Applicant's description of all trials submitted with this NDA including Trial B1871008 3160 A4 3000 WW (Trial 3000) and Trial B1871006 3160 A4 200 WW (Trial 200);
- Review of supporting tables and data listings of various aspects of the trials, especially objective response rates and adverse events, for evaluation of the Applicant's claims;
- Review of datasets submitted as SAS transport files;
- Review of patient narratives of serious adverse events and deaths;
- Review of meeting minutes conducted during drug development;
- Review of reviews conducted by other disciplines including Pharmacology/ Toxicology, Clinical Pharmacology, Biopharmacology, Biostatistics, CMC, and Office of New Drug Quality Assessment;
- Review of consultations with Office of Scientific Investigations, Division of Medication Error Prevention and Analysis, Interdisciplinary Review Team for QT Studies, and the Division of Drug Marketing, Advertising and Communications;
- Requests for additional information from the Applicant;
- Formulation of conclusions and recommendations;
- JMP analyses of datasets of patient demographics, prior therapies, disease state, response criteria, laboratory data, and adverse events to confirm the Applicant's major analyses; and
- Evaluation of proposed labeling.

5.3 Discussion of Individual Clinical Trials

Trial 200 is the primary focus of this review although Trials 2203 and 3000 are summarized in this section and with the safety review in section 7.

<u>Trial 200</u>
Trial 200 was a single arm, Phase 1/2, open label trial that enrolled patients with CML in one of its three stages: CP, AP, and BP or Ph+ 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.

Trial Objectives
(Source: Clinical Study Report, Section 9.0)

Part 1—Dose Escalation Component
Primary
- Define the maximum tolerated dose, less than or equal to 1000 mg/day, in subjects with CML in chronic phase resistant or refractory to imatinib.
- Evaluate the overall PK parameters in this population

Secondary
- Determine the rate of Major Cytogenetic Response in chronic phase subjects at various dose levels of SKI-606
- Obtain data on the ability of SKI-606 to inhibit phosphorylation of CrkL and BCR-Abl at various dose levels

Exploratory
- Explore the pharmacogenomic effects of SKI-606 in subjects with chronic phase CML

Part 2—Efficacy Component

Primary Endpoints
- Determine the rate of attaining major cytogenetic response in subjects entering with imatinib-resistant chronic phase CML, who have no prior Src, Abl, or Src-Abl kinase inhibitor exposure other than imatinib
- Determine the population PK parameters of this population

Secondary Endpoints
1. Estimate the time to and duration of MCyR in subjects entering with imatinib-resistant chronic phase CML, who have no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
2. Estimate MCyR rate in subjects with CP CML intolerant of imatinib, who have no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
3. Estimate the time to and duration of MCyR in subjects with CP CML intolerant of imatinib, who have no prior Src, Abl, or Src/Abl kinase inhibitor exposure other than imatinib
4. Estimate the time to and duration of CHR in the imatinib-resistant and imatinib-intolerant groups.
5. Estimate MCyR rate in subjects with CP CML who have failed imatinib and are resistant to other tyrosine kinase inhibitors (dasatinib or nilotinib)
6. Estimate MCyR rate in subjects with CP CML who have failed imatinib and are intolerant of dasatinib or nilotinib

7. Estimate the overall survival (OS) and progression free survival (PFS) rates at 1 and 2 years
8. Estimate CHR rate in subjects with advanced leukemia (AP CML, BP CML, Ph+ ALL)
9. Estimate OHR rate in subjects with imatinib-resistant accelerated phase and blast phase CML
10. Assess the safety of bosutinib during prolonged oral exposure in a leukemic population

Exploratory Endpoints

- Estimate the rate of molecular responses in those whose best prior response was CCyR and cytogenetic responses in those previously attaining only CHR.
- Define PD effects of bosutinib on activation of Src-family kinases and downstream substrates
- Evaluate patient reported outcomes endpoints by administering quality of life questionnaires

The Statistical Analysis Plan called for three interim analyses (futility at 25% and 50% enrollment and efficacy at 75%) with alpha expenditure at each analysis. Only one cohort met the boundary for futility, the cohort of patients receiving second line treatment for CP CML who were intolerant of imatinib; however the Applicant made the decision to continue the trial in this cohort after a literature review of patient responses to dasatinib indicated that the pre-specified futility boundary had been set too high.

Patients took bosutinib daily and could continue treatment until disease progression, unacceptable toxicity, subject request, protocol violation, non-compliance, or other reason. During part 2, a subject's dose could be increased to 600 mg for lack of efficacy (failure to reach CHR by week 8 or CCyR by week 12) if the subject did not have a grade ≥3 drug related adverse event (AE). The protocol also contained provisions for dose reduction in 100-mg decrements for toxicity to a minimum dose of 300 mg. Responses were determined by local investigators who made their assessments using the results of local laboratories.

Applicant's Definitions of Resistance and Intolerance

Dosing Requirements
Full Dose imatinib: 600 mg/day for Chronic Phase and 800mg/day for Advanced Phase
Full Dose dasatinib: ≥ 100 mg/day
Full Dose nilotinib: 400 mg/day

Imatinib Resistant

- Primary - subjects who fail to achieve adequate response while taking full-dose imatinib, or have no prior MCyR or CHR on imatinib with an increasing WBC count on ≥ 2 consecutive evaluations. Inadequate responses are defined below.
- Acquired - subjects who have failed to maintain a major cytogenetic response, or failed to maintain any hematologic response. Subjects previously confirmed as responses in any of these categories that have disease progression (loss of MCyR or any hematologic

response), or an increasing WBC on two consecutive weekly evaluations during the first year are eligible.
- Resistant to imatinib with a mutation – progressed while taking ≤ 600 mg imatinib and with a genetic mutation in BCR-Abl gene that is associated with imatinib resistance.

Imatinib Intolerant
- Unable to take imatinib due to imatinib-related, grade 4 hematologic toxicity lasting more than 7 days, or imatinib-related grade ≥3 non-hematologic toxicity, or persistent grade 2 toxicity, not responding to dose reductions and medical management, or progression on less than full-dose imatinib and unable to receive a higher dose of imatinib due to previous toxicity thought to be due to imatinib

Dasatinib Resistant (previously imatinib resistant/intolerant):
- Primary - subjects who fail to achieve adequate response while taking full-dose dasatinib, or have no prior MCyR or CHR on dasatinib with an increasing WBC count on ≥ 2 consecutive evaluations. Inadequate responses are defined below.
- Acquired - subjects who have failed to maintain a MCyR, or failed to maintain any hematologic response. Subjects previously confirmed as responses in any of these categories that have disease progression (loss of MCyR or any hematologic response), or an increasing WBC on two consecutive weekly evaluations during the first year are eligible.

Dasatinib Intolerant (previously imatinib resistant/intolerant)
- Unable to take dasatinib due to dasatinib-related, grade 4 hematologic toxicity lasting more than 7 days, or dasatinib-related grade ≥3 non-hematologic toxicity, or persistent grade 2 toxicity, not responding to dose reductions and medical management, or progression on less than full-dose dasatinib, and unable to receive a higher dose of dasatinib due to previous toxicity thought to be due to dasatinib

Nilotinib Resistant (previously imatinib resistant/intolerant):
- Primary - subjects who fail to achieve an adequate response while taking full-dose nilotinib, or have no prior MCyR or CHR on nilotinib with an increasing WBC count on ≥ 2 consecutive evaluations. Inadequate responses are defined below.
- Acquired - subjects who have failed to maintain a major cytogenetic response, or failed to maintain any hematologic response. Subjects previously confirmed as responses in any of these categories that have disease progression (loss of MCyR or any hematologic response), or an increasing WBC on two consecutive weekly evaluations during the first year are eligible.

Inadequate responses to at least full dose imatinib, dasatinib or nilotinib unless otherwise specified:
- Subjects started on treatment in chronic phase who fail to achieve or have failed to maintain any hematologic improvement within four weeks, a CHR after 12 weeks, a cytogenetic response by 24 weeks, or a major cytogenetic response by 12 months.

- Progression from chronic to accelerated or blast phase during therapy with treatment lasting at least 4 weeks (≥ 400 mg/day of nilotinib or ≥100 mg/day of dasatinib or ≥ 800 mg/day imatinib).
- Subjects started on treatment in accelerated or blast phase who have rapid disease progression within 2 weeks, fail to achieve any hematologic response by 4 weeks, or a return to chronic phase by 12 weeks of therapy.
- Patients with Ph+ ALL who had progression or lack of response to at least 600 mg imatinib, 70 mg dasatinib bid (or lower if combined with chemotherapy), after 4 weeks

Definition of Progression

- A subject entering the study in chronic phase clearly progresses to advanced phase during the first 4 weeks of therapy (early progressor). A chronic phase subject with CP CML would be considered as early progressor if this subject had loss of CHR and withdrew from the study before 4 weeks.
- A subject evolving from chronic phase or return to chronic phase to accelerated phase or blast crisis (on two consecutive assessments at least a week apart).
- A subject evolving from accelerated phase to blast crisis (on two consecutive assessments at least a week apart)
- Increasing WBC defined as doubling of the count from the nadir to more than 20,000 per cubic millimeter or an increase by more than 50,000 per cubic millimeter on two occasions at least 2 weeks apart in a subject who had never strictly attained a CHR despite receiving maximally tolerated doses of therapy
- Loss of confirmed CHR/OHR for CP subjects and loss of MHR/OHR for advanced subjects that is confirmed by a subsequent hematologic assessment ≥ at least 2 weeks after the initial finding of loss
- Loss of MCyR with Ph+ rate increased by 30%
- Subjects with ALL – loss of previously attained hematologic response or complete remission (>5% marrow blasts)

Protocol Amendments

The protocol was amended five times. See Table 7.

Table 7 Protocol Amendments (Reviewer Table)

Amendment Number Date	Reasons for Amendment
Amendment 1 October 20, 2006	1) Personnel and contact information updated 2) Updated information on bosutinib and other therapies in Introduction 3) DLT data from Part 1 was included 4) Starting dose of 500 mg was identified for Part 2 5) Subjects were included in Part 2 if they had CP CMP that was resistant to or intolerant of imatinib 6) Additional exploratory populations were added to include

	patients with exposure to dasatinib 7) Secondary objectives were updated to address efficacy in subjects exposed to imatinib and dasatinib separately 8) Additional baseline testing was added: Echocardiogram or multiple gated acquisition scan, BCR-ABL sequencing, clinical laboratory evaluations, and patient-reported outcome assessments,. Ophthalmic examinations were discontinued and long-term follow-up was defined. 9) Inclusion criteria were modified: subjects not receiving oral anti-thrombotic therapy (OAT) had to have a normal INR; INR in patients receiving OAT must be ≤ 3. 10) Exclusion criteria were modified: subjects were not excluded if they had no evidence of leukemia in bone marrow, but were excluded for extramedullary disease; subjects with gastrointestinal disorders lasting > 2 days despite therapy were excluded; patients with unexplained syncope were no longer excluded; subjects with uncontrolled or symptomatic CHF within 3 months or MI within 6 months were excluded; and prior exposure to Src, Abl or Src-Abl kinase inhibitors was no longer an exclusion criterion. 11) Concomitant medications were modified: Neumega was included as a permitted treatment; CYP-3A4 inhibitors could be used with caution during part 2; azoles were permitted in subjects with AP CML who required anti-fungal therapy 12) Compliance was to be monitored at study sites and recorded on the CRFs. 13) Additional precautions and monitoring were added for subjects receiving warfarin. 14) Conditions for dose reductions, dose delays, or discontinuations due to AEs, clinical laboratory abnormalities, and OATS were modified. 15) SAP was updated to match changes in study population, number of subjects, and their inclusion in primary and secondary endpoints. 16) A second planned interim analysis was deleted.
Amendment 2 **November 21, 2008**	Specified dose escalation in Chinese subjects would start with 3 to 6 subjects at 400 mg and then could be increased to 500 mg if safety criteria were met (applied to China and Taiwan only)
Amendment 3 **December 20, 2007**	Statement added regarding SUSARs and the European Directive (applicable in UK only)
Amendment 4	1) Personnel and contact information updated

June 10, 2008	2) Updated information for imatinib, dasatinib, and nilotinib; additional clarifications for hematologic versus cytogenetic response (CyR) and how to determine CyR 3) Clarification of how patients were assigned to cohorts 4) Discontinued physical exams every 12 weeks; discontinued pharmacodynamic and pharmacogenomic testing; added ECG every 12 weeks in Taiwan; clarified timing of health outcome assessments; clarified that FISH analysis of bone marrow aspirate is acceptable for post-baseline assessments; clarified BCR-ABL sequencing was to be performed at the end of treatment for all subjects; no PK sample at week 2; physical exam procedures updated; added that peripheral blood count could be used at screening for sequencing if insufficient bone marrow aspirate; patient-reported outcomes assessment would only be performed where appropriate translations were available; updated efficacy descriptions; added new table to include more specific explanation of exploratory cohorts 5) Added a cohort for patients with imatinib resistant/intolerant and subsequently nilotonib-resistant CP CML was added 6) Based on interim analysis results, enrollment was modified to include additional subjects with AP and BP leukemias and to not enroll additional subjects with Ph+ ALL 7) Inclusion criteria changes included the following: no antileukemia treatment was permitted within 7 days of the first dose of bosutinib (except hydroxyurea and anagrelide); patients had to be able to take tablets as well as capsules; adequate bone marrow function was required only for subjects with a history of imatinib resistance 8) Exclusion criteria modifications included the following: uncontrolled cardiac disease was further defined; subjects with documented history of T315I BCR-ABL mutation were to be excluded. 9) Concomitant medication changes included the following: added exceptions for subjects with advanced phase leukemia; guidance clarified for other permitted concomitant medications; updated OAT precautions 10) Guidance updated for dose escalation and dose reduction due to toxicity with specific guidance added for hematologic toxicity 11) ECG guidance updated 12) SAP was updated to match the study population changes. 13) The numbers of subjects to be enrolled was increased to 459.

	14) Text was added to clarify wording about new cohorts 15) Additional text was added for AEs, SAEs, and SUSARs to reflect local regulatory requirements 16) Changes to attachments to refine descriptions of phases and treatment responses
Amendment 5 November 21, 2008	Deletion of requirement for RT PCR for BCR-ABL quantification testing for subjects in China, India, Russia and South Africa

Trial 2303
Trial 2303 was a single arm, Phase 1/2 trial of 58 subjects in Japan with imatinib resistant or intolerant CML. The CSR was not available for review. This review focuses on analysis of the safety data from Trial 2303 that was incorporated into the pooled 120 day safety update.

Trial 3000
Trial 3000 was a randomized, controlled trial of 502 subjects with newly diagnosed CML which compared complete cytogenetic response (CCyR) at one year in patients treated with bosutinib (Arm 1) to those treated with imatinib (Arm 2). It was a superiority trial which hypothesized superiority of bosutinib over imatinib; however the trial failed to demonstrate superiority. This review focuses on analysis of the safety data from Trial 3000.

5.3.1. Eligibility Criteria for Trial 200

Inclusion Criteria (Excerpted from Protocol)
1. Signed and dated institutional review board (IRB) or independent ethics committee (IEC)-approved informed consent form before any protocol-specific screening procedures.
2. Cytogenetic or PCR based diagnosis of any phase of Ph+ CML or Ph+ ALL whose disease is resistant to full-dose imatinib (≥600 mg), or are intolerant of any dose of imatinib.
3. Adequate duration of prior imatinib therapy
4. ECOG Performance Status of 0 or 1 for chronic phase subjects, and 0, 1 or 2 for Advanced Stage Subjects
5. No anti-proliferative or anti-leukemia treatment within 7 days of the first dose of SKI-606 (except hydroxyurea & anagrelide).
6. Recovered to Grade 0-1, or to baseline, from any toxicities of prior anticancer treatment, other than alopecia
7. At least 3 months post allogeneic stem cell transplantation
8. Able to take daily oral capsules or tablets reliably
9. Adequate bone marrow function (chronic phase patients with a history of imatinib resistance only)
   - Absolute neutrophil count > 1000/mm^3 (>1 x10^9/L)
   - Platelets ≥ 100,000/ mm^3 (>100 x10^9/L) absent any platelet transfusions during the preceding 14 days.
10. Adequate hepatic and renal function

- AST/ALT ≤ 2.5 × upper limit of normal (ULN) or ≤ 5 × ULN if attributable to liver involvement of leukemia
- Total bilirubin ≤ 1.5 × ULN Creatinine ≤ 1.5 × ULN

11. Age ≥ 18 years
12. Willingness of male and female subjects, who are not surgically sterile or postmenopausal, to use reliable methods of birth control (oral contraceptives, intrauterine devices, or barrier methods used with a spermicide) for the duration of the study and for 30 days after the last dose of SKI-606.
13. Documented normal INR if not on oral anticoagulant therapy (OAT), or, if on OAT consistent target INR ≤ 3.

Exclusion Criteria (Excerpted from Protocol)

1. Subjects with Philadelphia chromosome and BCR-Abl negative CML.
2. Subjects previously intolerant of imatinib – Part 1 (dose escalation only)
3. Overt leptomeningeal leukemia. Subjects must be free of CNS involvement for a minimum of 2 months. Subjects with symptoms of CNS involvement must have a diagnostic lumbar puncture prior to study enrollment.
4. Subjects with extramedullary disease only.
5. In part 1, no prior exposure to Src, Abl, or Src/Abl kinase inhibitors is allowed.
6. Ongoing requirement for warfarin or other OAT (Part 1 only)
7. Ongoing requirement for hydroxyurea or anagrelide (Part 1 only)
8. Graft Versus Host Disease (GVHD)
   - Part 1 – no previous GVHD allowed
   - Part 2 – no treated or untreated GVHD within 60 days of study start
9. Major surgery within 14 days or radiotherapy within 7 days before the first dose of SKI-606 (recovery from any previous surgery should be complete before day 1)
10. Ongoing clinical requirement for administration of a strong inhibitor of CYP-3A4 – Part 1 only
11. History of clinically significant or uncontrolled cardiac disease including:
    - history of or active congestive heart failure
    - uncontrolled angina or hypertension within 3 months
    - myocardial infarction (within 12 months)
    - clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes).
    - diagnosed or suspected congenital or acquired prolonged QT syndrome
    - unexplained syncope
    - history of prolonged QTc12.Prolonged QTc (>0.45 sec, average of triplicate readings at screening)
13. Concomitant use of or need for medications known to prolong the QT interval
14. Uncorrected hypomagnesemia or hypokalemia due to potential effects on the QT interval
15. Recent (within 30 days of study entry) or ongoing clinically significant gastrointestinal disorder (e.g., malabsorption, short bowel syndrome, bleeding, or grade >1 diarrhea, nausea or emesis lasting more than 2 days, despite adequate medical therapy)
16. Pregnant or breastfeeding women

17. Evidence of serious active infection, or significant medical or psychiatric illness
18. Known seropositivity to HIV, or current acute or chronic Hepatitis B or Hepatitis C (antigen positive), cirrhosis, or clinically significant abnormal laboratory finding that would, in the investigator's judgment, make the subject inappropriate for this study.
19. Documented history of T315I BCR-Abl mutation.

5.3.2 Schedule of Assessments

Table 8 Schedule of Assessments (Applicant Table)

Study Procedures	Screening[a]	Week ± 3 days								
Week		1		2	3	4	8	12	q12w[p]	End
Day (± 3 days after treatment start)	–14 to –1	1	7	14	21	28	56	84	168, 252 & 336	
Dose SKI-606[b]		----------Continuous Daily Dosing----------								
Informed Consent[c]	✓									
Inclusion/Exclusion	✓									
Medical History / Cancer History	✓									
PRBC & Platelet Transfusion Hx[d]	✓	✓[e]		✓	✓	✓	✓	✓	✓	✓
Chest X-Ray	✓						✓	When Clinically Indicated		✓
Complete Physical Exam (includes vital signs)	✓									✓
Interim Physical Exam & weight		✓[e]								
Digital ECG[f]	✓	✓			✓					✓
ECHO or MUGA	✓	When Clinically Indicated							Week 24 only	✓
ECOG Performance Status	✓		✓	✓			✓	✓	✓	✓
Long term follow up		After SKI-606 discontinuation, by phone every 3 months for survival, progression and other Tx.								
Health Outcomes Assessment[g]	✓					✓	✓	✓	✓	✓
SAEs & Adverse Events		----------								✓
Concomitant Treatments		----------								
Serum Pregnancy Test (for women of childbearing potential)	✓	As indicated by history/clinical evidence								✓
Testosterone, Free Testosterone, Progesterone, 17-Hydroxyprogesterone[h]	✓					✓	✓	✓	Weeks 24 & 48 only	
Urinalysis (Dipstick acceptable with microscopic if abnormal)	✓					✓		✓	✓	✓

Study Procedures	Screening[a]	Week ± 3 days								
Week		1		2	3	4	8	12	q12w[p]	End
Day (± 3 days after treatment start)	–14 to –1	1	7	14	21	28	56	84	168, 252 & 336	
Peripheral Blood										
Chemistry[i]	✓		✓	✓	✓	✓	✓	✓	✓	✓
LFTs[j]	✓		✓	✓		✓	✓	✓	✓	✓
Creatinine Kinase & Amylase/Lipase[j]	✓			✓					✓	
PT (INR)/PTT	✓		✓			✓	✓	✓	✓	
CBC & differential[k]	✓	✓[e]	✓	✓	✓	✓	✓	✓	✓	✓
PCR for BCR-Abl[l]	✓					✓[l]	✓[l]	✓	✓	✓
Pharmacokinetics	Please see PK flowchart for on-study assessments									
Bone Marrow Aspirate[m]	✓					A*	A*	✓	✓	✓
Cytogenetics, Morphology & Blast %	✓					A*	A*	✓	✓	✓
Site Response Assessment[n]						A*	A*	✓	✓	✓
BCR-Abl Sequencing	✓									✓[o]

* Advanced subjects only (Accelerated Phase CML/Blast Phase CML/Acute Lymphocytic Leukemia). Bone marrow aspiration will be done monthly (3X) on advanced phase subjects until a return to Chronic Phase is achieved (whichever comes first).

a. Screening visit within 14 days before registration of subject in CORE

b. The subject should receive the first dose of SKI-606 no more than 2 business days after registration in the CORE system. Day 2 dose will be withheld in Part 1 subjects only.

c. Signed and dated IRB or IEC-approved informed consent before any protocol-specific screening procedures are performed. Informed consent may be signed up to 28 days prior to the first dose of SKI-606. Procedures performed as standard of care prior to signed and dated ICF, and within the 14 day screening window may be used for study entry. Bone marrow is excepted – see footnote m

d. The approximate number and volume of transfusions of both blood and platelets given during the previous 1 month will be collected. If the patient was referred to the institution, patient/referring physician recollection is sufficient.

e. To be repeated if not performed within 3 days of Day 1.

f. Triplicate ECGs will be performed at screening, on day 1 prior to the first dose and at hours 2, 4 and 6 post-dose, and on day 21 prior to treatment and at hours 2, 4, 6 and 20-23 post-dose. End of treatment ECG should occur at least one week after the last dose to allow assessment of QTc after clearance of most of the SKI-606 from the blood. Digital ECG recorders are to be used, and will be provided by Wyeth through a third party vendor. An additional set of triplicate ECGs should be done if a clinically significant decrease in ejection fraction is detected while on study by ECHO or MUGA. In Taiwan, subjects will be monitored with ECGs performed every 12 weeks during treatment.

g. Health outcomes assessment that consists of FACT-Leu and EQ-5D will be completed at screening, weeks 4, 8 and 12, and then every 12 weeks thereafter (and at treatment completion) where appropriate language translations are available. The subjects will also complete the assessments at any visit when symptomatic grade 3 or grade 4 adverse events occur (unless medical conditions prohibit or if subject requires hospitalization), at the time of disease progression or patient early withdrawal

h. Testosterone, free testosterone, progesterone and 17-hydroxyprogesterone tests for all male patients at screening, and at weeks 4, 8, 12 and 24. These tests are only required if available locally.

i. Blood chemistries to include sodium, potassium, chloride, bicarbonate or carbon dioxide, calcium, phosphorus, magnesium, glucose, serum creatinine, and Urea Nitrogen (BUN or Urea). Uric Acid should be performed until the subject achieves Complete Hematologic Response (CHR) or No Evidence of Leukemia. See Attachment 1 for explanation of responses.

j. LFTs should be done as part of a panel that includes chemistry and LFTs when possible. Liver function tests to include total protein, albumin, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin (if total $\geq$ 1.5x ULN). Amylase, Lipase and CK should also be included at indicated times. Abnormal CK values should be confirmed and fractionated.

k. Hematology to include complete blood count (CBC) including a 5-part differential (abnormalities should be confirmed by manual differentials), platelet count, and absolute neutrophil count (ANC). Phase of disease at screening assignment will be based on first day of dosing CBC results. In the case of grade 4 hematologic toxicity, it is recommended that CBC be repeated at least every 2-3 days until recovered to $\leq$ grade 2 toxicity.

l. The 4 & 8 week PCRs may be omitted in situations in which the treating physician does not believe the subject is experiencing clinical benefit (i.e. 90% peripheral blasts). Due to logistical constraints in transporting the specimens from the investigational sites to the central laboratory, PCR for BCR-Abl quantification testing will not be performed for subjects enrolled in China, India, Russia and South Africa.

m. Bone marrow aspirate to be collected for morphology and cytogenetic analysis. Screening bone marrow may be obtained any time up to 28 days before the first dose of test article (day –28). Conventional cytogenetic analysis is required to confirm subject eligibility. For post-baseline disease assessments, FISH analysis may be used if the bone marrow sample is inadequate for cytogenetic analysis in order to confirm the presence of BCR-Abl fusion product and its percentage in marrow. Sequencing of BCR-Abl may be done on peripheral blood if adequate marrow is not available to determine mutation status. FISH data should be reported if obtained, but is not a required test. A marrow sample should be submitted at any time progression from best response occurs, and for confirmation of progression. This time point may, or may not, coincide with cessation of treatment (i.e. if a patient progresses from complete hematologic response to partial hematologic response, they have lost their best response but may not yet discontinue SKI-606).

n. Site Assessments are the PI's determination of time point responses

o. BCR-Abl Sequencing to be done at treatment completion visit for all subjects. Peripheral blood is acceptable for sequencing if bone marrow is not available.

p. Subjects benefiting from SKI-606 treatment may be eligible for continued treatment beyond the end of the first year with procedures continuing every 12 weeks for the second year of treatment, and then every 24 weeks thereafter beginning with the third year of treatment.

5.3.3 Dosing Regimens

Part 1

During the dose escalation part of the trial the initial cohort of subjects started with 400 mg of bosutinib daily. Dose escalations followed a standard 3 + 3 design escalating to 500 mg and then 600 mg daily doses. Although only one patient of 12 in the 600 mg daily cohort had grade 3 DLT, the phase 2 dose level was determined to be 500 mg daily with an option to increase to 600 mg for inadequate response.

Part 2

Patients were started at 500 mg with escalation to 600 mg if response was inadequate. Response was considered inadequate for failure to reach CHR by week 8 or CCyR by week 12.

6 Review of Efficacy

Efficacy Summary

This NDA is based on the responses observed from one single-arm trial with bosutinib given as a single agent for the treatment of 571 patients with CML who were resistant or intolerant to imatinib. The majority of the patients enrolled had chronic phase disease (71%), while 13% had accelerated phase, 11% had blast phase disease, and 4 % had Ph+ ALL. The primary endpoint for patients with CP CML was MCyR at 24 weeks. Evaluation of patients with advanced phases of disease was considered exploratory. The primary endpoint in the advanced phases was complete hematologic response (CHR); however the protocol was amended to include an endpoint of objective hematologic response (OHR), an endpoint which includes three other categories: Return to Chronic Phase (RCP), Minor Hematologic Response (MiHR) and No Evidence of Leukemia (NEL). Although the trial evaluated molecular responses in 75% of the patients, these responses were considered exploratory. All responses were determined by local laboratories.

6.1 Indication

The Applicant's proposed indication is as follows:
BOSULIF (bosutinib) is a tyrosine kinase inhibitor indicated for the treatment of chronic, accelerated, or blast phase Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML) in adult patients with resistance, or intolerance to prior therapy.

6.1.1 Methods

This clinical review is based mainly on the Trial 200 CSR, Case Report Forms, primary data sets for efficacy and toxicity submitted by the applicant, and a literature review for CML. Safety data from Trial 3000 was also reviewed. The Applicant's definitions of disease phases at diagnosis, and hematologic, cytogenetic and molecular responses to treatment are presented in Tables 9, 10, 11, 12 and 13. The Applicant did not use definitions of disease phases as promulgated by the WHO in 2002; however the definitions used were the same as those used in the pivotal trials for the approvals of imatinib, dasatinib and nilotinib.

Table 9 Definition of Disease Phases at Diagnosis (Applicant Table)

	Peripheral Blood Findings	Marrow Findings
Blast Phase CML or ALL	≥ 30% Blasts in blood or bone marrow Extramedullary Involvement other than Liver/spleen These two evaluations take preference over chronic and accelerated criteria	
Accelerated Phase	15-29% Blasts ≥ 30% Blasts + promyelocytes ≥ 20% Basophils Platelets < $100x10^9$/L (not related to therapy)	15-29% Blasts or ≥ 30 % Blasts + Promyelocytes ≥ 20% Basophils
Chronic Phase	< 15% Blasts < 20% Basophils < 30% Blasts + promyelocytes Plt. ≥ $100x10^9$/L	< 15% Blasts < 30% Blasts + Promyelocytes No extramedullary (except Liver/Spleen)

Observance of any one criterion in the worse disease phase achieves that phase as the diagnosis (i.e. 20% basophils alone elevates the diagnosis from Chronic to Accelerated Phase.

Table 10 Definition of Hematologic Responses to Treatment in CP CML (Applicant Table)

Subjects with Chronic Phase CML	
Hematologic Responses	**Definition**
No Evidence of Leukemia (NEL)	0.5 $x10^9$ ≤ ANC < 1.0 $x10^9$/L $20x10^9$ ≤ Platelets < 100 $x10^9$/L No blood blasts or promyelocytes < 20% basophils in blood Myelocytes + metamyelocytes < 5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Complete Hematologic Response	No Peripheral blasts or promyelocytes Myelocytes + metamyelocytes < 5% in blood ANC ≥ 1.0 $x10^9$/L WBC ≤ institutional ULN Platelets ≥ 100 but < 450 $x10^9$/L, unless related to therapy < 20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)

Table 11 Definition of Hematologic Responses to Treatment in Advanced Phases of CML (Applicant Table)

Subjects with Accelerated or Blast Phase CML, or Ph+ ALL	
Hematologic Responses	**Definition**
Return to Chronic Phase (not applicable for Ph+ ALL)	Disappearance of features defining accelerated & blast phases, but still in chronic phase (May have platelets <100 x10^9/L, if related to therapy) Persistence of clonal evolution, if present at the time of therapy, is acceptable for return to chronic phase
Minor Response	< 15% blasts in marrow and blood < 30% blasts + promyelocytes in marrow and same in blood < 20% basophils in peripheral blood No extramedullary disease other than spleen and liver
No Evidence of Leukemia (NEL)	Blast < 5% in bone marrow 0.5 x10^9 ≤ ANC < 1.0 x10^9/L 20x10^9 ≤ Platelets < 100 x10^9/L No blood blasts or promyelocytes < 20% basophils in blood Myelocytes + metamyelocytes < 5% in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Complete Hematologic Response	≤ 5% marrow blasts No peripheral blasts or promyelocytes Myelocytes + metamyelocytes < 5% in blood ANC ≥ 1.0 x10^9/L WBC ≤ institutional ULN Platelets ≥ 100 but < 450 x10^9/L, unless related to therapy < 20% basophils in blood No extramedullary involvement (incl. hepato- or splenomegaly)
Overall Hematologic Response (OHR)	Complete + NEL + Minor + Return to Chronic Phase (if applicable)
Major Hematologic Respone (MHR)	Complete + NEL

Table 12 Definition of Cytogenetic Responses to Treatment (Applicant Table)

Before Treatment	Cytogenetic Responses*	% Philadelphia chromosome positive cells
Any phase	None	> 95%
	Minimal	66-95%
	Minor	36-65%
	Partial	1-35%
	Complete	0%
	Major	Complete + Partial Rates

* Based on analysis of 20 metaphases. or For post-baseline disease assessments, FISH analysis may be used if the bone marrow sample is inadequate for cytogenetic analysis in order to confirm the presence of BCR-Abl fusion product and its percentage in marrow.

Table 13 Definition of Molecular Responses to Treatment (Applicant Table)

Before Treatment	Molecular Responses	PCR (BCR-Abl/Abl ratio)
Any phase	None	No Change
	Partial	< 3 log reduction from standardized baseline
	Major	≥ 3 log reduction from standardized baseline
	Complete	Undetectable BCR-Abl

6.1.2 Demographics

Trial 200 enrolled more males than females, most subjects were younger than age 65, and the trial population was predominately white. The trial was conducted in 26 countries at 79 sites. The trial population was comprised of 31% of patients from Asia, 27% of patients from Europe, 26% of patients from the U.S., and 11 % of patients from South America and Mexico. All patients had received imatinib as prior therapy. Almost one half of the patients with CP CML had only one prior therapy; more than half of the patients with AP and BP CML and Ph+ ALL had two or more prior lines of therapy. ECOG performance status was less than 2 in almost all patients with CP CML and scores increased with advanced disease phases. See Tables 14 and 15.

Table 14 Demographics and Disease Parameters at Baseline in Trial 200 (Reviewer Table)

Parameter	CP N=406 N (%)	AP N=77 N (%)	BP N=64 N (%)	ALL N=24 N (%)
Sex				
Male	206 (51)	43 (56)	41 (64)	12 (50)
Female	200 (49)	34 (44)	23 (36)	12 (50)
Age (years)				
< 65	317 (78)	66 (86)	51 (80)	13 (54)
≥ 65	89 (22)	11 (14)	11 (17)	11 (46)
Unknown	0	0	2 (3)	0
Median	54	51	49	59
(Range)	(18-91)	(18-83)	(19-82)	(24-84)
Race				
White	271 (67)	46 (60)	38 (59)	19 (79)
Asian	67 (17)	11 (14)	10(16)	0
Black	22 (5)	6 (8)	11 (17)	2 (8)
Other	43 (11)	14 (18)	5 (8)	3 (13)
Number of Prior Therapies				
1	193 (48)	29 (38)	30 (47)	0
2	151 (37)	22 (29)	16 (25)	1 (4)
3	15	19 (25)	16 (25)	8 (33)
4 or more	2 (<1)	6 (8)	2 (3)	15 (63)
ECOG PS				
0	306 (75)	41 (54)	22 (34)	9 (38)
1	97 (24)	33 (43)	28 (44)	11 (46)
2	1 (<1)	2 (3)	14 (22)	4 (17)
missing	2 (<1)	1	0	0

Table 15 Countries Where Patients Were Enrolled and Number of Patients per Country (Reviewer Table)

Country	Number	Country	Number Enrolled
Argentina	20	Italy	53
Australia	9	Korea	32
Austria	2	Mexico	4
Brazil	26	Netherlands	17
Canada	16	Norway	3
Chile	2	Peru	6
China	43	Russia	66
Columbia	4	Singapore	5
Finland	7	Spain	10
Germany	40	Sweden	1
Great Britain	9	South Africa	9
Hong Kong	6	Taiwan	2
Hungary	10	United States	146
India	22		

6.1.3 Subject Disposition

At the time of data cut off there were 99 patients continuing bosutinib treatment: 63 with CP CML in second line treatment; 10 with CP CML in third line treatment; 6 with AP CML, 1 with BP CML; and none with Ph+ ALL continuing treatment. The reason for the largest number of early discontinuations from the trial was adverse events for patients with CP CML, but was disease progression for patients with advanced phases of disease. See Table 16.

Table 16 Disposition of Subjects in Trial 200 (Reviewer Table)

Disposition	CP Second Line N=288 n (%)	CP Third Line N=118 n(%)	AP N=77 n (%)	BP N=64 n (%)	Ph+ ALL N=24 n (%)
Discontinued	159 (55)	84 (71)	61 (80)	61 (95)	23 (96)
Adverse Event	64 (22)	24 (20)	18 (24)	5 (8)	3 (13)
Disease Progression	41 (14)	20 (17)	25 (33)	36 (56)	13 (54)
Unsatisfactory Response	21 (7)	25 (21)	8 (11)	6 (9)	3 (13)
Subject Request	18 (6)	3 (3)	3 (4)	4 (6)	0
Other	7 (2)	4 (3)	1 (1)	3 (5)	0
Death	5 (2)	4 (3)	6 (8)	6 (9)	3 (13)
Lost to Follow Up	2 (<1)	2 (2)	0	1 (2)	0
Investigator Request	1 (<1)	1 (<1)	0	0	1 (4)
Completed Trial + 2	66 (23)	24 (20)	10 (13)	2 (3)	1 (4)

Year Follow Up					
Continuing Treatment at Time of Censoring	63 (22)	10 (8)	6 (8)	1(2)	0

6.1.4 Analysis of Primary Endpoints

Patients with CP CML in Second-line Treatment with Bosutinib

The MCyR at week 24 for second-line treatment of patients with CP CML who were resistant to imatinib was 36% (95% CI = 29, 42). 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.

The MCyR rate at week 24 for second line treatment of patients with CP CML who were intolerant of imatinib was 30% (95% CI = 20, 40). This cohort did not reach the pre-specified MCyR rate of 53%. The median duration was not reached. Although MCyR rate and duration of response were secondary endpoints in this cohort, they are presented here since they were patients with CP CML in second-line treatment. See Table 17.

Table 17 Efficacy of Bosutinib in Second-line Treatment of Patients with CP CML (Reviewer Table)

Cohort	Number of evaluable subjects	MCyR At Week 24 N (%)	Median Duration of Response In Weeks
Imatinib Resistant (95% CI)	186	66 (36) (29, 42)	Not reached
Imatinib Intolerant (95% CI)	80	24 (30) (20, 40)	Not reached

The other primary endpoint of Trial 200 was to determine population pharmacokinetics. See Section 4.4.3.

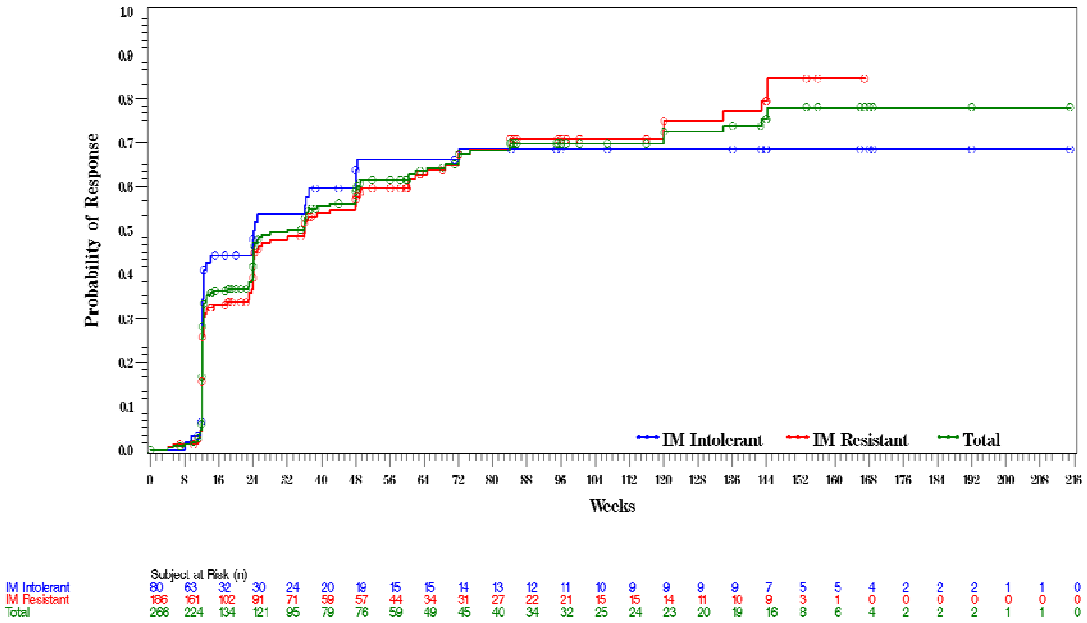
Reviewer Comment: Bosutinib treatment of patients with CP CML that is resistant to imatinib resulted in a MCyR rate of 36%, and is supportive of clinical efficacy in this cohort. Although bosutinib treatment of patients with CP CML who were intolerant of imatinib failed to meet the pre-specified rate of 53%, MCyR rate of 30% is indicative of clinical activity in this cohort.

6.1.5 Analysis of Secondary Endpoints

Time to MCyR in Subjects with CP CML in Second-line Treatment with Bosutinib

The Kaplan-Meier median time to MCyR for imatinib-resistant subjects was 36.0 weeks (95% CI, 24.1, 49), and for imatinib-intolerant subjects was 24.4 weeks (95% CI, 12.3, 48). See Figure 2.

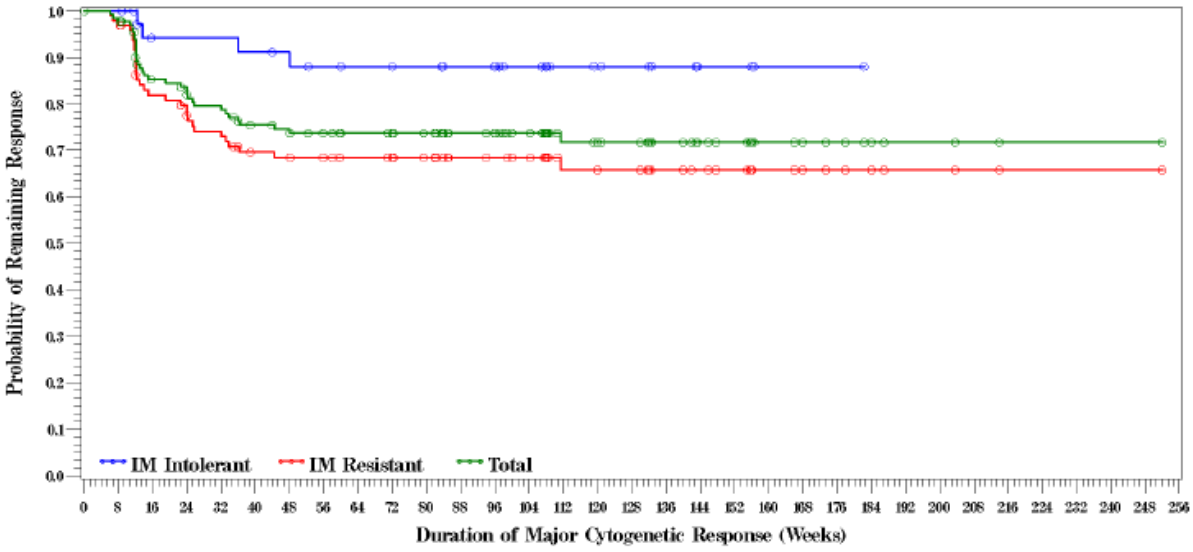
Figure 2 Kaplan-Meier Estimate of Time to MCyR in Patients with CP CML in Second-line Treatment with Bosutinib (Applicant Figure)



Duration of MCyR in Patients with CP CML in Second-line Treatment with Bosutinib
The Kaplan-Meier 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. See Figure 3.

The median duration of response for imatinib intolerant subjects has not been reached. The Kaplan-Meier estimate of maintaining MCyR at Year 1 and Year 2 was 88% (95% CI, 71.1, 95.3) for both years in this cohort. See Figure 3.

Figure 3 Kaplan-Meier Estimate of Maintaining MCyR at Year 1 and at Year 2 in Patients with CP CML Treated with Bosutinib as Second-line Therapy (Applicant Figure)



Subject at Risk (n)

IM Intolerant	39	37	31	31	31	30	29	27	26	26	24	22	22	17	11	10	9	6	4	4	1	1	1	0	0	0	0	0	0	0	0	0
IM Resistant	103	94	75	71	66	59	58	56	54	53	48	39	38	36	25	25	24	18	16	14	9	8	6	5	3	3	2	1	1	1	1	0
Total	142	131	106	102	97	89	87	83	80	79	72	61	60	53	36	35	33	24	20	18	10	9	7	5	3	3	2	1	1	1	1	0

Time to CHR in Patients with CP CML in Second-line Treatment with Bosutinib

The Kaplan-Meier median time to confirmed (achieved or maintained) CHR in the evaluable population was 2.1 weeks (95% CI, 2.0, 2.6). If a patient entered the trial with CHR at baseline, the earliest CHR could be confirmed/maintained was on Day 7. If CHR was present on Day 7 and confirmed at least 4 weeks later, it was considered to have occurred on Day 7.

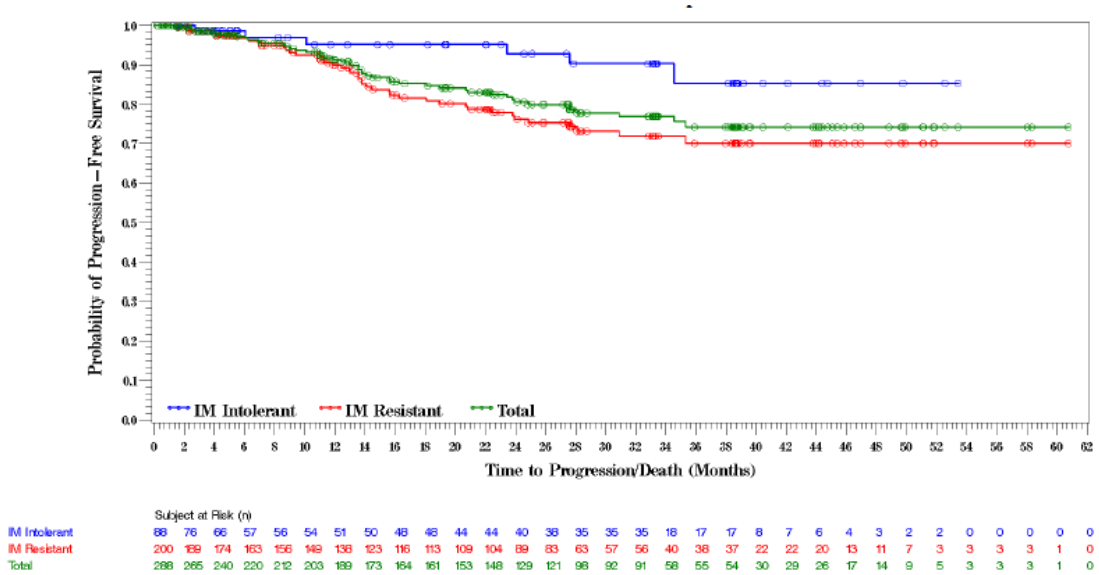
Duration of CHR in Patients with CP CML in Second-line Treatment with Bosutinib

The median duration has not been reached. Of the 244 (85.0%) subjects who either attained a confirmed CHR or maintained their baseline CHR, 182 (74.6%) had maintained the response as of the last assessment before the database snapshot. Of the 244 patients who attained or maintained a CHR, 103 (42.2%) had a CHR at baseline. The K-M estimates of retaining a CHR was 84.6% (95% CI: [79.0, 88.8]) at Year 1 and 72.1% (95% CI: [65.2, 77.8]) at Year 2.

PFS in Patients with CP CML in Second Line Treatment with Bosutinib

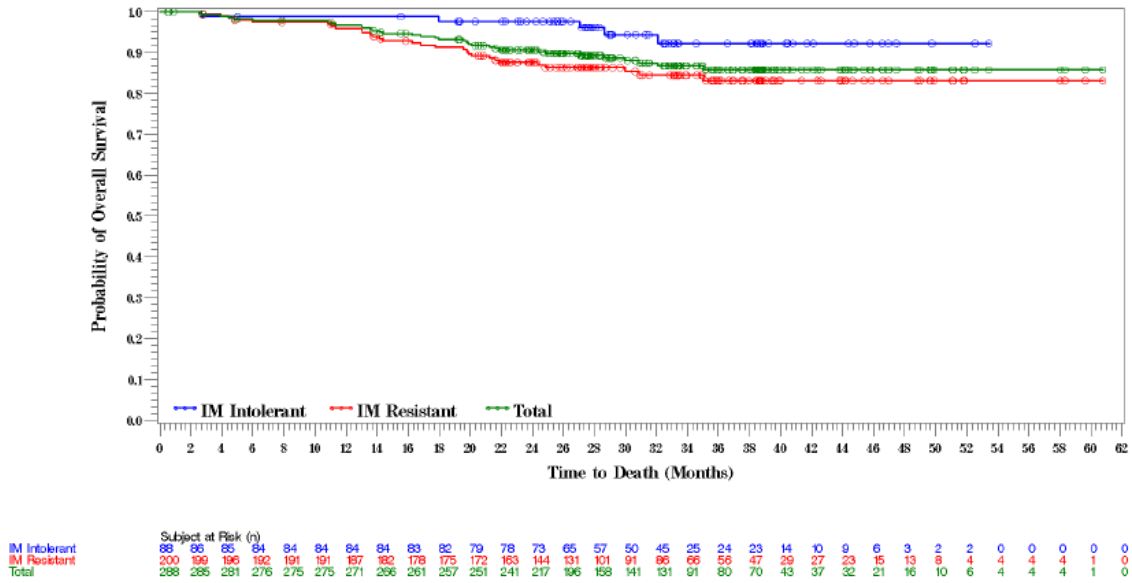
The Kaplan-Meier estimates of PFS in the all-treated population at Year 1 and Year 2 were 91.3% (95% CI: [86.8, 94.3]) and 80.6% (95% CI: [74.3, 85.4]), respectively. The Kaplan-Meier median PFS has not been reached. See Figure 4.

Figure 4 Kaplan-Meier Estimates of PFS in Patients with CP CML in Second Line Treatment with Bosutinib



<u>OS rate at 1 and 2 years in Patients with CP CML in Second-line Treatment</u>
The Kaplan-Meier estimate of OS in Patients with CP CML in second line treatment with Bosutinib at Year 1 was 96.8% (95% CI: 94, 98.3) and at Year 2 was 90.6% (95% CI: 86.5, 93.5). The median OS has not been reached. See Figure 5.

Figure 5 Kaplan-Meier Estimates of Overall Survival in Patients with CP CML in Second Line Treatment with Bosutinib



Patients with CP CML in Third Line Treatment with Bosutinib

The MCyR by week 24 for third-line treatment of patients with CP CML was 27%. The median duration of MCyR was reached for only one cohort, patients who were resistant to imatinib and dasatinib, and was 24 weeks; median duration of response for all other third line cohorts had not been reached at the time of censoring. Duration of MCyR at Year 1 and Year 2 was best in the Imatinib + Nilotinib Intolerant group and worst for the Imatinib + Dasatinib Resistant group. The median time to MCyR in patients in third line treatment was 88 weeks. See Table 18 and Figures 6 and 7.

Table 18 Efficacy of Bosutinib in Third-line Treatment of Patients with CP CML (Reviewer Table)

Cohort	Number of evaluable subjects	MCyR by Week 24 N (%)	Median Duration of Response in Weeks (Range)
Imatinib and Dasatinib Resistant (95% CI)	35	9 (26) (11 , 40)	24 (8-72)
Imatinib and Dasatinib Intolerant (95% CI)	43	11 (26) (13 , 39)	Not reached
Imatinib and Nilotinib Resistant (95% CI)	26	7 (27) (10 , 44)	Not reached
Imatinib, Dasatinib and/or Nilotinib Resistant (95% CI)	4	NA	NA

NA= Not applicable (sample size too small)

Figure 6 Kaplan-Meier Estimate of Duration of MCyR at Year 1 and at Year 2 in Patients with CP CML Treated with Bosutinib as Third Line Therapy (Applicant Figure)

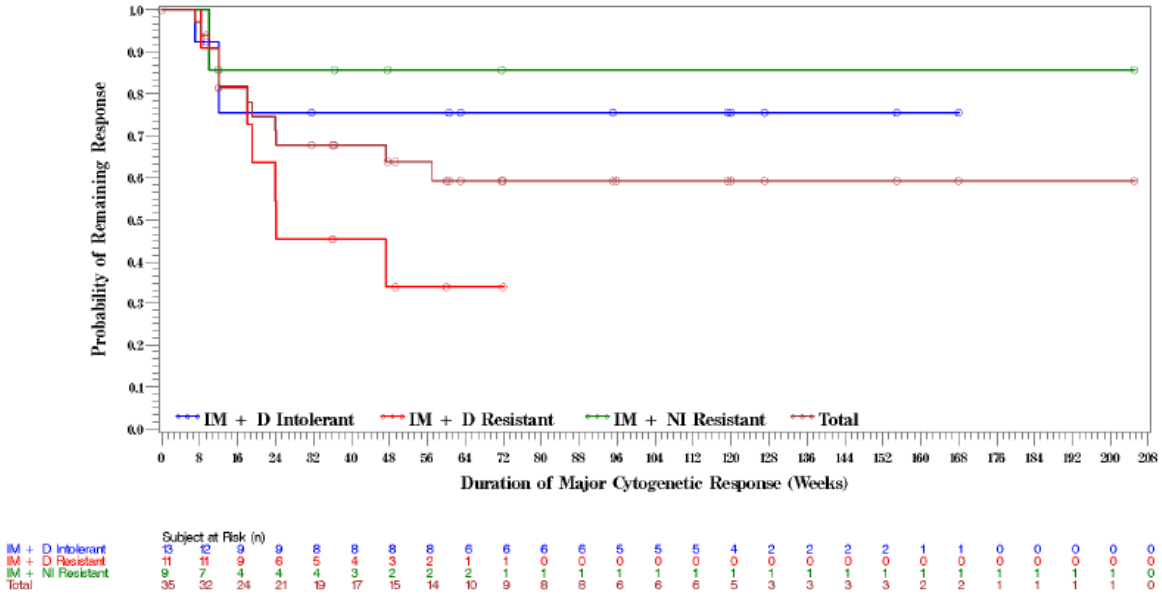
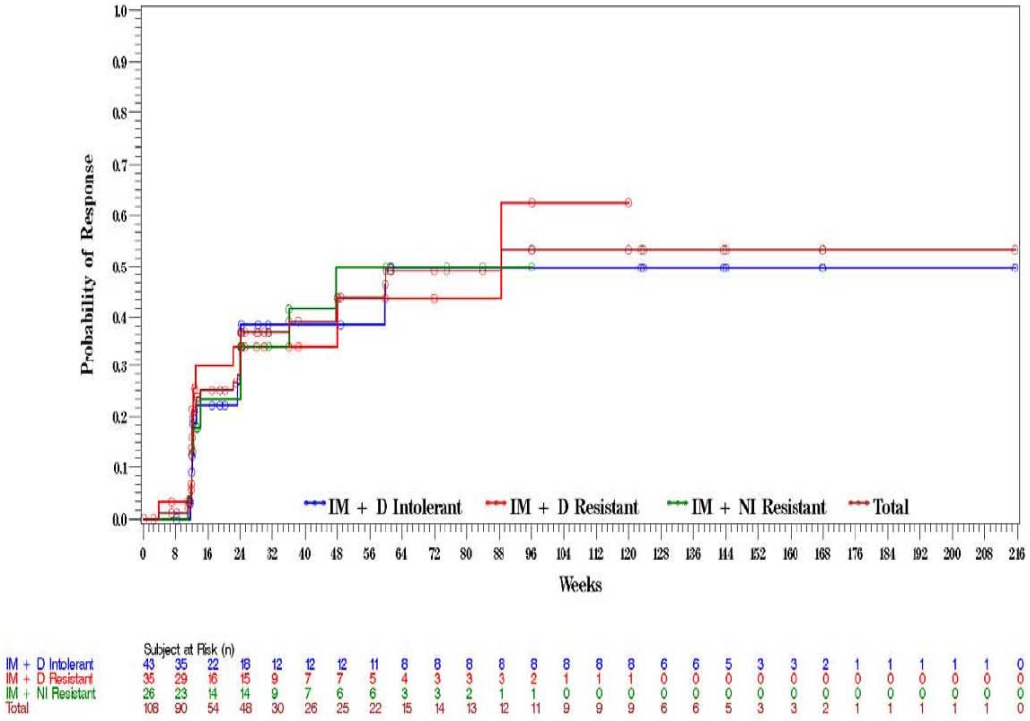


Figure 7 Kaplan-Meier Estimate of Time to Major Cytogenetic Response in Patients in Third Line Treatment with Bosutinib for CP CML (Applicant Figure)



Reviewer Comment: *Support for clinical efficacy in third line cohorts is less robust due to small sample size in most cohorts and the single arm trial design; however, the trial showed evidence of activity in patients in all third line cohorts. Median duration of response was not reached for all cohorts except patients who were resistant to imatinib and resistant to dasatinib. Although the Applicant's time to event analyses have been included in this review, time to event analyses such as PFS, OS, and TTF are generally not interpretable in single arm trials, and would not constitute substantial evidence for labeling purposes.*

Patients with Advanced Phase CML (AP, BP, and Ph+ ALL)

OHR and CHR Rates in Patients with AP CML

The confirmed OHR rate by week 48 in patients with AP CML and prior therapy with more than one TKI (AP multi TKI) was 43% (95% CI 26, 63) with a median duration of 42 weeks. Confirmed CHR rate in the same cohort was 27% (95% CI: 11, 42) with a median duration of 74 weeks. The confirmed OHR rate by week 48 in patients with AP CML and prior imatinib only was 64% (95% CI 44, 79) with a median duration of 53 weeks. Confirmed CHR rate in the same cohort was 41% (95% CI: 26, 56) with a median duration of 69 weeks. See Table 20.

OHR and CHR Rates in Patients with BP CML

The confirmed OHR rate by week 48 in patients with BP CML and prior therapy with more than one TKI (BP multi TKI) was 19% (95% CI: 6, 38) with a median duration of 31 weeks. Confirmed CHR in the same cohort was 4% (95% CI: 0, 20). The confirmed OHR rate by week 48 in patients with BP CML and prior imatinib only was 36% (95%CI: 20, 55) with a median duration of 29 weeks. The confirmed CHR in the same cohort was 24 % (95% CI: 10, 39). See Table 20.

OHR and CHR in Patients with Ph+ ALL

All patients in this cohort had prior therapy with multiple TKIs. The confirmed OHR and CHR rates by week 48 in patients with Ph+ ALL was 9% (95%CI: 1, 29) and 9% (95% CI: 1, 29) with median durations of 79 and 76 weeks respectively. See Table 20.

Table 19 Efficacy of Bosutinib in Patients with Advanced Phases of CML and ALL (Reviewer Table)

Cohort	OHR n (%)	Median Duration of Response in Weeks (Range)	CHR n (%)	Median Duration of Response in weeks (Range)
AP multi TKI, N=30* (95% CI)	13 (43) (26, 63)	42 (8-180)	8 (27)	74 (29-156)
AP imatinib only, N=39* (95% CI)	25 (64) (47, 79)	53 (9-208)	16 (41)	69 (20-208)
BP multi TKI, N=27* (95% CI)	5 (19) (6, 38)	31 (8-188)	1(4)	NA
BP imatinib only, N=33* (95% CI)	12(36) (20, 55)	29 (8-87)	8 (24)	26 (8-82)
Ph+ ALL, N=22* (95% CI)	2 (9) (1, 29)	79 (10-143)	2 (9)	76 (110-143)

*Evaluable patients NA = Not Applicable

6.1.6 Analysis of Exploratory Endpoints

The Applicant studied three exploratory endpoints in the pivotal trial: Pharmacodynamics, Health Outcomes Endpoints and Molecular Response.

Effects of bosutinib on Activation of Src-family kinases and downstream substrates

PK and pharmacodynamic studies were performed in which flow cytometry was used to monitor inhibition of Bcr-Abl tyrosine kinase activity in the peripheral blood of CP CML patients treated with bosutinib. The goal of this work was to estimate the suppression of kinase activity in subject cohorts defined by disease type (CP CML or Ph+ ALL), stage of disease, prior therapies, and different doses of bosutinib. A protocol-specified secondary objective of Part 1 (dose escalation phase) of the study was to obtain data on the ability of bosutinib to inhibit Bcr-Abl kinase activity at various dose levels. Part 1 comprised 18 imatinib-resistant subjects (17 with CP CML and 1 with AP CML) who received the following doses: 400 mg (n=3), 500 mg (n=3) and 600 mg (n=12). Whole blood was drawn immediately prior to and 6 hours after bosutinib dosing on days
1, 8 and 15, for a total of 6 measurements, with the first blood draw providing the baseline measurement.

Phosphorylation of CrkL(Y207), a well-known Bcr-Abl target, was monitored in whole blood cells, as well as in the CD3+ (T cell), CD19+ (B cell), and CD34+ (blast cell) compartments. All

work was performed at [redacted] (b) (4) following approval of an assay validation document prior to the evaluation of clinical samples. p-CrkL signals were consistently highest in the whole blood assays, whereas the other compartments did not stain consistently for p-CrkL, and showed no staining in some samples. Thus, by necessity, the pharmacodynamic analysis was focused on the p-CrkL signal in the whole blood compartment.

A total of 287 patients (Part 1 and Part 2) provided a baseline sample that was successfully evaluated by flow cytometry, and between 50 and 220 samples were measured at each of the 5 time points during treatment. The results were tabulated for each subject, and also summarized for each cohort (where cohorts are defined based on bosutinib dose in Part 1, and based on disease stage and prior therapies in Part 2).
At the cohort level, no consistent trends suggesting decreased p-CrkL levels in response to bosutinib were noted relative to the corresponding mean baseline signal. In addition, virtually all datasets were accompanied by high CVs. Therefore, the team further evaluated the dataset by reviewing p-CrkL signals over time for individual subjects. For most subjects, the lack of discernable trends in p-CrkL levels over time reinforced the conclusions from the cohorts; these analyses also indicated points where fluorescence activated cell scanning (FACS) data were not successfully generated.

Reviewer Comment: *Because the trial did not elucidate any trends regarding p-Crkl levels in response to bosutinib, and FACS data were not successfully generated, the pharmaco-dynamics of bosutinib are not fully characterized at this time.*

Health Outcomes Endpoints Using Quality of Life Questionnaires
Health-related quality-of-life (HRQoL) was assessed through the Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale. Overall health status was assessed by the EQ-5D over the course of treatment. Patients completed FACT-Leu questionnaires at each visit. Questions addressed five areas: physical well-being, social/family well being, emotional well-being, functional well-being and additional concerns related to symptoms. Patients answered items based upon their 7-day recall and provided answers according to a Likert scale ranging from “Not at all” to “Very Much.” Higher scores reflected better states of well-being in each category.

The EQ-5D is comprised of a descriptive system and a visual analogue scale. The descriptive system includes five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Patients self-scored each dimension at one of three levels: no problems, some problems and extreme problems, and rated their assessment of general state of health on the visual analogue score (zero reflected worst imaginable state of health and 100 reflected best imaginable state of health).

Overall, scores at baseline were consistent with scores of patients with leukemia in the general population. During early treatment, scores declined consistent with toxicities such as diarrhea, nausea, vomiting, fatigue, fever, and headache. As treatment continued, scores returned to baseline or improved in the majority of patients.

Reviewer Comment: *Patient reported outcomes are not evaluable in a single arm trial, and do not provide substantial evidence for labeling claims.*

Molecular Response

The trial evaluated molecular response as an exploratory endpoint for patients with CP CML in second line treatment who achieved CCyR but excluded patients enrolled in Russia, China, India, Taiwan, Singapore, Hong Kong and South Africa because the Applicant did not believe that specimen adequacy could be assured. Exclusion of these patients represented 25% of the evaluable population.

To determine molecular response, Bcr-Abl/Abl ratios were measured in bone marrow or peripheral blood samples using a reverse transcriptase-polymerase chain reaction (RT-PCR) assay. The assessments were performed by (b) (4) which reported a linear detection range of 50pg-5ug fusion transcript (5 to 500,000 leukemia cells) and 5-log level of sensitivity for this assay.

Study 200-WW was initiated prior to validation and widespread use of the International Scale (IS) and (b) (4) had not subsequently standardized the assay to allow reporting of transcript data using IS. MMR was assigned when at least a 3-log reduction from the current (b) (4) laboratory internal baseline (4.1325) had been achieved (the (b) (4) t internal baseline was based upon the PCR data of 120 previously untreated CML patients). Complete molecular response (CMR) corresponds to an undetectable Bcr-Abl/Abl ratio using a cycle threshold (Ct) of 45.

To be considered a responder for MMR or CMR, a subject must have had at least a 3-log reduction from the (b) (4) standardized baseline, a detectable Bcr-Abl transcript at baseline or any time post-baseline and must have maintained or attained a CCyR.

Major Molecular Response (MMR) was evaluated in 183 subjects in the all-treated population of patients with CP CML in second line treatment. This analysis excluded 88 subjects from China, India, Russia, and South Africa. Among patients receiving second line treatment for CP CML the MMR rate was 27% (95% CI: 27, 33) and the CMR rate was 22% (95% CI: 16, 28). See Table 21.

Table 20 Major Molecular Response in Patients with CP CML Receiving Second Line Treatment with Bosutinib (Reviewer Table)

Response	**Imatinib Resistant N=127 n (%)**	**Imatinib Intolerant N=56 n (%)**	**Total N=183 n (%)**
MMR (95% CI)	33 (26) (18, 34)	16 (27) (17, 40)	49 (27) (27, 33)
CHR (95% CI)	26 (20) (20, 27)	15 (27) (15, 38)	41 (22) (16 , 28)

Reviewer Comment: *The regulatory standard for labeling claims regarding molecular response has not been met for the following reasons: Molecular response is not standardized across laboratories, a large number (25%) of evaluable patients were not evaluated for molecular response, and molecular response was considered exploratory.*

6.1.7 Subpopulations

The following subpopulation analyses were performed: Gender, Race, Age, and Geographic region. In general, more males responded than females; more Caucasians responded than Asians; more patients younger than 65 responded than those 65 years of age or older; and more patients in North America responded than people in other parts of the world. Response refers to MCyR in patients with CP CML and OHR in patients with AP and BP CML. There were only two responders in the cohort of patients with ALL; therefore the ALL cohort is not included in this analysis. See Table 22.

Table 21 Subpopulation Analysis of Response in Patients with CP CML Who Achieved MCyR and in Patients with AP and BP CML Who Achieved OHR

	Gender		Age		Race		Geographic Region			
Phase of CML	**Male N (%)**	**Female N (%)**	**<65 N (%)**	**≥ 65 N (%)**	**White N (%)**	**Asian N (%)**	**NA N (%)**	**SA N (%)**	**Eur N (%)**	**Asia N (%)**
CP 2nd line N=90	59 (66)	31 (34)	73 (81)	17 (19)	61 (68)	29 (32)	27 (30)	9 (10)	26 (32)	27 (30)
CP 3rd line N=29	15 (52)	14 (48)	25 (86)	4 (14)	25 (86)	4 (14)	7 (24)	4 (14)	12 (41)	6 (21)
AP N=69	38 (55)	31 (45)	59 (86)	10 (14)	42 (61)	27 (39)	26 (38)	1 (1)	18 (26)	24 (35)
BP N=31	23 (74)	8 (26)	21 (68)	10 (32)	22 (71)	9 (29)	14 (45)	1 (3)	12 (39)	4 (13)

NA = North America (Canada, Mexico, U.S.) Eur = Europe/Australia/South Africa
SA = South America
Asia = China, Hong Kong, India, Korea, Russia, Taiwan, and Singapore

6.1.8. Analysis of Clinical Information Relevant to Dosing Recommendations

Bosutinib has linear PK in the dose range of 200 – 800 mg. The median T_{max} ranges from 3 to 6 hours and a 2 – 3 mean accumulation ratio is observed at steady-state. The absolute bioavailability of bosutinib has not been assessed. A high-fat meal caused a 2-fold increase in exposure. However, food also increased tolerability to bosutinib, therefore bosutinib was co-administered with food in patient trials after PK were established.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

There is no long-term efficacy data available at this time and therefore, no evidence of tolerance.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant studied three additional issues in the pivotal trial: Correlation of baseline Bcr-Abl status with response, transformation to more advanced phases of CML, and emergence of new mutations during treatment with bosutinib.

Correlation of Baseline Bcr-Abl Status With Response
Approximately 65% of patients with CP CML receiving bosutinib as second or third line therapy had Bcr-Abl mutation status assessed at baseline. Of the patients tested 9% had inadequate testing. Less than half of the patients tested (45%) had no point mutations, 43% had one point mutation and 2% had two or more point mutations. In four of the patients tested there were discordant results when testing was done more than once during screening, that is, results of one test identified no point mutation and results of another test identified a point mutation. There was no correlation of baseline Bcr-Abl point mutation status and response (MCyR).

Transformation of CP CML to advanced phase CML
Of the 288 subjects in the second-line CP CML all-treated population, 11 subjects (3.8%; 95% CI: [1.9, 6.7]) had confirmed disease transformation to AP or BP while on treatment with bosutinib. In the imatinib-resistant cohort, 10 subjects (5.0%; 95% CI: [2.4, 9.0]) had disease transformation: 4 transformed to AP with time to transformation ranging from 415 to 630 days after the first dose, and 6 transformed to BP with time to transformation ranging from 42 to 476 days after the first dose. In the imatinib-intolerant cohort, 1 subject (1.1 %; 95% CI: [0.0, 6.2]) transformed to AP 246 days after the first dose. For this subject, a rising peripheral blood blast count (>15%) was noted on 2 occasions in the setting of multiple treatment interruptions and dose reductions for management of toxicity. The subject remained on treatment, subsequently returned to CP, and regained a confirmed CHR. See Table 23.

Table 22 Transformation of CP CML to AP/BP CML in Patients Treated with Second Line Bosutinib (Reviewer Table)

Cohort of Second Line CP CML	Transformed to AP/BP CML N (%) (95% CI)
Imatinib Resistant N = 200	10 (5) (2.4, 9)
Imatinib Intolerant N = 88	1 (1) (0, 6.2)

Of the 118 subjects in the third line CP CML population, 117 were included in the analysis; 1 subject in the third line dasatinib intolerant cohort had no post-baseline assessment available. Five subjects had confirmed disease transformation to AP/BP. Three subjects in the dasatinib resistant cohort had disease confirmed transformation to AP/BP. Three subjects in the dasatinib resistant cohort had confirmed disease confirmation to AP. See Table 24.

Table 23 Transformation of CP CML to AP/BP CML in Patients Treated with Third Line Bosutinib (Reviewer Table)

Cohort of Third Line CP CML	**Transformed to AP/BP CML N (%) (95% CI)**
Imatinib + Dasatinib Resistant N = 37	3 (8) (1.7, 21.9)
Imatinib + Dasatinib Intolerant N = 49	0
Imatinib + Nilotinib Resistant N = 27	1 (4) ((0.1, 19.0)
Imatinib, Dasatinib +/or Nilotinib N = 4	1 (25) (0.6, 80.6)

Emergence of New Mutations in Patients with CP CML in Second Line Treatment with Bosutinib

Of 200 patients with CP CML who were resistant to imatinib, 15 developed new mutations. Two of these patients had no response to bosutinib; 5 patients had a best response of MCyR; and 8 patients had a best response of CHR. The most prevalent new mutation was T315I which occurred in 7 patients. Most of the patients with new mutations discontinued therapy for unsatisfactory response or disease progression (87%). Two patients with new mutations discontinued treatment due to adverse events.

Of 88 patients with CP CML who were intolerant of imatinib, three patients developed new mutations. All three patients discontinued treatment for unsatisfactory response or disease progression. See Table 25.

Table 24 Emergence of New Mutations in Patients with CP CML in Second Line Treatment with Bosutinib (Applicant Table)

Subject Number	Baseline Mutation	Date of detection	Best Response to Bosutinib	Treatment Conclusion Date	Time toTreatment Discontinuation (days)	Treament Conclusion Reason	New Mutation	New Mutation Detection Date
Imatinib resistant								
000006	Not detected	28MAR2006	CHR	12MAR2007	343	Unsatisfactory Response - Efficacy	T315I	11APR2007
000212	E286G,H396P ,M351T	21MAR2006	CCyR	(b) (6)	396	Death	L273M	20FEB2007
000436	Y253F	27MAY2008	CHR	10SEP2008	106	Adverse Event	G250E	03SEP2008
000662	Not detected	26MAR2007	CHR	15JUL2008	478	Disease Progression	E450A	15JUL2008
000685	Not detected	03OCT2008	No Response	18NOV2008	42	Disease Progression	T315I	18NOV2008
000781	E255V	20JUL2007	CHR	16APR2009	634	Disease Progression	T315I	16APR2009
000843	Not detected	29OCT2007	CHR	22JAN2009	441	Disease Progression	T315I	22JAN2009
000864	L248V	06SEP2007	PCyR	30OCT2008	413	Disease Progression	K378E	30OCT2008
000881	M351T	23NOV2007	CHR	30JUN2008	217	Disease Progression	T315I	01JUL2008
001061	Not detected	31MAR2008	CHR	22SEP2008	168	Disease Progression	V299L	23SEP2008
001546	D421G	08OCT2008	CHR	28JUL2009	282	Unsatisfactory Response - Efficacy	E255V	28JUL2009
001548	G250E,L298V	07JAN2009	No Response	13JAN2011	725	Disease Progression	M244V	13JAN2011
001953	E255V	25NOV2008	CCyR	04AUG2009	243	Adverse Event	T315I	04AUG2009
002529	E355G	23SEP2008	PCyR	01DEC2009	429	Disease Progression	V299L	01DEC2009
003082	F359V	26JAN2009	PCyR	06JAN2010	338	Unsatisfactory Response - Efficacy	T315I	06JAN2010
				Imatinib intolerant				
000244	Not detected	23NOV2006	CHR	04JUN2008	553	Unsatisfactory Response - Efficacy	V299L	04JUN2008
000549	Not detected	13NOV2007	CHR	12OCT2010	1051	Disease Progression	T315I	12OCT2010
001923	E459K	18OCT2007	CHR	04NOV2009	748	Unsatisfactory Response - Efficacy	E450G	04NOV2009

7 Review of Safety

Safety Summary

Data from the pivotal trial (Trial 200) and the supportive trial (Trial 3000) demonstrated no unexpected toxicities. There was no prolongation of the QT interval. Diarrhea was experienced by more than 80% of patients but was manageable.

7.1 Methods

7.1.1 Clinical Trials Used to Evaluate Safety

The claim for efficacy and safety for the application is based on the phase 2 trial (Trial 200). Supportive data is provided from two additional trials: (1) a randomized phase 3 trial (Trial 3000) in patients with Ph+ CML and patients with Ph+ ALL and (2) a Japanese trial (Trial 2203) in patients with Ph+ CML. Safety data are provided from 18 additional trials: 4 bioavailability and bioequivalent trials, 5 hepatic and drug interaction trials, 4 PK trials, 1 QT trial and 4 efficacy trials in patients with breast cancer. Key features of trials 200, 3000 and

2203 are summarized in Table 6 in Section 5.1. Details of trial design for the 3 trials are discussed in section 5.3.

Efficacy results are presented in section 6. 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

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) v. 14. AEs were summarized by MedDRA system organ class (SOC) and preferred term (PT). AEs and SAEs were to be graded according to NCI-CTCAE version 3.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The 21 clinical trials submitted to the BLA provide safety data from more than 1600 subjects exposed to bosutinib. The database includes:

- 570 patients with CML treated with bosutinib in Trial 200
- 248 patients with CML treated with bosutinib in Trial 3000
- 52 patients with CML treated with bosutinib in Trial 2203-JA
- 339 patients exposed in phase 1 dose escalation studies or phase 2 studies in combination with other agents.
- 393 healthy volunteers in bioavailability and bioequivalence trials, hepatic metabolism and drug interaction trials, QT and PK trials

The Applicant integrated safety data from the 3 clinical trials conducted in patients with CML into a single safety database. This reviewer's safety analysis will present 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.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In trial 200 patients were to be treated with bosutinib 500 mg orally per day and patients could continue to take bosutinib indefinitely in the absence of unacceptable toxicity or disease progression. Patients could have bosutinib dose escalation to 600 mg daily for lack of efficacy (failure to reach CHR by week 8 or CCyR by week 12, if they had had no grade 3 or higher possibly-related adverse events. Dose decreases for pre-specified toxicities occurred in 100 mg decrements; patients were removed from the trial if more than two dose reductions were required.

The median time on treatment was 95.7 weeks in patients with CP-CML receiving bosutinib as second line treatment. Median time on treatment was progressively shorter with advancing disease stage. Approximately a quarter of patients received dose escalations for inadequate response. Almost a half of the patients with CP-CML required dose reductions for AEs. More than two thirds of the patients with CP-CML required dose interruptions for AEs. See Table 26.

Table 25 Patient Exposure to Bosutinib in Trial 200 (Reviewer Table)

	CP CML Second Line N = 288	**CP CML Third Line N=118**	**AP CML N=77**	**BP CML N=66**	**Ph+ ALL N=24**
Time on Treatment (median) weeks	95.7	31.4	36.1	10.6	3.1
Median Number of Cycles (range)	23.9 (1-66)	7.8 (1-59)	9.0 (1-51)	2.6 (1-51)	<1 (1-57)
Dose Escalations n (%) (inadequate response)	79 (27)	41 (35)	22 (29)	16 (24)	2 (8)
Dose Reductions n (%) (due to AEs)	141 (49)	59 (50)	32 (42)	18 (27)	1 (4)
Dose Interruptions n (%) (due to AEs)	205 (71)	78 (66)	45 (58)	27 (41)	9 (38)
Dose Intensity Median mg/day	484	475	463	500	500

7.2.2 Explorations for Dose Response

Explorations for dose response were not conducted.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical testing was adequate. Bosutinib was not genotoxic or mutatgenic in animal studies and *in vitro* studies.

7.2.4 Routine Clinical Testing

Subjects in Trial 200 were required to have baseline evaluations, which included a complete medical history and physical examination, ECOG performance status, chest X-ray, laboratory testing, electrocardiogram (ECG), and LVEF (left ventricular ejection fraction) by echocardiogram or MUGA within 14 days of start of bosutinib. Bone marrow aspiration was required for baseline cytogenetics and was repeated at week 12, every 12 weeks thereafter, and at end of treatment. If the requisite 20 cells in metaphase were not present for cytogenetic testing after baseline, FISH testing was permissible. The required baseline laboratory studies included hematology, biochemistry, coagulation (INR and aPTT or PTT). These tests were to be repeated weekly until week 4, then at weeks 8 and 12 and then every 12 weeks thereafter. Serum pregnancy test was to be documented to be negative for women of childbearing potential (WCBP) at baseline and at end of treatment. Male patients had the following tests at baseline and at weeks 4, 8 12 and 24: serum testosterone, free testosterone, progesterone and 17 hydroxytestosterone. Chest X-ray was repeated at week 8 and at end of treatment. ECGs were performed in triplicate at baseline and at week 1 day before treatment and at hours 2, 4 and 6 post-dose and on day 21 before treatment and at hours 2, 4, 6 and 20-23 post-dose.

7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant submitted data from 18 additional trials: 4 bioavailability and bioequivalent trials, 5 hepatic and drug interaction trials, 4 PK trials, 1 QT trial and 4 efficacy trials in patients with breast cancer.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant considered the following 10 adverse events as events of special interest as they have been toxicities for one or more other TKIs: Prolongation of the QT interval (nilotinib and dasatinib); fluid retention and edema (imatinib and dasatinib); myelosuppression (imatinib, dasatinib and nilotinib), hepatotoxicity (imatinib and nilotinib), gastrointestinal irritation (imatinib), congestive heart failure, left ventricular dysfunction and myocardial infarction (dasatinib), hemorrhage (imatinib and dasatinib); and tumor lysis syndrome (nilotinib). See Section 7.3.4.

7.3 Major Safety Results

In Trial 200 there were increasing numbers of deaths, discontinuations, and non-fatal SAEs with increasing severity of disease. Almost all patients experienced at least one AE during the trial. See Table 27.

Table 26 Safety Overview for Trial 200

	CP CML Second Line N=288 n (%)	CP CML Third Line N=118 n (%)	AP CML N=77 n (%)	BP CML N=66 n (%)	Ph+ ALL N=24 n (%)
Deaths within 30 days of treatment with bosutinib	5 (2)	5(4)	11 (14)	13 (20)	8 (33)
Discontinuations for AEs	65 (23)	24 (20)	20 (26)	5 (8)	3 (13)
Non fatal SAEs	103 (36)	35 (30)	41 (54)	35 (55)	16 (70)
Patients with AEs	287 (99.7)	118 (100)	76 (100)	63 (98)	23 (96)

7.3.1 Deaths

There were 42 deaths within 30 days of the last dose of bosutinib; 5, 5, and 32 occurred in patients with CP second line, CP third line and AP disease respectively. The Applicant attributed the cause of death to disease progression in 3, 2, and 19 patients with CP second line, CP third line and AP disease respectively; and attributed the cause of death to AEs related to bosutinib in 2, 3, and 12 subjects with CP second line, CP third line and AP disease respectively. At the time of this review there were missing narratives for two subjects. The Applicant has been queried for these narratives. While the Applicant attributed 57% of deaths within 30 days to disease progression and 40% to adverse events, this reviewer attributed the cause of death to disease progression in 52% of the patients and AEs to 43% of the patients. A more striking difference is evident when comparing the Applicant's attribution of relatedness versus unrelatedness of adverse events to patients' deaths. The Applicant identified four AEs as related and 13 as unrelated whereas this reviewer identified 11 deaths as AE-related. See Table 28.

Table 27 Agreement and Differences in Attributions of Cause of Death within 30 Days of Treatment with Bosutinib between Applicant and Reviewer (Reviewer Table)

Patient ID	Applicant	Reviewer	Explanation
CP Second Line			
000157	AE unrelated	AE unrelated	Acute, global cardiac decompensation (Pre-existing heart disease)
000869	DP	DP	NA
001049	DP	DP	NA
002059	DP	DP	NA
002527	AE related	AE related	Pneumonia
CP Third Line			
000556	AE unrelated	AE unrelated	Myocardial infarction (Pre-existing coronary artery disease)
001753	DP	AE related	Pneumonia; pulmonary edema
002384	DP	DP	NA
002498	AE related	AE related	Gastrointestinal bleeding
002827	AE unrelated	AE related	Myocardial infarction
Advanced Phase (AP, BP and ALL)			
000015	DP	DP	Subarachnoid hemorrhage
000033	AE unrelated	AE related	Left ventricular hemorrhage
000038	AE unrelated	AE related	Cerebral infarct
000053	DP	DP	NA
000154	DP	DP	NA
000164	AE related	AE related	Bilateral pneumonia
000219	DP	AE related	Sepsis
000220	DP	DP	NA
000233	DP	DP	NA
000262	DP	DP	NA
000313	AE unrelated	AE related	Septicemia
000361	DP	DP	NA
000415	AE unrelated	AE unrelated	Pneumonia
000423	DP	DP	NA
000461	AE related	AE related	Sepsis
000524	DP	DP	NA
000529	AE unrelated	AE related	Septic shock
000553	AE unrelated	AE related	Sepsis
000624	DP	DP	NA
000630	AE unrelated	AE unrelated	Myocardial infarction

000643	DP	DP	NA
000672	DP	AE related	Worsening of pre-existing pneumonia and thrombocytopenia
000673	DP	DP	NA
000676	DP	DP	NA
001490	AE unrelated	AE related	Congestive heart failure
001493	AE unrelated	AE unrelated	Pneumonia
001499	Unknown	AE related	*Clostridium difficile* colitis, sepsis
001701	DP	DP	NA
002064	DP	AE related	Sepsis
002288	AE unrelated	AE unrelated	Cerebral vascular accident
002793	DP	DP	NA
002798	DP	DP	NA

DP = Disease Progression AE = Adverse Event NA = Not Applicable

Discussion of Discordant Attributions for Cause of Death

- Patient 001753 was a 49 year old male on third line treatment for CP CML who started taking bosutinib August 15, 2007 and continued until October 10, 2007. Chest X-ray on October 20, 2007 revealed diffuse pulmonary infiltrates and pulmonary edema. The patient developed malaise, non-productive cough, fever (101° F) and dizziness on October 21, 2007, and bronchial culture revealed methicillin resistant *staphylococcus aureaus*. The patient died on

- Patient 002827 was a 72 year old female on third line treatment for CP CML was on treatment from May 27, 2008 to September 10, 2008. On July 2, 2008 the patient developed a non-productive cough. On August 20, 2008 she was diagnosed with mild cardiac failure and the dosage of bosutinib was reduced from 500 mg to 400 mg daily. Subsequently the patient reported dyspnea, abdominal distention, increased peripheral edema and the degree of cardiac failure was upgraded to moderate. The patient died (b) (6) of a suspected myocardial infarction.

- Patient 000219 was a 71 year old male with AP CML who was on treatment from August 11, 2006 to August 18, 2006 when the patient experienced hyperleukocytosis and sepsis from *enterococcus faecium.* Although the patient was mildly neutropenic at screening (ANC = 1.248 X 10^9/L), he became profoundly neutropenic after start of treatment with bosutinib (ANC = 0.075 X 10^9/L). The patient died on (b) (6)

- Patient 000038 was a 74 year old female with Ph+ ALL on treatment from February 21, 2007 to March 6, 2007. The patient became neutropenic with altered mental status, dehydration and renal insufficiency (b) (6) and developed atelectasis and pneumonia (b) (6) Although thrombocytopenic at screening (25 X10^9/L), the platelet count nadired at 12 X 10^9/L after the first week of therapy. MRI of the brain (b) (6)

(b) (6) showed a right PCA territory infarct. The patient died on (b) (6) from a PCA distribution infarct.

- Patient 000313 was a 73 year old female with AP CML on treatment from June 19, 2007 to June 8, 2008. The patient had a past medical history of coronary artery disease (CAD) with angioplasty, stent placement, myocardial infarction, congestive heart failure, cardiac pacemaker and angina pectoris. The death narrative reported that the patient "experienced coronary artery disease on (b) (6) and septicemia on (b) (6) Blood culture was positive for MRSA on (b) (6) The patient died (b) (6) and the cause of death was listed as CAD.

- Patient 000529 was a 60 year old male with Ph+ ALL on treatment from January 16, 2007 to March 16, 2007. He was diagnosed with *Pseudomonas aeruginosa* septicemia (b) (6) (b) (6). Although he was neutropenic at screening (ANC = 0.88 X 10^9/L), he became profoundly neutropenic (ANC = 0.08 after the first week of treatment and remained neutropenic during treatment. The patient died on (b) (6) from septicemic shock.

- Patient 000553 was 73 a year old female with Ph+ ALL on treatment from June 1, 2007 to June 21, 2007. Lung examination during screening was normal. The patient died on (b) (6) (b) (6) from pneumonia and sepsis.

- Patient 000672 was a 51 year old male with AP CML on treatment from September 21, 2007 to October 2, 2007. Lung examination during screening was normal. On (b) (6) (b) (6) the patient had "worsening of general condition" and "worsening of pre-existing pneumonia." The patient died on (b) (6) from worsening of pre-existing pneumonitis and thrombocytopenia.

- Patient 001490 was an 80 year old male with BP CML on treatment from June 18, 2007 through September 23, 2009. Baseline LVEF was 56 and MUGA was 68 (both values considered within the normal range. PMH included atrial fibrillation, congestive heart failure, and pulmonary hypertension. During treatment with bosutinib the patient had multiple episodes of fluid retention. The patient died on (b) (6) from congestive heart failure and end stage renal failure.

- Patient 001499 was a 60 year old male with AP AML who was on treatment from August 8, 2007 to May 5, 2008. The patient developed *Clostridium difficile* colitis on (b) (6) and died (b) (6).

- Patient 002064 was a 36 year old male with BP CML on treatment from December 20, 2007 to January 10, 2008. Screening physical examination identified normal lungs and screening chest X-ray did not identify lung abnormality. The patient developed a hypersensitivity reaction on (b) (6) which manifested as severe pruritic rash for which he was hospitalized. On (b) (6) he was diagnosed with *staphylococcus hemolyticus* pneumonia, and died of sepsis on (b) (6).

Reviewer Comment: *Evaluation of relatedness of treatment emergent AEs to cause of death is confounded by symptoms related to disease progression. One of the problems inherent in a single arm trial is that there is uncertainty about the lack of bias in making attributions. The case reports presented above appear to be at least possibly related to the study drug and not unrelated as claimed by the Applicant.*

7.3.2 Nonfatal Serious Adverse Events

Over a third of patients (203) experienced nonfatal SAEs. Of 288 patients with CP CML in second line treatment, 94 (33%) had non-fatal SAEs; of 118 patients with CP CML in third line treatment, 28 (24%) had nonfatal SAEs; and of 167 patients with AP CML, 81 (49%) had SAEs. The most frequent SAEs in descending order by SOC were the following: Infections and Infestations (91); Gastrointestinal (71), General Disorders and Administration Site Conditions (50), Cardiac Disorders (44), Respiratory, Thoracic and Mediastinal Disorders (44), Blood and Lymphatic System Disorders (41), and Nervous System Disorders (32). Please see Section 7.3.4 for a more detailed presentation of significant adverse events.

7.3.2 Dropouts and/or Discontinuations

About one-fifth of the patients with CP CML discontinued treatment with bosutinib due to AEs. About a quarter of patients with AP CML discontinued bosutinib due to AEs. Decreasing numbers of patients with BP and ALL discontinued due to AEs as the majority in both cohorts discontinued due to disease progression. The most frequent AEs responsible for discontinuations were thrombocytopenia (29 patients), elevated liver enzymes (17 patients), and neutropenia (11 patients). See Table 30.

Table 28 Discontinuations from Bosutinib Treatment Due to Adverse Events in Patients with CML

	CP CML Second Line N=288 n (%)	**CP CML Third Line N=118 n (%)**	**AP CML N=77 n (%)**	**BP CML N=66 n (%)**	**Ph+ ALL N=24 n (%)**
Discontinuations for AEs	65 (23)	24(20)	20 (26)	5 (8)	3 (13)

7.3.4 Significant Adverse Events

The Applicant collected narratives for ten events of special interest: Cardiac, hemorrhage, effusion, edema, myelosuppression/hematologic, liver function, infections, rash, hypersensitivity and gastrointestinal.

Cardiac Disorders
Myocardial infarction was a TEAE in eight patients. All had previous medical history of at least one of the following: coronary artery disease, vascular hypertensive disorder, supraventricular arrhythmia or congestive heart failure.

Congestive heart failure or left ventricular dysfunction occurred in 10 patients; each patient had a past medical history of heart disease or vascular hypertensive disorder.

Atrial fibrillation occurred in 6 patients; each patient had a past medical history of heart disease or vascular hypertensive disorder.

Pericardial effusion and pericardial hemorrhage will be presented in later paragraphs (Effusions and Hemorrhage) of this section.

Reviewer Comment: *Although cardiac disorders occurred during treatment with bosutinib, all of the patients with cardiac disorders had pre-existing heart disease or risk factors.*

Hemorrhage
Hemorrhage occurred in 79 patients (14%), was grade 3 or 4 in 13 patients (2%), and was a SAE in 18 patients (3%). The most frequent site of hemorrhage was the gastrointestinal tract. Most hemorrhagic events were related to thrombocytopenia.

Reviewer Comment: *Hemorrhage is an expected toxicity with thrombocytopenia. Thrombocytopenia is an expected finding in advanced stages of CML where the bone marrow precursors for platelet differentiation are crowded out by leukemic populations as well as a TEAE.*

Effusion
Pleural effusions occurred in 43 (8%) patients, and was responsible for two discontinuations. Pericardial effusions occurred in 11 (2%) patients, and was responsible for two discontinuations.

Edema
Localized and peripheral edema occurred in 87 (15%) patients, and was grade 1 or 2 severity in 95% of patients..

Reviewer Comment: *Although the Applicant initially hypothesized that symptoms of fluid retention would occur less frequently with bosutinib because it does not interact with the PDGF receptor, symptoms of fluid retention occurred in 54% of patients treated with bosutinib.*

Hematologic/myelosuppression
Thrombocytopenia, neutropenia and anemia occurred in 40%, 14%, and 23% of patients respectively. Grade 3 and 4 thrombocytopenia, neutropenia, and anemia occurred in 27%, 10%, and 12% of patients respectively.

Reviewer Comment: *TEAEs of myelosuppression were not unexpected in patients with CML receiving TKI therapy.*

Liver Function
Twenty percent of patients experienced elevation of one or more liver enzymes during treatment with bosutinib. A third of the liver enzyme elevations were of grade 3 or 4 severity. Most patients were able to continue therapy after a dose hold or dose reduction. A total of 18 (3%) patients discontinued treatment due to liver enzyme elevations. There were no Hy's Laws cases in Trial 200.

Reviewer Comment*: Although no Hy's Law cases occurred in Trials 200, 3000 or 2406, one Hy's Law case occurred in a patient with breast cancer who was receiving bosutinib in combination with letrozole. The patient developed grade 4 elevations of ALT and AST one week after starting combination bosutinib and letrozole therapy. The patient's liver function tests returned to normal after discontinuation of bosutinib therapy but continuation of letrozole.*

Infections
Sixteen percent of patients experienced an SAE of infection. Pneumonia was the infection which affected the most patients (35). Bacteremia, septicemia or sepsis affected 19 patients. Urinary tract infections occurred in 8 patients and upper respiratory tract and gastrointestinal infections occurred in 6 patients each.

Reviewer Comment: *Serious infections occurred in 16 percent of patients; although serious, infections in myelosuppressed patients are not unexpected, and can be managed with appropriate anti-infective therapy.*

Rash
Although 203 patients (36%) experienced rash as a TEAE, 36 (6%) were grade 3 or 4, and seven (1%) were SAEs.

Reviewer Comment: *Although rash occurred in more than a third of patients, 6 per cent were grade 3 or 4 and 1 per cent were SAEs. There were no cases of Stevens Johnson Syndrome or other serious dermatologic conditions.*

Hypersensitivity
Eight patients (1%) experienced symptoms of hypersensitivity, one patient had a dose reduction due to hypersensitivity, and one patient discontinued treatment. Three patients (0.5%) who experienced a hypersensitivity SAE during treatment with bosutinib.

Reviewer Comment: *Serious hypersensitivity reactions were rare in patients treated with bosutinib.*

Gastrointestinal
Diarrhea occurred in 81% of patients, was grade 3 or 4 in 8% of patients, was an SAE in 1% of patients, accounted for dose reductions in 5% of patients and for discontinuations in 1% of patients. Nausea occurred in 44% of patients, was grade 3 or 4 in 1% of patients, was an SAE in less than 1% of patients, accounted for dose reductions in 2% of patients, and for no discontinuations. Vomiting occurred in 37% of patients, was grade 3 or 4 in 3% of patients, was an SAE in less than 1% of patients, accounted for dose reductions in 2% of patients, and for no discontinuations. Abdominal pain occurred in 42% of patients, was grade 3 or 4 in 2% of patients, was an SAE in 1% of patients, accounted for dose reductions in 2% of patients, and for less than 1% of patients.

Reviewer Comment: *Although bosutinib treatment was associated with considerable gastrointestinal toxicity, most AEs were acceptable with medication for symptom management and in rare cases with dose reductions.*

7.3.5 Submission Specific Primary Safety Concerns

Tumor Lysis Syndrome (TLS) has been a complication of nilotinib treatment for CML. In Trial 200 four patients had reports of TLS; however after careful review of their laboratory results throughout the course of treatment none of the four patients met criteria for TLS. TLS usually manifests as a constellation of hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, and can be life-threatening. None of the four patients presented with the classic constellation of signs of TLS but presented with isolated electrolyte elevations. See Table 31.

Table 29 Review of Patients with CML Receiving Bosutinib Reported as Having Tumor Lysis Syndrome

Patient	Explanation
00053	TLS reported in week 2 but uric acid was not elevated; nor were other electrolytes
001701	TLS reported (b) (6); patient's Ph+ ALL was progressing. Patient had hyperkalemia and hyperphophatemia and hyperuriciemia, but BP was 65/35, the patient had been vomiting and creatinine was 296 (normal = 60-100)
001702	TLS reported in weeks 2, 3, 4, 8, 48 and completion; minor elevations of magnesium or uric acid at any one timepoint that resolved spontaneously
003035	TLS reported in weeks 2 and 3, but patient's disease was progressing rapidly; hyperuricemic at baseline with decreases in uric acid during treatment. Other electrolytes were within the normal range.

7.4 Supportive Results

7.4.1 Common Adverse Events

Almost every patient in Trial 200 experienced treatment emergent adverse events (TEAEs). The most frequent AEs were diarrhea, abdominal pain, thrombocytopenia, rash, vomiting, fatigue, upper respiratory tract infection, pyrexia, cough, anemia and headache. See Table 32.

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.

Table 30 Common Treatment Emergent Adverse Events in 10% or More 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 (%)
Gastrointestinal Disorders			
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)
Blood and Lymphatic System Disorders			
Thrombocytopenia	113 (39)	44 (37)	71 (43)
Neutropenia	34 (12)	18 (15)	27 (16)
Anemia	53 (18)	19 (16)	62 (37)
Skin and Subcutaneous Tissue Disorders			
Rash	109 (38)	37 (31)	57 (34)
Pruritus	29 (10)	19 (16)	11 (7)
General Disorders and Administration Site Disorders			
Fatigue	92 (32)	30 (25)	44 (26)
Pyrexia	66 (23)	17 (14)	59 (35)
Edema	47 (16)	14 (12)	26 (16)
Respiratory, Thoracic and Mediastinal Disorders			
Upper Respiratory Infection	77 (27)	23 (19)	23 (14)
Cough	61 (21)	20 (17)	31 (19)
Nervous System Disorders			
Headache	50 (17)	29 (25)	31 (19)

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.

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 (%)**
Blood and Lymphatic System Disorders			
Thrombocytopenia	68 (24)	29 (25)	60 (36)
Neutropenia	20 (7)	14 (12)	25 (15)
Anemia	21 (7)	7 (6)	39 (23)
Gastrointestinal Disorders			
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)
Skin and Subcutaneous Tissue Disorders			
Rash	25 (9)	4 (3)	7 (4)
Pruritus	2 (<1)	1 (<1)	0
General Disorders and Administration Site Disorders			
Fatigue	4 (1)	1 (<1)	6 (4)
Pyrexia	2 (<1)	0	3 (2)
Edema	3 (1)	0	2 (1)
Lower Respiratory Tract and Lung Infections			
Pneumonia	9 (3)	0	16 (10)

7.4.2 Laboratory Findings

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.

7.4.3 Vital Signs

In trial 200, mean, median and changes from baseline in temperature, diastolic and systolic blood pressure and pulse rate during treatment with bosutinib were obtained. There were no clinically meaningful changes observed in these parameters.

7.4.4 Electrocardiograms (ECGs)

Changes in ECGs that were considered to be abnormal were reported as adverse events and graded as per NCI CTCAE, v.3.0. ECGs were obtained during screening, immediately prior to first dose and at hours 2, 4 and 6 post-dose, on day 21 before dose, and at hours 2, 4, 6 and 20-23 post dose, and one week after completion of treatment. As mentioned previously in this review, there were no cardiac events in patients without a pre-existing heart disease or risk factors.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant submitted a thorough QT study that was reviewed by Venkatesh Bhattaram, M.D. of the FDA QT-Independent Review Team (IRT). He concluded that bosutinib does not cause a significant prolongation of the QT interval. For a detailed report, see his review.

Reviewer Comment: *There have been no cardiac safety signals identified to date in the bosutinib development program.*

7.4.6 Immunogenicity

There were no immunogenicity studies included in the application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There were no exploratory analyses of dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

There were no exploratory analyses of time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

There were no drug-demographic interactions identified.

7.5.4 Drug-Disease Interactions

There were no drug-disease interaction studies.

7.5.5 Drug-Drug Interactions

The Applicant conducted three drug-drug interaction trials in healthy volunteers. In a trial of CYP3A inhibitors the Applicant tested 24 healthy volunteers in which five daily doses of ketoconazole were co-administered with a single dose of 100 mg of bosutinib. In this trial ketoconazole increased bosutinib Cmax by 5.2-fold and bosutinib AUC in plasma by 8.6-fold, as compared with administration of bosutinib alone under fasting conditions.

The Applicant studied bosutinib exposure in 24 healthy volunteers who were administered a single dose of 500 mg of bosutinib with six daily doses of 600 mg of rifampin. Bosutinib exposure (Cmax and AUC in plasma) decreased to 14% and 6% respectively, of the values when 500 mg of bosutinib was administered alone in the fed state.

The Applicant studied co-administration of a single oral dose of 400 mg of bosutinib with multiple oral doses of 60 mg of lansoprazole in 24 healthy fasting subjects. Bosutinib Cmax and AUC decreased to 54% and 74% respectively, of the values seen when 400 mg of bosutinib was given alone.

An *in vitro* study indicated that bosutinib has the potential to increase the plasma concentrations of drugs that are P-glycoprotein substrates, such as, digoxin.

Reviewer Comment: *The Applicant included Drug Interaction warnings in the label as follows:*

(b) (4)

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The carcinogenic potential of bosutinib has been evaluated in long-term studies in one specie, the rat.. The results of these studies were submitted late in the review cycle (May 30, 2012). Another toxicologist within the Office of Hematology and Oncology, Shawna Weis, Ph.D. volunteered to review the carcinogenicity results, with plans to present findings to the Executive Carcinogenicity Assessment Committee (ECAC) prior to final labeling meetings and PDUFA deadline. The carcinogenicity studies in the rat were negative, but the Applicant will most likely be required to perform carcinogenicity studies in another specie.

7.6.2 Human Reproduction and Pregnancy Data

There have been no trials regarding human reproduction and pregnancy data.

7.6.3 Pediatrics and Assessment of Effects on Growth

Bosutinib has not been studied in children.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdoses have not been reported for bosutinib. There is no abuse potential and withdrawal considerations are not relevant to the submitted trials.

7.7 Additional Submissions / Safety Issues

The 120-day safety update was submitted March 8, 2012 and included safety data analyses, and some patient narratives and CRFs. It did not include datasets and narratives for all patients with SAEs. The FDA review team requested the datasets and narratives, and the Applicant submitted all datasets and narratives on April 5, 2012. The safety update was cumulative and updated safety information as follows:

- Trial 200 safety data was extended from March 28, 2011 to August 25, 2011.
- Trial 3000 safety data was extended from November 15, 2010 to August 29, 2011.
- Trial 2203 safety data was extended from November 15, 2010 to August 15, 2011.

The 120-day safety update provided no new safety signals.

8 Postmarket Experience

Bosutinib is a new molecular entity and has no postmarket experience.

9 Appendices

9.1 Literature Review/References

Arora, A and Scholar, E. Role of tyrosine kinase inhibitors in cancer therapy. Perspectives in Pharmacology 315: 971-979, 2005..

Baccarani M, Cortes J, Pane F et al. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 27: 6041-6051, 2009.

Cortes J, Jabbour E, Kantarjian H, et al. Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood 110: 4005-11, 2007.

Garg R, Kantarjian H, O'Brien S, et al. The use of nilotinib or dasatinib after failure to prior tyrosine kinase inhibitors: long term follow-up. Blood.114: 4361-8, 2009.

Giles F, Cortes J, Kantarjian H et al. Accelerated and blastic phases of chronic myelogeous leukemia. Hematology/Oncology Clinics of North America 18: 753-774, 2004.

Giles F, O'Dwyer M, Swords R. Class effects of tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia. 23:1698-1707, 2009.

Giles F, le Coutre P, Bhalla K, et al. Nilotinib therapy after dasatinib failure in patients with imatinib-resistant or -intolerant chronic myeloid leukemia (CML) in chronic phase (CP), accelerated phase (AP), or blast crisis (BC). Blood 110: 1029, 2007.

Hochhaus A, La Rosée P, Müller M. Impact of BCR-ABL mutations on patients with chronic myeloid leukemia. Cell cycle 10: 250-260, 2011.

Khoury H, Cortes J, Kantarjian H et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 119: 3403-3412, 2012.

Klyuchnikov E, Schathauser P, Kröger N et al. Second-generation tyrosine kinase inhibitors in the post-transplantation period in patients with chronic myelogenous leukemia or Philadelphia ALL. Acta Haematologica 122: 6-10, 2009.

Redaelli S, Piazza R, Rostagno R et al. Activity of bosutinib, dasatinib and nilotinib against 18 imatinib resistant BCR/Abl mutants. J Clin Oncol: 27: 469-471, 2009.

Rohon P. Biological therapy and the immune system in patients with chronic myeloid leukemia. Int J Hematology 96: 1-9, 2012.

Rossi, A, Brecchia, M, Abruzzes, E et al. Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors. Haematologica: epub, July, 2012, 1-15.

Sen, B and Johnson F. Regulation of Src family kinases in human cancers. J of Signal Transduction 2011: 1-14, 2011.

Soverini S, Gnani A, Colarossi S, et al.Philadelphia-positive patients who already harbor imatinib-resistant Bcr-Abl kinase domain mutations have a higher likelihood off developing additional mutations associated with resistance to second- or third-line tyrosine kinase inhibitors. Blood 114:2168-71, 2009.

Tam CS, Kantarjian H, Garcia-Manero G, et al. Failure to achieve a major cytogenetic response by 12 months defines inadequate response in patients receiving nilotinib or dasatinib as second or subsequent line therapy for chronic myeloid leukemia. Blood.112: 516-8, 2008.

9.2 Labeling Recommendations

There were extensive internal labeling discussions with all review disciplines. Key clinical labeling recommendations included the following:

- Addition of embryo-fetal warning in Warnings and Precautions
- Removal of Sections 6.2 and 14.2. Because Clinical Trial 3000 failed to meet its primary endpoint, superiority over imatinib, discussion of bosutinib in the treatment of patients with newly diagnosed CML cannot be included in the label.
- The incidences of all TEAEs in the label have been adjusted upward. The Applicant made attributions of relatedness to all TEAEs which resulted in smaller numbers; however because Trial 200 was a single arm trial and not a randomized, controlled trial, all TEAEs have been counted.

Analysis of the Applicant's Table of Adverse Reactions revealed that the incidence was similar between the second and third line CP CML populations. FDA will recommend replacing the existing table with the following table:

Table 32 Adverse Reactions that Occurred in ≥ 20% of Patients in Phase 1/2 Safety Population

SOC **Preferred Term**	**CP CML** **N=406** **n (%)**		**AP CML** **N=140** **n (%)**	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Gastrointestinal Disorders				
Diarrhea	343 (84)	107 (76)	107 (76)	7 (5)
Nausea	186 (46)	5 (1)	66 (47)	3 (2)
Abdominal Pain	169 (42)	7 (2)	41 (29)	7 (5)
Vomiting	153 (38)	12 (3)	59 (42)	5 (4)
Skin and Subcutaneous Disorders				
Rash	156 (38)	33 (8)	54 (39)	6 (4)
Pruritus	43 (11)	3 (4)	11 (8)	0
Blood and Lymphatic System Disorders				
Thrombocytopenia	138 (34)	91 (22)	61 (44)	54 (39)
Anemia	79 (19)	30 (7)	51 (36)	36 (26)
Neutropenia	59 (15)	40 (10)	25 (18)	24 (17)
General Disorders and Administrative Site Conditions				
Fatigue	130 (32)	9 (2)	37 (26)	37 (26)
Pyrexia	93 (23)	2 (<1)	52 (37)	52 (37)
Edema	60 (15)	2 (<1)	18 (13)	18 (13)
Infections and Infestations				
Upper respiratory tract infection	98 (24)	2 (<1)	23 (16)	0
Investigations				
Alanine aminotransferase increased	81 (20)	30 (7)	14 (10)	7 (5)
Aspartate aminotransferase increased	64 (16)	15 (4)	15 (11)	4 (3)
Nervous System Disorders				
Headache	82 (20)	3 (<1)	25 (18)	6 (4)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	80 (20)	0	30 (21)	0

CP CML = Chronic Phase CML; AP CML = Advanced Phase CML(includes patients with Accelerated Phase and Blast Phase CML

9.2 Advisory Committee Meeting

There was no advisory committee meeting for this application; however a briefing document was prepared by the clinical team leader for an independent medical reviewer and expert in hematologic malignancies, Judith Karp, M.D. In addition, the clinical team leader prepared a briefing document for a patient representative who will also provide an independent review. As of the date of this review, Dr. Karp has not yet been cleared by the Advisors and Consultants staff to participate in the Divisional Assignment.

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

/s/

KAREN M MCGINN
07/23/2012

VIRGINIA E KWITKOWSKI
07/23/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203341 **Applicant: Wyeth Pharmaceuticals** **Stamp Date: 11/17/2011**

Drug Name: Bosulif (Bosutinib) **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b) (1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? **Study Number:** 3160A4-200-WW **Study Title**: A Phase ½ Study of SKI-606 in Philadelphia Chromosome Positive Leukemias **Sample Size:** 571 **Arms:** 1 **Location in submission:** Module 5	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1** **Indication:** Treatment of chronic, accelerated, or blast	X			1 Single-arm, multicenter, multination-al trial

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	phase Philadelphia chromosome positive CML in patients with resistance or intolerance to prior therapy. **Pivotal Study #2** **Indication:**			X	
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			1 Single-arm, multicenter, multinational trial
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	26% of patients were from the US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		An Information Request has been sent to the Sponsor 12/21/2011.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X	X		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		The Sponsor has agreed to resubmit the data in a format that will allow a more expeditious review by COB 12/23/2011.
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	There was no prior discussion with the Division.
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		X		The Sponsor submitted CRFs for SAEs attributed to the test article only. Since the trial was a single arm trial, the Sponsor will be asked to submit CRFs for all SAEs. An IR has been sent to the Sponsor 12/21/2011.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes___

If the Application is not fileable from the clinical 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.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

KAREN M MCGINN
12/22/2011

VIRGINIA E KWITKOWSKI
12/22/2011