CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL TEAM LEADER REVIEW MEMO

NDA/Serial Number:	203341/0000
Drug Name:	Bosulif® (Bosutinib) Tablets
Indication(s):	Adult Patients with Relapsed or Refractory Chronic, Accelerated or Blast Phase Chronic Myeloid Leukemia (CML)
Applicant:	Wyeth Pharmaceuticals, Inc.
Submitted date:	November 17, 2011
PDuFA date:	September 17, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
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Keywords: Single arm study

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1. EXECUTIVE SUMMARY

The purpose of this review is to present and comment on rationales on what populations should be included in the possible approval of Bosulif and provide recommendations and conclusions.

This NDA submission consists of results from study 3160A4-200-WW, an open-label, 2-part, safety and efficacy study of bosutinib once daily orally in subjects with Ph+ leukemia. This study consists of two parts. Part 1 was a dose-escalation study in subjects with chronic phase (CP) chronic myelogenous leukemia (CML) who were resistant to imatinib for the purpose of establishing the maximum tolerated dose and determining a dose for part 2. Eighteen (18) subjects total were enrolled, at dose levels of 400 mg, 500 mg and 600 mg. Based on part 1 data, and the starting dose for part 2 was selected to be 500 mg. Part 2 studied the efficacy of bosutinib 500 mg daily in subjects with chronic, accelerated, or blast phase Philadelphia-positive (Ph+) CML in adult patients with resistance, or intolerance to prior therapy. The study also enrolled a small number of patients with Ph+ acute lymphoblastic leukemia (ALL).

The primary objective of study 3160A4-200-WW was to rule out a major cytogentic response (MCyR) rate of 23% or less for the imatinib-resistant cohort. There was a variety of cohorts entered into the study (see Section 1.2 for further details).

The results of study 3160A4-3000-WW in subjects with newly diagnosed Ph+ leukemia were also submitted as a supportive study. Study 3160A4-3000-WW was a randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed chronic phase Philadelphia chromosome positive CML. The primary objective was the demonstration of a greater complete cytogenetic response (CCyR) rate at 1 year for the bosutinib arm relative to the imatinib arm. Study 3160A4-3000-WW failed to demonstrate a superior CCyR rate at 1 year for bosutinib compared to imatinib.

1.1 Conclusions and Recommendations

The primary objective on MCyR at week 24 for the imatinib-resistant CP CML cohort was met. In the sponsor's final clinical study report, they write that the endpoint of MCyR at week 24 in patients with imatinib-intolerant CP CML was not met. Additionally, a Simon 2-stage design appears to have been used in the evaluation of MCyR at week 24 in patients with imatinib-intolerant disease. A Simon 2-stage design is traditionally a design to address a "go no-go" question, not for drawing conclusion on efficacy. Other than the imatinib-resistant and imatinib-intolerant cohorts, the analyses were expressed as exploratory for the other cohorts in the protocol dated November 21, 2008 and in the final study report. From just these facts, it clear how a conclusion or recommendation can be made that approval and labeling claims be made for only patients with imatinib-resistant CP CML.

Based on the statistical analysis plan dated March 28, 2011 (which was also the data cutoff date), the cohorts had separate designs and decision rules. The specified uninterested response rates in the designs are arbitrary. The evaluations of the endpoints for these smaller cohorts were pre-specified as secondary endpoints in the protocol dated

November 21, 2008. These are single arm evaluations on response rates in a second-line or later setting. The benefit in such setting is generally based on the magnitude of the response rate and the durability of the responses. In this application the responses were fairly durable. For example, from the statistical review of Dr. Kallappa Koti

> "Thirty-nine imatinib-intolerant CP CML subjects achieved MCyR. Eighteen major cytogenetic imatinib-intolerant CP CML responders were censored by 104.3 weeks (by 2 years) and four responders lost response by 104.3 weeks. The remaining 17 (43.6%) imatinib-intolerant responders maintained MCyR at Year 2."

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

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

1.2 Brief Overview of Study 3160A4-200-WW

A total of 571 patients were enrolled in study 3160A-200-WW. Among these patients, 288 patients with CP CML were previously treated with imatinib only, 118 patients with CP CML were previously treated with both imatinib and at least one additional tyrosine kinase inhibitor, 76 patients with accelerated phase CML were previously treated with at least imatinib, and 64 patients with blast phase CML were previously treated with at least imatinib. The study enrolled its first patient w on January 18, 2006 and its last patient on April 20, 2010. The data cutoff date was March 28, 2011. Among these 571 patients, 503 with CML were in the evaluable (analysis) population (defined as all enrolled patients who received at least one dose of bosutinib and had an adequate baseline efficacy assessment).

The primary objective was the determination of efficacy in patients with CP CML resistant to imatinib who have had no prior exposure to other tyrosine kinase inhibitors. The determination of efficacy was based on MCyR rate at 24 weeks. The hypotheses on the MCyR rate at 24 weeks (p) were H_0: $p \leq 0.23$ against the 1-sided alternative H_1: $p > 0.23$. Testing was based on a one-sided type 1 error rate of 0.05 and 80% power at $p = 0.33$. The design of the primary cohort incorporated a 4-stage group sequential design, with interim analyses at 25%, 50%, and 75% information fraction based on a maximum sample size of 167 evaluable subjects for the imatinib-resistant cohort.

A secondary objective involved the MCyR rate in the imatinib-intolerant cohort. The hypotheses on the MCyR rate at 24 weeks (p) were H_0: $p \leq 0.56$ and H_1: $p > 0.73$. Testing and the intended sizing of the cohort was based a Simon 2-stage design. For alpha = 0.05, beta = 0.2, a maximum of 55 patients are required with 16 patients evaluated for response in the first stage.

The sponsor's conclusion in the final clinical study report are:

> "The primary objective of MCyR rate at Week 24 in imatinib-reistant second-line CP CML subjects was met; 35.5% (95% Cl: [29.7, 41.7]) of subjects attained MCyR at Week24."
>
> "The secondary objective of the protocol, MCyR at Week 24, was not met for second-line imatinib-intolerant CP CML subjects; 30% (90% CI: [21.6, 39.5]) of subjects attained MCyR at Week 24. When cumulative MCyR was assessed including subjects who maintained or achieved MCyR as responders, 61.3% of imatinib-intolerant subjects had MCyR."

There were separate designs (sample size and analysis) for the various cohorts. Some of these are provided below via the statistical analysis plan dated March 28, 2011.

1. *CP CML patients who have failed imatinib and are resistant to dasatinib (cohort 7):* The design was based on a Simon 2-stage design with interesting and uninteresting 24 week MCyR rates of 30% and 10%, respectively, a one-sided alpha=0.05 and power =80%. The first stage would be based on a sample size of ten and the second stage would be based on a sample size of 29.

2. *CP CML patients who have failed imatinib and are intolerant of dasatinib (cohort 8):* The design was based on a Simon 2-stage design with interesting and uninteresting 24 week MCyR rates of 37% and 17%, respectively, a one-sided alpha=0.05 and power =80%. The first stage would be based on a sample size of 12 and the second stage would be based on a sample size of 35.

3. *CP CML cohort of patients who have failed imatinib and are resistant to nilotinib (cohort 9):* The design was based on a Simon 2-stage design with interesting and uninteresting 24 week MCyR rates of 30% and 10%, respectively, a one-sided alpha=0.05 and power =80%. The first stage would be based on a sample size of ten and the second stage would be based on a sample size of 29.

4. "Patients in cohort 2 (failed imatinib and either nilotinib intolerant or treated with both nilotinib and dasatinib) will be described. No testing is planned for this group."

5. *Advanced disease (AP, BP and ALL cohorts combined) with failure on imatinib and unexposed to other kinase inhibitors (cohort 3):* The design was based on a Simon 2-stage design with interesting and uninteresting 24 week complete hematological response (CHR) rates of 29% and 9%, respectively, a one-sided alpha=0.05 and power =80%. The first stage would be based on a sample size of 11 and the second stage would be based on a sample size of 24.

6. *Advanced disease (AP, BP and ALL cohorts combined) with failure on imatinib and on other TKI treatment (cohort 4):* The design was based on a Simon 2-stage design with interesting and uninteresting 24 week complete hematological response CHR rates of 26% and 6%, respectively, a one-sided alpha=0.05 and

power =80%. The first stage would be based on a sample size of 6 and the second stage would be based on a sample size of 26.

The statistical analysis plan also states the following "amendment" during the study to perform separate analyses for BP and AP patients in cohort 3 on the endpoint of overall hematological response (OHR):

"Preliminary analysis of the cohort of advanced Ph+ leukemia patients who had failed imatinib and were unexposed to other tyrosine kinase inhibitors in addition to emerging data from studies of other agents suggested that efficacy should be assessed in AP and BP cohorts of imatinib-resistant patients unexposed to other tyrosine kinase inhibitors, using the endpoint of 48 week OHR. The revised analysis strategy is as follows."

7. *Imatinib-resistant/intolerant CML patients in AP, unexposed to other tyrosine kinase inhibitors (cohort 31)*: The design was based on a Simon 1-stage design with interesting and uninteresting 48 week OHR rates of 61% and 43%, respectively, an alpha=0.05 and power =80%. The maximum sample size is 49 with an interim look based on the response rates from 42 patients.

8. *Imatinib-resistant/intolerant CML patients in BP, unexposed to other tyrosine kinase inhibitors (cohort 32)* The design was based on a Simon 1-stage design with interesting and uninteresting 48 week OHR rates of 48% and 30%, respectively, an alpha=0.05 and power =80%. The maximum sample size is 45 with an interim look based on the response rates from 41 patients.

9. *Imatinib-resistant/intolerant CML patients in AP exposed to other tyrosine kinase inhibitors (cohort 41)* and *Imatinib-resistant/intolerant CML patients in BP exposed to other tyrosine kinase inhibitors (cohort 42)* will be analyzed descriptively.

The protocol dated November 21, 2008 included the following in a list of secondary endpoints:

- Estimate MCyR rate in CP CML patients who have failed imatinib and are resistant to other tyrosine kinase inhibitors (dasatinib or nilotinib)

- Estimate MCyR rate in CP CML patients who have failed imatinib and are intolerant to dasatinib

- Estimate CHR rate in advanced leukemia patients and

- Estimate OHR rate in imatinib-resistant accelerated phase and blast phase CML patients

The protocol listed the following efficacy endpoint as exploratory

- Estimate the rate of molecular responses in those whose best prior response was CCyR and cytogenetic responses in those previously attaining only CHR.

The efficacy results are summarized in Tables 1-3.

Table 1. Efficacy Results in Ph+ CP CML Patients Previously Treated with Imatinib

	IM Resistant (n=186)	IM Intolerant (n=80)
MCyR at Week 24	35.5%	30.0%
(95% CI)	(28.6%, 42.8%)	(20.3%, 41.3%)
CCyR at Week 24	24.2%	25.0%
(95% CI)	(18.2%, 31.0%)	(16.0%, 35.9%)

Table 2. Efficacy Results in Ph+ CP CML PatientsPreviously Treated with Imatinib and Dasatinib and/or Nilotinib

	IM + (NI + D) or IM + NI Intolerant (n=4)	IM + D Resistant (n=35)	IM + D Intolerant (n=43)	IM + NI Resistant (n=26)
MCyR by Week 24	50.0%	25.7%	25.6%	26.9%
(95% CI)	(6.8%, 93.2%)	(12.5%, 43.3%)	(13.5%, 41.2%)	(11.6%, 47.8%)
CCyR by Week 24	25.0%	8.6%	18.6%	11.5%
(95% CI)	(0.6%, 80.6%)	(1.8%, 23.1%)	(8.4%, 33.4%)	(2.5%, 30.2%)

Table 3. Efficacy Results in Accelerated-Phase and Blast Phase Patients Previously Treated with at Least Imatinib

	AP Total (N=69)	BP Total (N= 60)
OHR by Week 48	55.1%	28.3%
(95% CI)	(42.6%, 67.1%)	(17.5%, 41.4%)

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/s/

MARK D ROTHMANN
07/27/2012

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07/27/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA Serial Number:	203341 / 0000
Drug Name:	Bosulif® (Bosutinib) Tablets
Indication(s):	Chronic, accelerated, or blast phase Ph+ chronic myelogenous leukemia (CML)
Applicant:	Wyeth Pharmaceuticals, Inc.
Submitted date:	17-NOV-2011
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Review Priority:	Standard
Biometrics Division:	DB V / CDER
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Keywords: Proportion, confidence interval, Kaplan-Meier estimate

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1. EXECUTIVE SUMMARY

BOSULIF® (bosutinib monohydrate) is 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. Evidence of the efficacy of Bosulif® (bosutinib) in the proposed indication derives primarily from the ongoing Phase 1/2 Study 3160A4-200-WW (Study 200-WW) of bosutinib in subjects with Philadelphia chromosome positive (Ph+) leukemia whose disease is resistent or intolerant to prior tyrosine inhibitor (TKI) therapy, based on a database snapshot date of 28 March 2011. The maximum tolerance dose (MTD) of bosutinib, which was used in Study 200-WW was 500 mg. Bosutinib capsules or tablets (100 mg dosage strength) were supplied in bottles. The primary efficacy endpoint in Study 200-WW was the major cytogenetic response (MCyR) rate at Week 24.

This NDA also includes the efficacy conclusions of the supportive Phase 3 Study 3000-WW in subjects with newly diagnosed Ph+ leukemia. Study 3160A4-3000-WW (Study 3000-WW) was a Phase 3 randomized, open-label study of bosutinib versus imatinib in subjects with newly diagnosed chronic phase Philadelphia chromosome positive CML. The complete cytogenetic response (CCyR) rate at 1 year was the primary endpoint.

Key results from Study 3160A4-200-WW:

- The primary objective of MCyR rate at Week 24 in imatinib-resistant second-line chronic phase (CP) CML subjects was met. MCyR rate at Week 24 was significantly greater than 23% (p-value < 0.0001). The MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was 35.5% (66/186 subjects; 95% CI: 28.6%, 42.4%).

- The median duration of MCyR was not reached for the second-line CP CML imatinib-resistant cohort. Only 34.9% [95% CI: (25.7%, 44.6%)] of the responders in the imatinib-resistant cohort maintained MCyR at Year 2.

- The MCyR rate at Week 24 in imatinib-intolerant second-line CP CML evaluable subjects was 30% (24/80 subjects; 95% CI: 20%, 40%). MCyR rate at Week 24 in imatinib-intolerant subjects was significantly lower than the expected rate of 56% (see Sponsor's sample size rationale in Section 3.2 of this review).

- CCyR at Week 24 in imatinib-resistant second-line CP CML evaluable subjects was 26.3% [49/186; 95% CI: (20%, 32.7%)].

- CCyR at Week 24 in imatinib-intolerant second-line CP CML evaluable subjects was 35% [28/80; 95% CI: (24.5%, 45.5%)].

- Overall hematologic response (OHR) rate in AP Total patients who were treated with at least imatinib was 50% [38/76; 95% CI: (38.8%, 61.2%)]. A 28.9% [95% CI: (14.5%, 43.4%)] of the responders in the AP Total cohort maintained OHR at Year 2.

- OHR rate in BP Total patients who were treated with at least imatinib was 26.6% [17/64; 95% CI: (15.7%, 37.4%)]. The median duration of OHR was 31.5 weeks [95% CI: (24.3, 48)]. Only 11.8% [95% CI: (1.5%, 36.4%)] of the responders in the BP Total cohort maintained OHR at Year 2.

Key results from Phase 3 Study 3000-WW:

- There was no significant difference in the primary endpoint 1-year CCyR rates between the bosutinib and imatinib arms. The CCyR rate at 1 year was numerically higher on the bosutinib arm (70%, 175/250 subjects; 95% CI: 64.3%, 75.7%) compared to the imatinib arm (67.9%, 171/252 subjects; CI: 62.1, 73.6), although this did not reach statistical significance (p-value = 0.6).

Overall conclusion and recommendation:

- Except the imatinib-resistant cohort analysis in Study 3160A4-200-WW, all other cohorts' analyses were either exploratory or indicated inefficacy or were based on small samples. Efficacy results from cohorts other than imatinib-resistant cohort should not be used to support labeling claims.

2. INTRODUCTION

2.1 Overview

Two clinical trials are reviewed in this review. Basic details are provided in Table 2.1.1 below, followed by an overview of each study.

Table 2.1.1: List of studies reviewed

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
200-WW	1/2	Until PD	≥ 2 years	Total of 571	CP CML
3000-WW	3	Until PD	8 years	250 per arm	Ph+ CML

2.1.1 Study 3160A4-200-WW

Study 3160A4-200-WW was a Phase 1/2, open-label, 2-part, multicenter, safety and efficacy study of SKI-606 once daily orally in subjects with Philadelphia chromosome positive leukemias. It was conducted during the period of 18 January 2006 to 28 March 2011. Part 1 was a dose escalating study in CP CML subjects who were resistant or refractory to imatinib to establish the MTD in this subject population and determine a dose for part 2. Part 2 studied the efficacy of Bosutinib 500 mg daily in subjects with CP, imatinib-resistant/refractory CML, who had no prior Src, Abl, or Src-Abl inhibitor exposure other than imatinib.

Subjects 18 years of age or older with a cytogenetic or polymerase chain reaction (PCR) based diagnosis of any phase of Ph+ CML or Ph+ ALL whose disease was resistant to full-dose imatinib (≥600 mg), or was intolerant of any dose of imatinib were included. Subjects who had received prior treatment with dasatinib or nilotinib in addition to imatinib were also eligible to be included in the study.

A total of 686 subjects were screened for Part 2 and 571 were enrolled in 80 study sites. The five countries enrolling the most subjects were the United States (147), Russia (66), Italy (53), China (43), and Germany (39). The remaining 223 subjects came from other countries. Part 2 also included exploratory cohorts of the subjects: (i) CP CML Second-line imatinib intolerant, (ii) CP CML Third-line, and (iii) Advanced Leukemias (AP CML, BP CML, Ph+ ALL). In part 2, efficacy was determined based on physical examination and peripheral blood and bone marrow analyses. MCyR at week 24 was the primary endpoint.

2.1.2 Study 3160A4-3000-WW

Study 3160A4-3000-WW was a Phase 3 randomized, open-label study of Bosutinib versus imatinib in subjects with newly diagnosed chronic phase Philadelphia chromosome positive Chronic Myelogenous Leukemia. It was conducted during the period 05 February 2008 to 15 November 2010. A total of 173 sites enrolled subjects including 21 sites in the United States and 2 sites in Canada. A total of 581 subjects were assessed for eligibility and 502 were randomized 1:1 to receive either bosutinib 500 mg per day or imatinib 400 mg per day. Enrollment has been completed, and follow-up of patients in the study is ongoing.

Randomization of subjects into each arm was stratified based on site-entered Sokal score (low, intermediate, high) and geographical region (United States, Canada, and Western Europe vs. Eastern Europe vs. South America).

Complete cytogenetic response (CCyR) rate at 1 year was the primary endpoint in Study 3000-WW. Key pre-specified secondary and long-term endpoints included: MMR at 1 year, duration of CCyR, duration of MMR, duration of CHR, time to transformation from CP to AP or BP, and event-free survival (EFS). The efficacy results were analyzed in the intent-to-treat (ITT) and evaluable populations.

A sample size of 370 was aimed to detect a difference in CCyR rates at one year of 0.15 (improvement from 0.65 in the imatinib arm to 0.8 in the bosutinib arm), with 90% power and one interim analysis at 40% information, using a 1-sided test of the rate difference at the 2.5% significance level. Assuming that 10% of the subjects enrolled are not evaluable, approximately 412 subjects were needed to have 370 evaluable subjects.

The primary endpoint of CCyR rate at 1 year in the ITT population showed no statistically significant difference between study arms.

Sponsor's results

In the ITT population of Study 3000-WWW, the CCyR rate at 1 year was numerically higher on the bosutinib arm (70%, 175/250 subjects; 95% CI: 64.3%, 75.7%) compared to the imatinib arm (67.9%, 171/252 subjects; CI: 62.1, 73.6), although this did not reach statistical significance. The 2-sided p-value was 0.6 [Cochran-Mantel-Haenszel (CMH) test, adjusted for Sokal score and geographic region]. This reviewer verified the sponsor's analysis.

2.2 Data Sources

The path to the CDER Electronics Document Room (EDR) is:
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The SAS dataset used in this review: CYTO.XPT, CONCLU.XPT, CYTRES.XPT, ENDPT.XPT, and ENDEFS.XPT.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The SAS dataset cyto.xpt was the efficacy dataset for Study 200-WW. It was possible to easily reproduce the primary analysis results. It did not contain baseline demographic variables, which were needed in the subgroup analyses in this review. Considerable effort was needed to process and analyze the data. The SAS dataset endpt.xpt was the efficacy dataset for Study 3000-WW. It was possible to easily reproduce the primary analysis results.

3.2 Evaluation of Efficacy

This section focuses on results from Study 200-WW. The results from Study 3000-WW are provided in section 2.1.2.

Study Design and Endpoints

Study 200-WW was an open-label, multicenter, 2-part, safety and efficacy study of bosutinib once daily orally in subjects with Ph+ leukemia. Part 1 was a dose-escalation study in subjects with CP CML who were resistant/refractory to imatinib to establish the MTD in this subject population and determine a dose for part 2. After completion of part 1, the starting dose for part 2 was determined to be 500 mg.

Chronic myelogenous leukemia (CML) has three phases, chronic, accelerated and blast, of increasing leukemia blast count and clinical severity. Bone marrow morphology was used to determine the blast and immature myeloid cell counts in order to define disease phase. The definitions of these phases are provided in the appendix at the end of this review. The definition of imatinib resistance included failure to achieve or maintain any hematologic improvement within four weeks, or achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response, or presence of a genetic mutation in the BCR-Abl gene associated with imatinib resistance. Imatinib intolerance was defined as inability to tolerate imatinib due to toxicity, or progression on imatinib and inability to receive a higher dose due to toxicity. The definitions of resistance and intolerance to both dasatinib and nilotinib were similar to those for imatinib.

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

CP CML Second-line

- CP CML imatinib intolerance

CP CML Third-line

- CP CML imatinib resistance/intolerance followed by dasatinib resistance
- CP CML imatinib resistance/intolerance followed by dasatinib intolerance
- CP CML imatinib resistance/intolerance followed by nilotinib resistance

- CP CML imatinib resistance/intolerance followed by dasatinib and nilotinib resistance/intolerance (4th line) or CP CML imatinib resistance/intolerance followed by nilotinib intolerance (3rd line)

Advanced Leukemia (AP CML, BP CML, Ph+ ALL)

- Second-line: Advanced Ph+ leukemia with imatinib resistance/intolerance
- Multiple TKI exposure: Advanced Ph+ leukemia with resistance/intolerance to imatinib, dasatinib, and/or nilotinib.

Duration of Part 2 treatment phase participation was estimated to be up to 58 weeks (2 weeks for screening, 52 weeks on study drug, and 4 weeks for final visit). Total study duration (Part 1 + part 2) was 41 months.

Table 3.2.1: Study 200-WW Flowchart

Study Procedure	Screening	Week ± 3 days								
Week		1		2	3	4	8	12	Q12w	End
Day (± days after treatment)	-14 to -1	1	7	14	21	28	56	84	168, 252, 336	
Informed consent	x									
Dose SKI-606	Continuous Daily Dosing									
PRBC & Platelet trans. Hx	x	x		x	x	x	x	x	x	x
ECOG performance status	x		x	x			x	x	x	x
CBC & Differential	x	x	x	x	x	x	x	x	x	x
PCR for BCR-Abl	x					x	x	x	x	x
SAEs & Adverse Events	----------									x
Long term follow up	After SKI-606 discontinuation, by phone every 3 months for survival, progression and other Tx.									
Bone Marrow Aspirate	x					x*	x*	x	x	x
Cytogenetics, Morphology & Blasts%	x					x*	x*	x	x	x
Site Response Assessment						x*	x*	x	x	x
BCR-Abl Sequencing	x									x

* Advanced subjects only

Efficacy in Study 200-WW was determined based on physical examination and peripheral blood and bone marrow analyses. Major cytogenetic response (MCyR) at week 24 was the primary endpoint for CP CML second-line imatinib-resistant subjects in Study 200-WW. A MCyR was defined as having a complete cytogenetic response (CCyR) or a partial cytogenetic response (PCyR). Definitions of CCyR and PCyR are provided in the Appendix of this review. Disease status was assessed at baseline and every 12 weeks during the first 2 years of treatment, every 24 weeks thereafter, and at the time of treatment completion. A subject had to attain a better post-baseline response than the status at baseline to be counted as a responder.

Duration of response was defined as the interval from the first date of response until the first date of confirmed loss of response. If the subject did not experience a loss, censoring occurred on the last date the subject was assessed for response.

Progression-free survival (PFS) was the time from first dose to disease progression as assessed by the investigator, or death within 30 days of last dose. If the subject was last known alive without progression, censoring occurred at the last date the patient was known to be progression free. PFS at 1 and 2 years was a secondary endpoint for all subjects.

Overall survival (OS) was the interval from the date of first dose to the date of death due to any cause. Subjects without death documented were censored at the last date when the subject was known to be alive. OS at 1 and 2 years was a secondary endpoint for all subjects.

Overall hematologic response (OHR) by Week 48 was the key efficacy secondary endpoint in advanced leukemia subjects. OHR included CHR, NEL, minor hematologic response (MiHR), or return to chronic phase (RCP). Definitions of hematologic responses are provided in the Appendix at the end of this review.

3.2.1 Sponsor's sample size rationale

- Published dasatinib data have suggested that a MCyR rate at 24 Weeks of 0.33, in imatinib-resistant subjects, is of interest. Taking the interesting and uninteresting rates for MCyR rate at 24 weeks to be $p_1 = 0.33$ and $p_0 = 0.23$, respectively, it was desired to test the null hypothesis of H_0: $p \leq 0.23$ against the 1-sided alternative H_1: $p > 0.23$ with a type 1 error rate of 0.05 and 80% power at $p = 0.33$. The design of the primary cohort incorporated a 4-stage group sequential design, with interim analyses at 25%, 50%, and 75% information fraction, a Pocock (rho = 1) nonbinding futility boundary, and an O'Brien-Fleming (rho = 3) efficacy boundary function, requiring a maximum sample size of 167 evaluable subjects, with a sample size of 115 expected when the true MCyR rate was $p = 0.33$. The test statistic, standardized using the empirical variance estimate, was assessed for efficacy at an overall 1-sided significance level of 0.05, and assessed for futility at an overall 1-sided significance

level of 0.20. The decisions concerning stopping for efficacy or futility were based on the error spending functions at the actual number of enrolled subjects at the interim analyses.

- For CP CML subjects with imatinib-intolerance, testing the null hypothesis H_0: $p \leq 0.56$ against the alternative H_1: $p \geq 0.73$ was considered, where p is the MCyR rate at 24 weeks. The optimum Simon 2-stage for alpha = 0.05, beta = 0.2, required a maximum of n = 55 subjects with 16 in the first stage.

3.2.2 Statistical Methodologies

Pivotal study 200-WW: The null hypothesis of overall response rate (ORR) of 10% was tested using the z-test. Point estimate of ORR and 95% confidence interval on the ORR were also calculated. Kaplan-Meier method was used to estimate the median duration of response, median progression-free survival, and median overall survival.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 200-WW was a multicenter trial conducted in North America, the Europe Union, Africa, and Asia. A total of 686 subjects were screened for Part 2 and 571 were enrolled. There were 374 (65.6%) Caucasian, 89 (15.6%) Asian, 41 (7.2%) African American subjects in Study 200-WW. Ethnic origin of 38 (6.7%) subjects was unknown. There were 27 (4.7%) subjects who belonged to other ethnic groups. The study consisted of 302 (53%) males and 269 (47%) females. The average age of a patient was 51.6 years. Median age was 53 years. The youngest patient was 18 years of age and the oldest was 91.

The efficacy component of Study 200-WW (Part 2) is ongoing, although now closed to recruitment. The data cut-off date was 28 March 2011. A total of 159 discontinued the treatment for various reasons. The numbers of subjects who discontinued treatment along with the reasons for discontinuation are provided in Table 3.2.2 below.

Table 3.2.2: Reasons for treatment discontinuation in Study 200-WW

Conclusion status Reason	Imatinib-Resistant N = 200 (%)	Imatinib-Intolerant N = 88 (%)	Total N = 288 (%)
Discontinued	**108 (54.0)**	**51 (58.0)**	**159 (55.2)**
Adverse Event	33 (16.5)	31 (35.2)	64 (22.2)
Disease Progression	35 (17.5)	6 (6.8)	41 (14.2)
Unsatisfactory response- Efficacy	17 (8.5)	4 (4.5)	21 (7.3)

Subject Request	11 (5.5)	7 (8.0)	18 (6.3)
Other	4 (2.0)	3 (3.4)	7 (2.4)
Death	5 (2.5)	0	5 (1.7)
Lost to Follow-up	2 (1.0)	0	2 (0.7)
Investigator Request	1 (0.5)	0	1 (0.3)

A total of 66 (23%) subjects have completed both the active treatment phase of the study and the 2-year follow-up period. An additional 54 (18%) subjects have discontinued participation in the study before or during the long term follow-up period. The reasons for discontinuing participation in the study were death (11%), subject request (3.5%), lost to follow-up (3.5%), and other (0.7%).

3.2.4 Sponsor's results and conclusions from Study 200-WW

- The primary efficacy objective of MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was met (1-sided $p < 0.001$); 35.5% (66/186 subjects; 90% CI: 29.7, 41.7) of subjects attained MCyR at Week 24.

- The secondary efficacy objective of the protocol, MCyR at Week 24, was not met for the second-line imatinib-intolerant CP CML subjects; 30% [24/80 subjects; 90% CI: (21.6, 39.5); 1-sided $p = 1.0$] attained MCyR at Week 24.

- The cumulative MCyR for second-line CP CML subjects (including both imatinib-resistant and imatinib-intolerant subjects) was 53.4% (142/266 subjects, 95% CI: 47.2, 59.5), and 42.9% (114/266 subjects) had a CCyR.

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

- A total of 142 subjects (53.4%) attained a MCyR during the study, and 108 (76.1%) of those subjects had maintained the response as of the last assessment prior to the database snapshot. In the imatinib-resistant cohort, 73 (70.9%) subjects maintained the response as of the last assessment prior to the database snapshot and in the imatinib-intolerant cohort, 35 (89.7%) have maintained the response. The median duration has not been reached in both cohorts.

3.2.5 Reviewer's analyses and results from Study 200-WW

3.2.6.1 MCyR in enrolled subjects

Out of 711 enrolled subjects, 200 subjects were imatinib-resistant second-line CP CML subjects. Test of the null hypothesis that MCyR rate at Week 24 equals 0.23 versus the alternative hypothesis that it is greater than 23% resulted in a p-value of 0.0004. That is, the primary efficacy objective of MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was met; 33% (66/200 subjects; 95% CI: 26.4%, 39.5%) of subjects attained MCyR at Week 24. All treated population was defined as all enrolled patients who received at least one dose of SKI-606. The MCyR rates at Week 24 for all enrolled patients and the corresponding 95% confidence intervals for other cohorts are shown in Table 3.2.3 below.

Table 3.2.3: Primary endpoint MCyR at Week 24- all enrolled subjects

COHORT	Number of subjects	Number of Responders	Percent of Responders	95% Confidence Interval
Acute lymphocytic leukemia (ALL)	24	0	0%	-
AP – IM only	46	14	30.4%	(17%, 43.7%)
AP – Multi TKI	31	3	9.7%	(0%, 20.1%)
AP Total	76	17	22.4%	(13%, 31.7%)
BP – IM only	35	6	17.1%	(4.7%, 29.6%)
BP – Multi TKI	29	0	0%	-
BP – Total	64	6	9.4%	(2.2%, 16.5%)
IM + D Intolerant	50	8	16%	(5.8%, 26.2%)
IM + D Resistant	37	6	16.2%	(4.3%, 28.1%)
IM + NI +/or D	4	2	50%	-
IM + NI Resistant	27	4	14.8%	(1.4%, 28.2%)
IM Intolerant	88	24	27.3%	(18%, 36.6%)
IM Resistant*	200	66	33%	(26.4%, 39.5%)

* Protocol specified primary efficacy cohort

As seen from Table 3.2.3, out of 288 imatinib-resistant or imatinib-intolerant second-line CP CML subjects, 90 (31%) subjects achieved MCyR at Week 24 [95% CI: (25.9%, 36.6%)].

Eighty-five (29.5%) subjects out of the 288 second-line CP CML patients resistant or intolerant to imatinib achieved complete cytogenetic response (CCyR) at Week 24. As noted from Table 3.2.3, 200 patients were imatinib-resistant and 88 were imatinib-intolerant. Fifty-five (27.5%) imatinib-resistant subjects achieved CCyR at Week 24 [55/200; 95% CI: (21.3%, 33.7%)]. Thirty (34%) imatinib-intolerant patients achieved CCyR at Week 24 [30/88; 95% CI: (24.2%, 44%)].

3.2.6.2 MCyR in evaluable subjects

Evaluable population was defined as all enrolled patients who received at least one dose of SKI-606 and had an adequate baseline efficacy assessment. Out of 200 IM resistant subjects, fourteen subjects were classified as un-evaluable. The patients were: 000187, 000221, 000453, 000784, 000787, 000794, 000989, 001504, 002032, 002033, 002079, 002275, 002276, and 002558. That is, out of 711 subjects, 186 evaluable subjects were imatinib-resistant second-line CP CML subjects. Test of the null hypothesis that MCyR rate at Week 24 equals 0.23 versus the alternative hypothesis that it is greater than 23% resulted in a p-value of less than 0.0001. The primary efficacy objective of MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was met; 35.5% (66/186 subjects; 90% CI: 29.7, 41.7) of subjects attained MCyR at Week 24. The MCyR rates at Week 24 for evaluable patients and the corresponding 95% confidence intervals for other cohorts are shown in Table 3.2.4 below.

Table 3.2.4: Primary endpoint MCyR at Week 24 in Evaluable subjects

COHORT	Number of subjects	Number of Responders	Percent of Responders	95% Confidence Interval
Acute lymphocytic leukemia (ALL)	19	0	0%	-
AP – IM only	42	14	33.3%	(19.1%, 47.6%)
AP – Multi TKI	27	3	11.1%	(2.3%, 29.2%)*
AP Total	69	17	24.6%	(14.5%, 34.8%)
BP – IM only	29	6	20.7%	(5.9%, 35.4%)
BP – Multi TKI	25	0	0%	-
BP – Total	54	6	11.1%	(2.7%, 19.5%)
IM + D Intolerant	43	8	18.6%	(07%, 30.2%)
IM + D Resistant	35	6	17.1%	(4.7%, 29.6%)
IM + NI +/or D	4	2	50%	-
IM + NI Resistant	26	4	15.4%	(4.4%, 35.9%)*
IM Intolerant	80	24	30%	(20%, 40%)
IM Resistant*	186	66	35.5%	(28.6%, 42.4%)

* Clopper-Pearson CI

The MCyR rate at Week 24 in imatinib-intolerant second-line CP CML evaluable subjects was 30% (24/80 subjects; 95% CI: 20%, 40%). MCyR rate at Week 24 in imatinib-intolerant subjects was much lower than the expected rate of 56%.
As seen from Table 3.2.4, out of 266 imatinib-resistant or imatinib-intolerant evaluable second-line CP CML subjects, 90 (33.8%) subjects achieved MCyR at Week 24 [95% CI: (28.1%, 39.5%)].

3.2.6.3 MCYR by Week 24

Major cytogenetic response by 24 weeks was secondary endpoint. Table 3.2.5 below shows the MCYR by 24 weeks in chronic phase third line patients.

Table 3.2.5: MCyR by 24 weeks in chronic phase third line patients

COHORT	Number of subjects	Number of Responders	Percent of Responders	95% Confidence Interval
IM + D Resistant	37	9	24.3%	(10.5%, 38.1%)
IM + D Intolerant	50	11	22%	(10.5%, 33.5%)
IM + NI Resistant	27	7	25.9%	(9.4%, 42.5%)
Total	114			

3.2.6.4 Confirmed OHR

Overall hematologic response (OHR) by Week 48 was the key secondary endpoint in advanced leukemia subjects. Table 3.2.6 below shows the confirmed overall hematologic response by Week 48 in Advanced Leukemia ≥1 prior TKI (AP, BP, ALL) patients.

Table 3.2.6: Confirmed OHR by Week 48 in advanced leukemia subjects

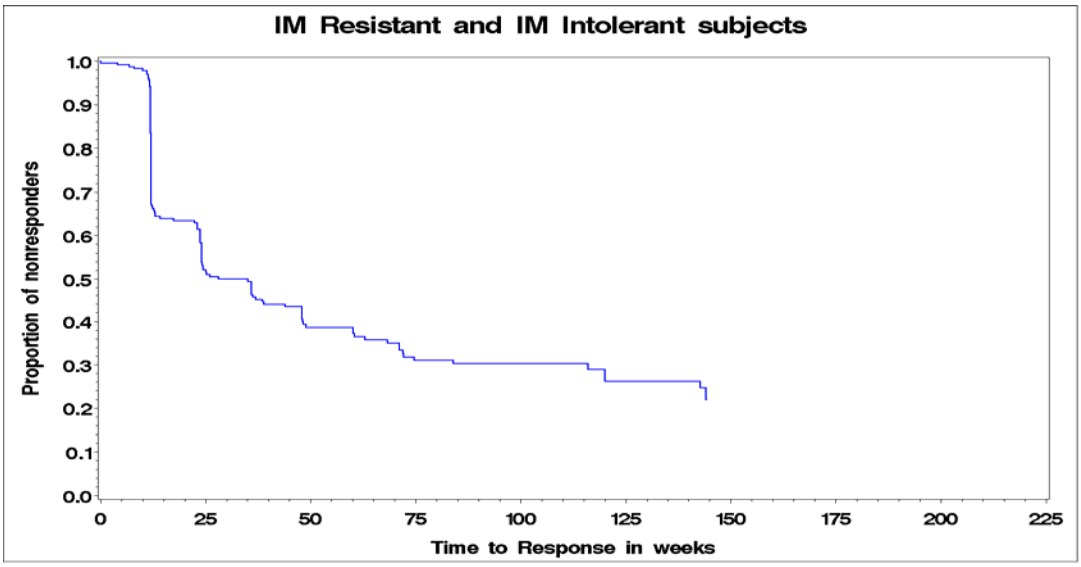
COHORT	Number of subjects	Number of Responders	Percent of Responders	95% Confidence Interval
Acute lymphocytic leukemia (ALL)	24	1	4.2%	(0.1%, 21.1%)*
AP – IM only	46	25	54.3%	(40%, 68.7%)
AP – Multi TKI	31	13	41.9%	(24.6%, 59.4%)
BP – IM only	35	12	34.3%	(18.6%, 50%)
BP – Multi TKI	29	5	17.2%	(3.5%, 31%)
Total	165			

* Clopper-Pearson CI

3.2.6.5 Time to MCyR

Time to MCyR was a secondary endpoint for imatinib-resistant cohort. Out of 186 evaluable subjects in this cohort, 103 (55.4%) subjects achieved MCyR. Time to MCyR of 83 (44.6%) subjects was censored. As claimed by the Sponsor, the K-M median time to a response was 36.0 weeks [95% CI: (24.1, 49.0)] for imatinib-resistant subjects. Out of 80 evaluable imatinib-intolerant subjects, 39 (48.7%) subjects achieved MCyR. Time to MCyR of 41 (51.3%) subjects was censored. The K-M median time to a response was 24.4 weeks [95% CI: (12.3, 48.0)] for imatinib-resistant subjects. The K-M median time to MCyR was 32.1 weeks [95% CI: (24.1, 48.0)] for all evaluable patients that were previously treated with imatinib. This was based on 142 events and 124 censored observations. The Kaplan-Meier curve for time to MCyR is shown in Figure 3.2.1 below.

Figure 3.2.1: Time to MCyR for imatinib-resistant and imatinib intolerant cohorts combined



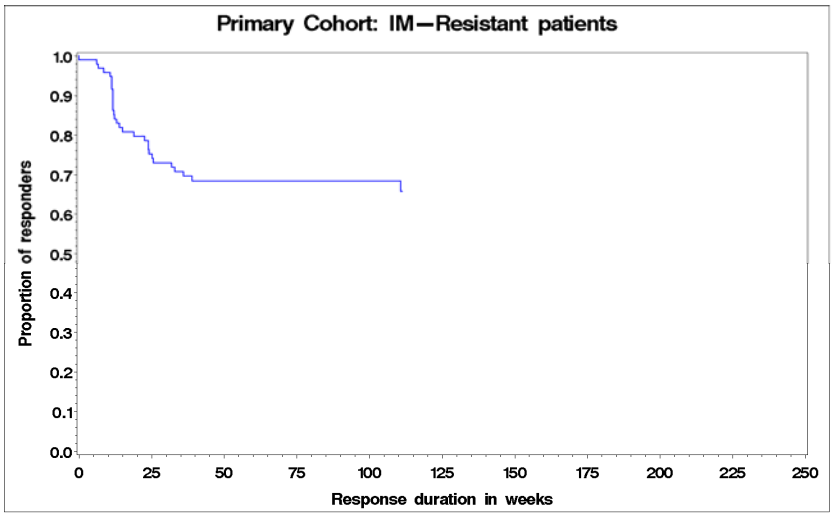
3.2.6.6 Cumulative MCyR

A patient was counted as having MCyR by Week X if any visit-level cytogenetic response was complete or partial up to and including the last day in the applicable day ranges for Week X. Subject must also have a better than baseline response to be classified as a responder. Cumulative MCyR rate in imatinib-resistant subjects was 51.5% [103/200; 95% CI: (44.6%, 58.4%)]. Cumulative MCyR rate in imatinib-intolerant subjects was 44.3% [39/88; 95% CI: (33.9%, 54.7%)].

3.2.6.7 Duration of MCyR

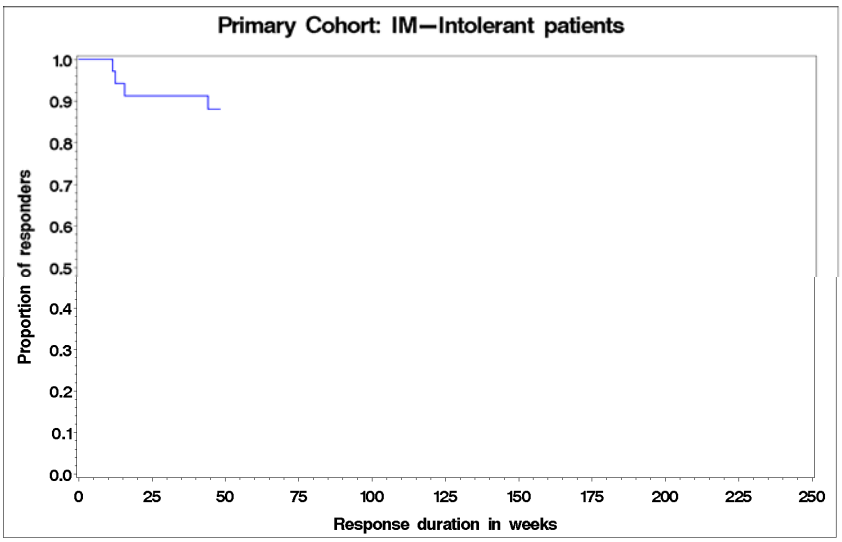
MCyR duration in imatinib-resistant subjects was a secondary endpoint. Out of the 200 enrolled imatinib-resistant subjects, 103 had achieved MCyR. Thirty (29%) responders lost MCyR by the data cut-off date. Duration of response for 7 subjects (Patient #: 000195, 000791, 001003, 001661, 002056, 002114, and 003082) were censored at 0. Seventy-three (71%) responders maintained the response as of the last assessment prior to the database snapshot. Median response duration was not reached. Kaplan-Meier curve is shown in Figure 3.2.2 below.

Figure 3.2.2: Kaplan-Meier curve for MCyR duration in the 103 IM-resistant patients



Out of the 88 enrolled imatinib-intolerant subjects, 39 had achieved MCyR. Four (10%) responders lost MCyR by the data cut-off date. Thirty-five (88%) responders maintained the response as of the last assessment prior to the database snapshot. Median response duration was not reached. Kaplan-Meier curve is shown in Figure 3.2.3 below.

Figure 3.2.3: Kaplan-Meier curve for MCyR duration in the 39 IM-intolerant patients



3.2.6.8 Duration of MCyR: proportion of responders at Year 2

As noted earlier, 103 imatinib-resistant CP CML subjects achieved MCyR. Thirty-eight major cytogenetic imatinib-resistant CP CML responders were censored by 104.3 weeks (by 2 years) and twenty-nine responders lost response by 104.3 weeks. The remaining 36 (34.9%) imatinib-resistant responders maintained MCyR at Year 2. A 95% confidence interval was (25.7%, 44.6%).

Thirty-nine imatinib-intolerant CP CML subjects achieved MCyR. Eighteen major cytogenetic imatinib-intolerant CP CML responders were censored by 104.3 weeks (by 2 years) and four responders lost response by 104.3 weeks. The remaining 17 (43.6%) imatinib-intolerant responders maintained MCyR at Year 2. A 95% confidence interval was (28%, 59.2%).

There were 118 CP CML subjects who were previously treated with imatinib and dasatinib and/or nilotinib. They were classified as being either in "IM + D Intolerant" or in "IM + D Resistant" or in "IM + D Resistant" or in "IM + NI Intolerant". Of these 118 subjects 108 were evaluable. Thirty-five (32.4%) achieved MCyR. Median response duration was not reached. Only 6 (17.1%) of the 35 responders maintained response beyond 104.3 weeks (at Year 2). A 95% Clopper-Pearson confidence interval was (6.6%, 33.6%).

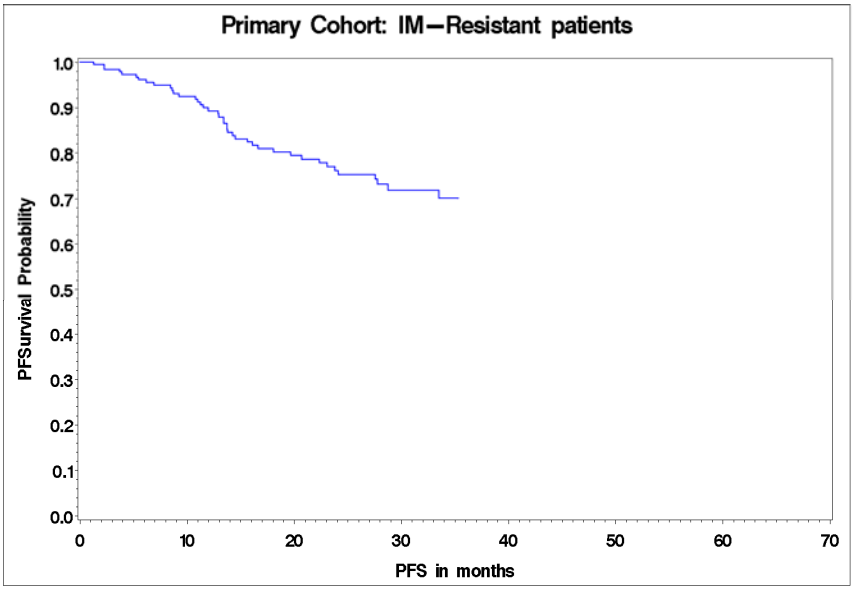
3.2.6.9 Progression-Free survival

Forty-one PFS events occurred among the 200 IM-Resistant CP CML subjects. Twenty-nine of these 200 IM-Resistant CP CML subjects died during the treatment. There was insufficient follow-up for estimating the median PFS. The Kaplan-Meier curve for PFS is shown in Figure 3.2.4 below. No inference is drawn from PFS data.

3.2.6.10 Overall survival

Twenty-nine (14.5%) subjects of the enrolled 200 imatinib-resistant subjects died with in 3 years after randomization. Five (14.5%) subjects of the enrolled 88 imatinib-intolerant subjects died with in 2.7 years after randomization. No inference is drawn from overall survival data.

Figure 3.2.4: Kaplan-Meier curve for PFS in IM-Resistant patients



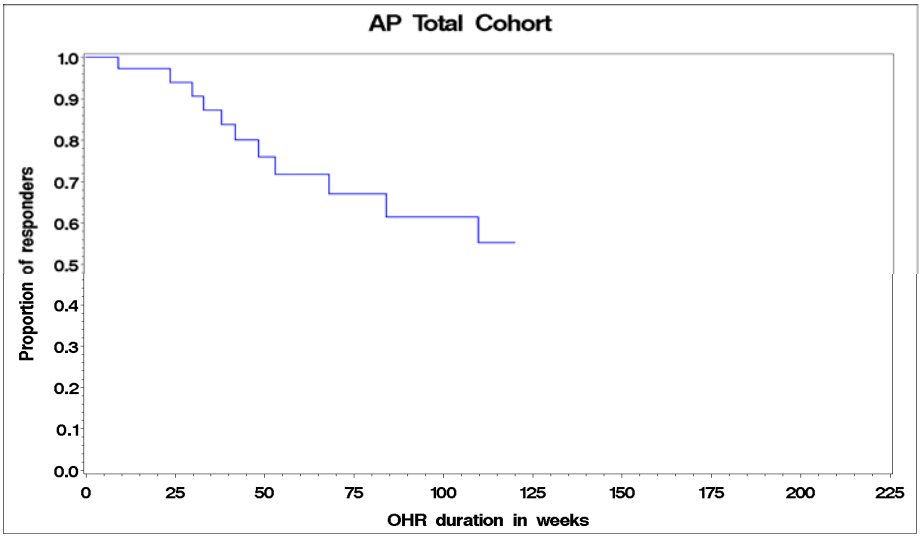
3.2.6.11 Subjects in AP Total and BP Total cohorts

As seen from Table 3.2.4, the primary efficacy endpoint of MCyR rate at Week 24 in second-line accelerated phase (AP) CML subjects was 24.6% [95% CI: (14.5%, 34.8%)]. The primary efficacy endpoint of MCyR rate at Week 24 in second-line blast phase (BP) CML subjects was 11.1% [95% CI: (2.7%, 19.5%)].

Overall hematologic response (OHR) was the key secondary endpoint for both AP CML and BP CML subjects. There were 76 AP Total subjects who were treated with at least imatinib. Among these 76 AP subjects, 38 (50%) subjects achieved OHR by Week 48 (95% CI: 38.8%, 61.2%).

Eleven (29%) responders in the AP Total cohort lost OHR as of the last assessment prior to the database snapshot. OHR duration was censored for the remaining 27 (71%) subjects. There was insufficient follow-up for estimating the median OHR. Kaplan-Meier curve for OHR duration in AP Total subjects is shown in Figure 3.2.5 below.

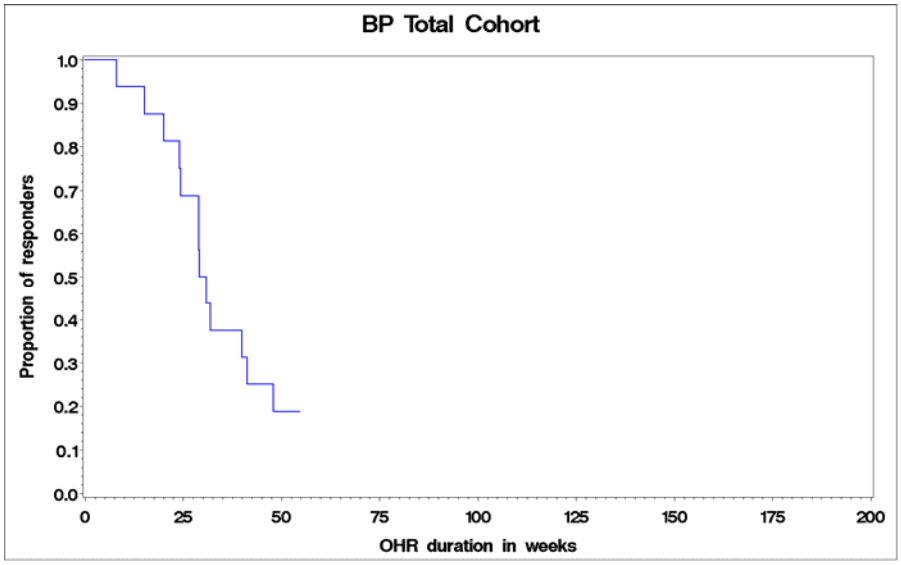
Figure 3.2.5: Kaplan-Meier curve for OHR duration in the AP Total patients



As noted earlier, 38 AP Total subjects achieved OHR. Seventeen responders were censored by 104.3 weeks (by 2 years) and ten responders lost response by 104.3 weeks. The remaining 11 (28.9%) responders in the AP Total cohort maintained OHR at Year 2. A 95% confidence interval was (14.5%, 43.4%).

There were 64 BP Total patients who were previously treated with at least imatinib. Out of the 64 BP Total subjects, 17 (26.6%) subjects achieved OHR by Week 48 (95% CI: 15.7%, 37.4%). The median duration of OHR was 31.5 weeks [95% CI: (24.3, 48)]. Kaplan-Meier curve for OHR duration in BP Total subjects is shown in Figure **3.2.6** below. Only 2 (11.8%) responders in the BP Total cohort maintained OHR at Year 2. A 95% Clopper-Pearson confidence interval was (1.5%, 36.4%).

Figure 3.2.6: Kaplan-Meier curve for OHR duration in the AP Total patients



3.3 Evaluation of Safety

See the medical officer's report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Imatinib Resistant CP CML subjects

Forty-six (41.4%) of the 111 evaluable IM Resistant males achieved MCyR at Week 24. Twenty (26.7%) of the 75 evaluable IM Resistant females achieved MCyR at Week 24.

Forty-four (36.7%) of the 120 evaluable IM Resistant Caucasian (white) subjects achieved MCyR at Week 24. Eight (25.8%) of the 31 evaluable IM Resistant Oriental (Asian) subjects achieved MCyR at Week 24. Numbers of subjects in other ethnic groups were very small. Therefore, subgroup analyses of MCyR are not performed in these ethnic groups.

Median age of the subjects in the study was 53 years. There were 105 evaluable IM Resistant subjects who were 53 years of age or younger. Forty (38.1%) of these 105 subjects achieved MCyR at Week 24. There were 81 evaluable IM Resistant subjects who were over 53 years of age. Twenty-six (32.1%) of these 81 subjects achieved MCyR at Week 24.

There were 150 evaluable IM Resistant subjects who were younger than 65 years of age. Fifty-six (37.3%) of these 150 subjects achieved MCyR at Week 24. There were only 36 evaluable IM Resistant subjects who were 65 or over 65 years of age. Ten (27.8%) of these 36 subjects achieved MCyR at Week 24.

4.1.2 Imatinib Intolerant CP CML subjects

Fourteen (41.2%) of the 34 evaluable IM Intolerant males achieved MCyR at Week 24. Ten (21.7%) of the 46 evaluable IM Intolerant females achieved MCyR at Week 24.

Seventeen (36.2%) of the 47 evaluable IM Intolerant Caucasian (white) subjects achieved MCyR at Week 24. Five (23.8%) of the 21 evaluable IM Intolerant Oriental (Asian) subjects achieved MCyR at Week 24. Numbers of subjects in other ethnic groups were very small. Therefore, subgroup analyses of MCyR are not performed in these ethnic groups.

There were 36 evaluable IM Intolerant subjects who were 53 years of age or younger. Eleven (30.6%) of these 36 subjects achieved MCyR at Week 24. There were 44 evaluable IM Intolerant subjects who were over 53 years of age. Thirteen (29.6%) of these 44 subjects achieved MCyR at Week 24.

4.2 Other Special/Subgroup Populations

No other subgroups analyses are done in this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The Sponsor's pre-specified maximum number of evaluable imatinib-resistant subjects in Study 200-WW was 167. But 186 evaluable subjects were recruited. Of the 19 imatinib-resistant subjects who were recruited last, nine achieved MCyR.

The proportions of responders who maintained MCyR at year 2 was not a pre-specified efficacy endpoint.

The Sponsor has stated: "The K-M estimates of PFS were 91.3% [95% CI: (86.8, 94.3)] and 80.6% [95% CI: (74.3, 85.4)] at Years 1 and 2, respectively; the K-M median PFS has not been reached. The K-M estimates of OS were 96.8% [95% CI: (94.0, 98.3)] and 90.6% [95% CI: (86.5, 93.5)] at Years 1 and 2, respectively; the K-M median OS has not been reached." These conclusions are based on a very small number of events and/or on insufficient follow-up for PFS and OS in Study 200-WW.

As mentioned in Section 3.2.7, the objective of Study 3000-WW was not met.

In this reviewer's opinion, the collective evidence does not support the approval of this application as a whole.

5.2 Conclusions and Recommendations

- The primary objective of MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was met. MCyR rate at Week 24 was significantly greater than 23% (p-value < 0.0001). The MCyR rate at Week 24 in imatinib-resistant second-line CP CML subjects was 35.5% (66/186 subjects; 95% CI: 28.6%, 42.4%).

- The median duration of MCyR was not reached for the second-line CP CML imatinib-resistant cohort as well as for the imatinib-intolerant cohort. Only 34.9% [95% CI: (25.7%, 44.6%)] of the responders in the imatinib-resistant cohort maintained MCyR at Year 2. Only 43.6% [95% CI: (28%, 59.2%)] of the responders in the imatinib-intolerant cohort maintained MCyR at Year 2.

- The MCyR rate at Week 24 in imatinib-intolerant second-line CP CML evaluable subjects was 30% (24/80 subjects; 95% CI: 20%, 40%). MCyR rate at Week 24 in imatinib-intolerant subjects was significantly lower than the expected rate of 56%.

- CCyR at Week 24 in imatinib-resistant second-line CP CML evaluable subjects was 26.3% [49/186; 95% CI: (20%, 32.7%)]. CCyR at Week 24 in imatinib-intolerant second-line CP CML evaluable subjects was 35% [28/80; 95% CI: (24.5%, 45.5%)].

- Cumulative MCyR rate in imatinib-resistant second-line CP CML subjects was 51.5% [103/200; 95% CI: (44.6%, 58.4%)]. Cumulative MCyR rate in imatinib-intolerant second-line CP CML subjects was 44.3% [39/88; 95% CI: (33.9%, 54.7%)].

- Overall hematologic response (OHR) rate in AP Total patients who were treated with at least imatinib was 50% [38/76; 95% CI: (38.8%, 61.2%)]. A 28.9% [95% CI: (14.5%, 43.4%)] of the responders in the AP Total cohort maintained OHR at Year 2.

- OHR rate in BP Total patients who were treated with at least imatinib was 26.6% [17/64; 95% CI: (15.7%, 37.4%)]. The median duration of OHR was 31.5 weeks [95% CI: (24.3, 48)]. Only 11.8% [95% CI: (1.5%, 36.4%)] of the responders in the BP Total cohort maintained OHR at Year 2.

- In the supportive Phase 3 Study 3000-WW, there was no significant difference in the primary endpoint 1-year CCyR rates between the bosutinib and imatinib arms.

- Except the imatinib-resistant cohort analysis in Study 3160A4-200-WW, all other cohorts' analyses were either exploratory or indicated inefficacy or were based on small samples. Efficacy results from cohorts other than imatinib-resistant cohort should not be used to support labeling claims.

APPENDICES

Tables Defining Disease Phase and Responses to Treatment

A. Initial diagnoses

	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 evaluation take preference over chronic and accelerated criteria	
Accelerated Phase	15-29% Blasts ≥30% Blasts + promyelocytes ≥20% Basophils Platelets < 100×10^9/L (not related to therapy)	15-29% Blasts ≥30% Blasts + promyelocytes ≥20% Basophils
Chronic Phase	<15% Blasts	<15% Blasts

	<20% basophils <30% Blasts + promyelocytes Platelets ≥ 100×10^9/L	<30% Blasts + promyelocytes No extramedullary (except Liver/ Spleen)

Definition of Cytogenetic Response

A cytogenetic response was based on the prevalence of Ph+ cells in metaphase from a bone marrow (BM) sample. Twenty-five (25) metaphases, but at least 20 metaphases, from BM sample were considered ideal for evaluation. Evaluation of the cytogenetic response using only peripheral blood fluorescence-in situ hybridization (FISH) was not acceptable. The criteria for evaluation of cytogenetic response were as follows:

- CCyR: 0% Ph+ cells in metaphase
- Partial Cytogenetic Response (PCyR): 1% to 35% Ph+ cells in metaphase
- Minor Cytogenetic Response: 36% to 65% Ph+ cells in metaphase
- Minimal Cytogenetic response: 66% to 95% Ph+ cells in metaphase
- No Cytogenetic response: 96% to 100% Ph+ cells in metaphase

Best on-study cytogenetic response was assessed based on the percentage of metaphases in the BM that were positive for the Philadelphia chromosome. MCyR was defined as CCyR plus PCyR. A confirmed complete cytogenetic response was defined as a response noted on 2 consecutive occasions (at least 28 days part). If a subject achieved his or her first CCyR within 12 months and the second assessment confirming the CCyR occurred beyond 12 months, this was still counted toward the primary endpoint.

Definition of Hematologic Response

- A CHR was obtained when all the following criteria were met in peripheral blood:
- WBC ≤ 10,000/mm^3
- Platelets < 450,000/ mm^3
- Peripheral blood basophils < 5%
- No blasts or promyelocytes in peripheral blood
- < 5% myelocytes plus metamyelocytes in peripheral blood
- No extramedullary involvement (including no hepatomegaly or splenomegaly)

A confirmed CHR was obtained if all the above criteria were consistently maintained for subsequent assessments for at least 28 days after they were first met.

Definition of Molecular Response

Molecular response was assessed using BCR-ABL transcript levels measurement by quantitative real-time polymerase chain reaction (QRT-PCR). A MMR was defined according to the

recommendations of Hughes et al. The standardized baseline, as established in the IRIS trial, was taken to represent 100% on the International Scale (IS), and a 3-log reduction in BCR-ABL transcripts from the standardized baseline (MMR) was fixed at 0.1%. In this study, a ratio of BCR-ABL/ABL $\leq$ 0.1% on the international scale (IS) was considered a MMR (i.e., at least a 3-log reduction from a standardized baseline value).

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer:

_____
Dr. Kallappa M. Koti
Mathematical Statistician

Date:

Statistical Team Leader: Dr. Mark Rothmann

Biometrics Division Director: Dr. Rajeshwari Sridhara

cc:
HFD-150/Ms. Diane Hanner
HFD-150/Dr. Karen McGinn
HFD-150/Dr. Virginia Kwitkowski
HFD-150/Dr. Ann Farrell
HFD-711/Dr. Mark Rothmann
HFD-711/Dr. Rajeshwari Sridhara
HFD-700/Ms. Lillian Patricia

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/s/

KALLAPPA M KOTI
07/20/2012

MARK D ROTHMANN
07/23/2012
See my review

RAJESHWARI SRIDHARA
07/24/2012
TL memo reflects the conclusion and recommendations

STATISTICS FILING CHECKLIST FOR NDA 203341:
CML in adult patients

NDA Number: 203341 **Applicant:** Wyeth Pharma., Inc. **Stamp Date:** NOV-17-2011

Drug Name: Bosutinib **NDA Type:** Original

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? **YES**

If the NDA/BLA is not file-able from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

STATISTICS FILING CHECKLIST FOR NDA 203341:
CML in adult patients

Reviewing Statistician	12-21-2011 Date
Supervisor/Team Leader	12-21-2011 Date

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/s/

KALLAPPA M KOTI
12/20/2011

MARK D ROTHMANN
12/21/2011