CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986 & 22-072

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 Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	22-072 / N000
Drug Name:	Dasatinib (BMS-354825)
Indications:	Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.
Applicant:	Bristol-Myers Squibb Company
Date(s):	Submission Date: December 28, 2005 PDUFA Date: June 28, 2006
Review Priority:	Priority.
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Team Leader: Raji Sridhara, Ph.D. Division Director: Aloka Chakravarty, Ph.D.
Medical Division:	Division of Oncology Drug Product (HFD-150)
Clinical Team:	Reviewers: Edvardas Kaminskas, M.D. Vicki Goodman, M.D. Michael Brave, M.D. Team Leader: Ann Farrell, M.D.
Project Manager:	Amy Baird

Keywords: Superiority, log-rank test.

Please refer to complete statistical review of NDA21986 for the statistical review of NDA22072.

NDA 21-986 was submitted for two indications: 1) Adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. 2) Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

For administrative purpose, NDA 21986 is split into two NDAs: NDA21986 is for the indication of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. NDA22072 is for the indication of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy. Please refer to complete statistical review of NDA21986 for the statistical review of NDA22072.

Table of Contents

Table of tables

Table of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted this application to seek an accelerated approval for dasatinib. This application includes 5 pivotal phase II studies and 1 supportive phase I study. The effectiveness of dasatinib is based on the rates of hematologic and cytogenetic responses. No statistical comparison was conducted in these 5 pivotal studies and therefore no statistical inference will be drawn from those studies. The sponsor claimed that dasatinib was effective in subjects with all phases of CML and Ph+ ALL, resulting in durable hematologic and cytogenetic responses. Per sponsor, hematologic and cytogenetic responses were achieved in both imatinib resistant and imatinib-intolerant subjects in these 5 studies. After median treatment duration 2.8 months to 5.6 months, the subjects in these 5 studies who achieved a major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) range from 30% to 58%, 31% to 59 % and 36% to 80%, respectively. Moreover, by the time of data cutoff for this NDA submission, the duration of MCyR ranged from 0 to 4.7 months for chronic CML patients, and the durations of MaHR ranged from 0.5 to 9.5 months and from 1.2 to 7.8 months for accelerated phase CML patients and myeloid blast phase CML patients, respectively. Whether its effectiveness is adequate for accelerate approval and the proposed disease indications will be determined by clinical judgment. This application was presented at the Oncology Drugs Advisory Committee (ODAC) on June 02, 2006 at Atlanta, Georgia. The committee unamously voted in favor of warranting accelerated approval in CML patients resistant or intolerant to imatinib in Chronic, Accelerated, Myeloid blast, or Lymphoid blast phases (only one member abstained for patients intolerant to imatinib). The majority of the committee members voted in favor of warranting regular approval in Philadelphia-positive ALL patients resistant or intolerant to imatinib. See more details about the ODAC discussion in Section 5.2.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, efficacy and safety data were collected from 5 pivotal studies (Phase II multicenter studies) and one supportive Phase I dose escalation trial. These six studies were conducted to determine the efficacy and safety of dasatinib in patients with chronic, accelerated and blast chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of treatment with imatinib. Subjects in 5 Phase 2 studies were treated with dasatinib at 70 mg twice daily (BID), once in the morning and once in the evening. Among all 5 phase II studies, one was randomized phase II study and other 4 were single arm phase II studies. Study CA180017 was a randomized, non-comparative study of dasatinib (70 mg BID) and high-dose imatinib (400 mg BID) in chronic CML subjects who were resistant to imatinib. While only 36 subjects were randomized in study CA180017 prior to the randomization cut-off date (30-Jun-2005) for this application, this study was designed to provide important data on the efficacy of dasatinib and of escalated-dose imatinib after failure to respond to the approved doses of imatinib. The single-arm study CA180013 enrolled subjects

who were resistant to or intolerant of imatinib at any dose. The other 3 single-arm studies (CA180005, CA180006, and CA180015) were performed to evaluate the activity and safety of dasatinib in advanced stage CML and Ph+ ALL. The dasatinib studies enrolled subjects with all phases of Ph+ leukemia. Most subjects had a long history of leukemia and were heavily pretreated. These 5 pivotal studies were conducted at multicenter worldwide ranging from 18 to 41 centers. Per sponsor, these 5 pivotal studies are still ongoing.

The data cut-off date for this submission was May 12, 2005 for study CA180005, CA180006 and CA180013. May 23, 2005 and June 30, 2005 were the data-cut off dates. By the data cut-off dates for this application, a total of 481 patients were enrolled and treated in these 5 studies. Of those 481 patients, 107 subjects had accelerated phase chronic myeloid leukemia (CML) resistant to or imatinib mesylate in study CA180005, 74 subjects had myeloid blast phase chronic myeloid leukemia resistant to or intolerant of imatinib mesylate in study CA180006, 186 subjects had chronic phase Philadelphia chromosome positive chronic myeloid leukemia who have disease that is resistant to high dose imatinib mesylate (Gleevec®) or who are intolerant of imatinib in study CA180013, 78 subjects had lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate in study CA180015.

The primary endpoints in these studies were major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR).

In this review, this statistical reviewer will only focus on the efficacy results of the 5 pivotal studies.

1.3 STATISTICAL ISSUES AND FINDINGS

In this NDA, 4 single arm phase 2 studies and 1 randomized non-comparative phase 2 study were conducted to establish efficacy of dasatinib in patients with chronic, accelerated and blast chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of treatment with imatinib. The primary efficacy endpoints were major cytogenetic response (MCyR) in study CA180013 and CA180017. Major hematologic response (MaHR) rate and overall hematologic response (OHR) were co-primary endpoints in study CA180005, CA180006 and CA180015.

Statistical Issues:

No statistical comparison was conducted in 5 pivotal studies including one randomized pivotal study. Per sponsor, these 5 studies still are ongoing.

There is no substantial statistical issue in this NDA except the following:

- From the results of study CA180017, the point estimate of the difference of treatment effect between dasatinib and imatinib is 24.0% with 95% confidence interval (CI) for the difference of treatment effect between dasatinib and imatinib is (-9.9%, 51.2%). This CI does not exclude 0. It means that it does not exclude the possibility of dasatinib having the same treatment effect as the imatinib or even worse than imatinib. However, it is pre-

mature to have any conclusion based on the results obtained from data with limited number of subjects (36 subjects).

Findings

- Following Table A and Table B show that 31% to 90% of subjects across all phases of CML or Ph+ ALL achieved a hematologic response (CHR for chronic CML and MaHR for advanced CML or Ph+ ALL). In particular, CHR for chronic CML reached 90% with 95% CI [85, 94], and 31% to 59% of subjects across all phases of CML or Ph+ ALL achieved a major cytogenetic response.

Table A: Sponsor's Efficacy Results in Phase 2, Single-arm Studies

(All treated Population)

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph+ ALL (N = 36)
Hematologic Response Rate (%)[a]					
OHR (95% CI)	NAc	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	90	33	24	26	31
NEL	NA	26	8	5	11
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)[b]					
MCyR (95% CI)	45 (37 - 52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	33	21	27	43	58

[a] *≥ 6-month follow-up. Hematologic response criteria (all confirmed responses were maintained at least 4 weeks)*
[b] *≥ 6-month follow-up. Cytogenetic response criteria:* ***CCyR*** *(0% Ph+ metaphases) or PCyR (> 0 % -35%).*
MCyR *= CCyR + PCyR.*
The results in Shaded boxes are the results of primary endpoints

Table B: Hematologic and Cytogentic Response Results in All treated Population from 4 Single-arm Phase 2 Studies (FDA's Analysis)

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph+ ALL (N = 36)
Hematologic Response Rate (%)[a]					
OHR (95% CI)	NA	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	90 (85-94)	33 (24-42)	24 (15-36)	26 (15-36)	31 (16-48)
NEL	NA	26 (18-36)	8 (3-17)	5 (0.6-16)	11 (3.1-26)
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)[b]					
MCyR (95% CI)	45 (37-52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	33(26-40)	21 (14-30)	27 (17-39)	43 (28-59)	58 (41-74)

[a] *≥ 6-month follow-up. Hematologic response criteria (all confirmed responses were maintained at least 4 weeks)*
[b] *≥ 6-month follow-up. Cytogenetic response criteria:* ***CCyR*** *(0% Ph+ metaphases) or PCyR (> 0 % -35%).*
MCyR *= CCyR + PCyR.*
The results in Shaded boxes are the results of primary endpoints

- The sponsor claimed that dasatinib was effective resulting in durable hematologic and cytogenetic responses. Except for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate, 98% to 100% of patients with other phases of CML who had MaHR and MCyR were still in responses by the date of data-cutoff, hence the duration of responses could not be estimated. The following Table C shows the sponsor's results of duration of responses.

Table C: Sponsor's Results of Durations of Hematologic and Cytogenetic Response in All treated Population from 4 Single-arm Phase 2 Studies

Study	Range of Duration of Response (Months)	Intolerant	Resistant	Total
	MaHR	3.1- 8.5	0.5 - 9.5	0.5 - 9.5
CA180005	**OHR**	1.4 - 8.5	0.9 - 9.5	0.9 - 9.5
CA180006	**MaHR**	5.7-5.7	1.2 - 7.8	1.2 - 7.8
	CHR	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
CA180013	**MCyR**	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7

- In study CA180017, Results at the 12-week assessment from the first 36 randomized patients are included in this submission. As shown in the Table D, the results of these 36 subjects (22 in the dasatinib arm and 14 in the imatinib arm) show that a CHR was achieved in >90% of patients in both arms, a MCyR occurred in 45% of patients receiving dasatinib and 21% of patients receiving imatinib, a complete cytogenetic response (CCyR) occurred in 32% of patients receiving dasatinib and 7% of patients receiving imatinib. Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. However, it is too early to draw any inference conclusion based on the limited number of patients.

- Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients in study CA180017. The Following Table D and Table E show the sponsor's and FDA's results. The sponsor's results show the results for the subjects in both treatment groups regardless of the subject's crossover status while FDA's results show the results of pre-crossover and post-crossover between the two treatment groups. Please see section 3.1.6.4.1 for more detail of criteria of crossover.

Table D: Sponsor's Results of Efficacy in Subjects with Chronic CML Resistant to Imatinib (Study CA180017)

	Dasatinib N=22	**Imatinib** N=14
Median duration of treatment (months)	3.7	2.7
MCyR,[a] n (%)	10 (45)	3 (21)
CCyR,[a] n(%)	7 (32)	1 (7)
CHR,[b] n(%)	21 (95)	13 (93)

[a] ***CCyR*** *(0% Ph+ metaphases) or partial cytogenetic response (PCyR) (> 0 % - 35%).* ***MCyR*** *= CCyR + PCyR.* [b] ***CHR:*** *complete hematologic response*
[Source: sponsor's Clinic-overview TABLE 4.3.1*]*

Table E: Efficacy of Dasatinib and Imatinib in Subjects with Chronic CML Resistant to Imatinib in Study CA180017 (FDA's Analysis)

	Dasatinib N=22		**Imatinib N=14**	
	Dasatinib N=20	**Dasatinib /Imtinib** N=2	**Imatinib** N=3	**Imatinib /Dasatinib** N=11
MCyR,[a] n (%)	10 (50)	0	2 (66)	1
CCyR,[a] n(%)	7 (35)	0	1 (33)	1
CHR,[b] n(%)	20 (100)	1	3 (100)	10

[a] ***CCyR*** *(0% Ph+ metaphases) or partial cytogenetic response (PCyR) (> 0 % - 35%).* ***MCyR*** *= CCyR + PCyR.* [b] ***CHR:*** *complete hematologic response*

- This statistical reviewer performed an analysis on duration of major hematologic response based on the data adjudicated by the clinical reviewer for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Table E shows the results of the sponsor and FDA analyses of duration of MaHR in study CA180015. There are two more patients who progressed in lymphoid blast groups according to the data adjudicated by the clinical reviewer. In a single arm study, the results of any time to event endpoints such as duration of MaHR can be only considered as descriptive.

Table F: Summary of the Results on Duration of MaHR in Study CA180015

Sponsor's Results		
	Lymphoid Blast CML (n=42)	**PH+ all (n=36)**
# Patient who reached MaHR	13	15
# Patients progressed	6	3
Median duration time (95% CI)	3.71 (2.79, *)	*
FDA Results		
#Patient who reached MaHR	13	15
# Patients progressed	6	5
Median duration time (95% CI)	3.71 (2.79, *)	4.83 (2.89, *)

*: *Values could not be reached or estimated.*

- This reviewer performed several subgroup exploratory analyses on the primary endpoints MCyR, MaHR and OHR. Table F summarizes the results of these subgroup analyses, in the subgroups of patients who were less than 65 years old, all male, all female, and Caucasian. These results of subgroups are similar to the respective overall population.

Table G: Hematologic Response and Cytogenetic Response in Subgroups

(FDA's Analysis)

	CA180013 Chronic (N=186)	**CA180005 Accelerated (N = 107)**	**CA180006 Myeloid Blast (N = 74)**	**CA180015 Lymphoid Blast (N = 42)**	**CA180015 Ph+ ALL (N = 36)**
Patients whose age<65 years					
# Patients	126	80	57	36	30
OHR(n[%])	NA	65 (81)	29 (51)	14 (39)	14 (47)
MaHR (n[%])	NA	46 (58)	16 (28)	12 (33)	13 (43)
MCyR (n[%])	57 (45)	23 (29)	17 (30)	20 (56)	19 (63)

Patients whose age>=65 years					
# Patients	60	27	17	6	6
OHR(n[%])	NA	21 (77)	10	1(17)	3(50)
MaHR (n[%])	NA	17 (63)	8	1(17)	2(33)
MCyR (n[%])	26 (43)	10 (37)	5(29)	1(17)	2(33)
Male Patients					
# Patients	86	55	41	22	23
OHR(n[%])	NA	43 (78)	26 (63)	10 (45)	11 (48)
MaHR (n[%])	NA	27(49)	15(37)	9 (41)	9 (39)
MCyR (n[%])	39 (45)	17 (31)	16 (39)	14(64)	14(61)
Female Patients					
# Patients	100	52	33	20	13
OHR(n[%])	NA	42 (81)	13 (39)	5(25)	6 (5)
MaHR (n[%])	NA	36 (69)	9(27)	4 (20)	6 (5)
MCyR (n[%])	44 (44)	16 (31)	6 (18)	7 (35)	7 (54)
Caucasian Patients					
# Patients	173	92	56	40	35
OHR(n[%])	NA	43 (78)	33 (59)	14 (35)	16 (46)
MaHR (n[%])	NA	27(49)	22(39)	13 (33)	14 (40)
MCyR (n[%])	77 (45)	29 (31)	16 (39)	20 (50)	20 (57)

2 INTRODUCTION

2.1 OVERVIEW

Dasatinib (BMS-354825) is a potent oral inhibitor of multiple oncogenic kinases. It is currently under development for treatment in subjects with all phases of chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), and solid tumors. In

this application, safety and efficacy data are provided to support the indications for CML and Ph+ ALL in patients who are resistant or intolerant to treatment with imatinib mesylate (imatinib, Gleevec®). The sponsor claimed the effectiveness of dasatinib based on the rates and durability of hematologic response and cytogenetic response.

In this NDA submission, interim efficacy data, with a minimum of 6-months of follow-up, were provided by the sponsor for each of 5 pivotal studies. Per sponsor, all Phase 2 studies are ongoing; the patients would be treated and followed in these studies for up to 24 months to confirm the efficacy reported in this application. The sponsor submitted this NDA to seek an accelerated approval on the indications: *"1) Treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy including imatinib; 2) Treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy."* dasatinib tablets are available for oral administration in strengths of 20 mg, 50 mg, and 70 mg of dasatinib. With conventional treatment, CML is a fatal disease with a median survival of 4 years for patients with chronic CML and ≤6 months for patients in blast phase. Stem cell transplant, available to a limited subset of patients with CML (e.g. young, newly diagnosed patients with chronic CML), is the only curative therapy.

Among 5 phase II pivotal studies for this NDA submission, 4 of them (CA180005, CA180006, CA180013, and CA180015) were single-arm studies. Only CA180017 was randomized, open-label study. Since CA180017 was the last study to start and close enrollment, interim efficacy data were provided with only 36 chronic patients who were randomized in CA180017 prior to the randomization cutoff for this application.

In the randomized study CA180017, patients who were resistant to imatinib ≤600 mg per day were randomized in a 2:1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID. Crossover to the alternate therapy was permitted in the event of disease progression or intolerable toxicity. No imatinib-intolerant patients were enrolled. Results at the 12-week assessment from the first 36 randomized patients are included in this submission.

By the time of data cutoff for the analyses, there were 186 chronic, 107 accelerated, 74 Myeloid blast patients, 78 lymphoid Blast CML and Ph+ All patients. Major cytogenetic response (MCyR) was the primary endpoint for both study CA180017 and study CA180013, and major hematologic response (MaHR) and overall hematologic response (OHR) were the primary endpoints for study CA180005, study CA180006 and study CA180015. Complete hematologic response (CHR) is one of secondary endpoints for all 5 pivotal studies.

The Sponsor submitted the protocol for studying dasatinib under IND No. 66,971, which was originally submitted on March 4, 2003.

2.2 DATA SOURCES

Data used for this review were from the electronic submission received in December 2005. The network path was "\\Cdsesub1\n021986\N000\2005-12-28" in the EDR.

3 STATISTICAL EVALUATION

This review focuses on major efficacy results of 4 single arm phase II studies CA180005, CA180006, CA180013, and CA180015 and the randomized phase II study CA180017. Section 3.1 includes efficacy evaluation for these 5 pivotal studies.

3.1 EVALUATION OF EFFICACY

This section provides the brief description of Study CA180017, CA180013, CA180005, CA180006 and CA180015 based on the sponsor's study reports. Any difference between the sponsor's study reports and the protocols are also discussed in this section.

3.1.1 STUDY OBJECTIVES

The primary objective of study CA180017 was to estimate the major cytogenetic response (MCyR) rates of BMS-354825 and imatinib at 800 mg daily at 12 weeks in subjects with chronic phase Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) who had disease that was resistant to imatinib.

The secondary objectives of the study CA180017 were as follows:

- To estimate the MCyR at any time (prior to crossover) in both treatment arms
- To assess the durability of major cytogenetic response and time to MCyR prior to cross over in both treatment arms
- To estimate complete hematologic response (CHR) rate prior to crossover in both treatment arms
- To assess the durability of CHR and time to CHR prior to crossover in both treatment arms
- To estimate major molecular response rates by measuring BCR-ABL transcripts in blood during treatment using quantitative RT-PCR prior to crossover
- To estimate post-crossover efficacy endpoints in subjects who cross over
- To assess the health-related quality of life in both treatment arms prior to crossover using the FACT-G
- To assess further the safety and tolerability of BMS-354825
- To collect blood samples for pharmacokinetic analysis of BMS-354825 given BID that will contribute to population pharmacokinetic modeling.

The primary objectives of the 4 single arm studies are as shown in following Table 1.

Table 1: Summary of the Primary Objectives in the 4 Single Arm Studies

Study	Primary Objective	#Patients Enrolled and Treated
CA180005	To estimate the major and overall hematologic response rates to dasatinib in accelerated phase chronic myeloid leukemia (CML) subjects with primary or acquired resistance to imatinib mesylate.	107
CA180006	To estimate the major and overall hematologic response rates to BMS-354825 in myeloid blast phase CML subjects with primary or acquired resistance to imatinib mesylate.	74
CA180013	To estimate the major cytogenetic response (MCyR) rate to dasatinib in subjects with chronic phase chronic myeloid leukemia (CML) who had disease that was resistant to imatinib.	186
CA180015	To estimate the major hematologic response (MaHR) rate and overall hematologic response (OHR) rate to dasatinib in lymphoid blast phase CML subjects and Ph+ ALL subjects with primary or acquired resistance to imatinib.	78

3.1.2 STUDY DESIGN

The study CA180017 was designed as an open-label, randomized, non-comparative Phase 2 study of dasatinib and imatinib in subjects with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. By the data cutoff date, 36 eligible subjects were randomized in a 2:1 ratio to receive either dasatinib 70 mg BID or imatinib 800 mg/day (400 mg BID) with continuous daily treatment. These 36 subjects had at least 12 weeks of follow-up data. Randomization was stratified by site and cytogenetic response on prior imatinib therapy (any response, i.e. complete, partial, minor, and minimal, versus no cytogenetic response). Dasatinib dose modifications were allowed in case of disease progression or lack of response, or to manage drug toxicity. No dose escalation was allowed for imatinib. Dosing of imatinib was at 400 mg PO BID, with continuous daily dosing. Subjects was treated until confirmed progression or intolerable toxicity, at which time subjects would cross over to the BMS-354825 treatment arm after a one-week washout of imatinib. If at 12 weeks the subject did not achieve MCyR or $\geq$ 30% absolute reduction in Ph+ metaphases, then the subject would be crossed over to the BMS-354825 arm of the study after a one-week washout of imatinib. No dose escalation was allowed; one dose reduction to 600 mg/d was allowed if the subject had not previously been treated at that dose level. Subjects randomized to imatinib would crossover if one of the following criteria was met: 1) The subject was intolerant of 800 mg imatinib (or 600 mg if subject is dose reduced), 2) The subject developed progression (confirmed if necessary), or 3) The subject did not achieve a MCyR or 30% absolute reduction in Ph+ metaphases by 12 weeks on therapy. Cytogenetic assessment was to be performed every 12 weeks and at the time of crossover. Hematologic assessment was to be performed weekly up to 12 weeks and every 2 weeks thereafter.

Following table summarizes the 4 single arm pivotal studies.

Table 2: Summary of 4 Open Label Single Arm Phase II Studies

Study	Treatment	Population
CA180005	Dasatinib 70 mg BID, dose escalation to 100 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
CA180006	Dasatinib 70 mg BID, dose escalation to 100 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
CA180013	Dasatinib 70 mg BID, dose escalation to 90 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib Mesylate (Gleevec®) or who are Intolerant of Imatinib
CA180015	Dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed as specified in the protocol for the management of disease progression or toxicity.	Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

Please refer to FDA clinical reviews provided by Drs. Edvardas Kaminskas, Vicky Goodman and Michael Brave for more detail of inclusion and exclusion criterion for the study populations in the 5 pivotal studies.

3.1.3 EFFICACY ENDPOINTS

3.1.3.1 Primary Efficacy Endpoint

The primary endpoint in study CA180017 was major cytogenetic response (MCyR) at 12 weeks. MCyR rate at 12 weeks is defined as the proportion of all randomized subjects at 12 weeks with best response of complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). Subjects that cross over prior to week 12 were classified as non-responders. MCyR rate was calculated for each arm as randomized.

The primary endpoints in other 4 single arm pivotal studies are displayed in following table.

Table 3: Summary of 4 Open Label Single Arm Phase II Studies

Study	Primary Endpoint
CA180005	major hematologic response (MaHR) and overall hematologic response (OHR)
CA180006	major hematologic response (MaHR) and overall hematologic response (OHR)
CA180013	major hematologic response (MaHR)
CA180015	major hematologic response (MaHR) and overall hematologic response (OHR)

As displayed in Table 3, major hematologic response (MaHR) and overall hematologic response (OHR) in the imatinib resistant group are the co-primary endpoints in study CA180005, CA180006 and CA180015. MaHR rate is defined as the proportion of all treated subjects with best response of complete hematologic response (CHR) or no evidence of leukemia (NEL). Overall hematologic response (OHR) rate is defined as the proportion of treated subjects with best response of major or minor hematologic response. The hematologic responses were evaluated with regular blood draws and the cytogenetic responses were evaluated with regular bone marrow biopsies.

In study CA180013, Cytogenetic responses are based on the prevalence of Ph+ metaphases among at least 20 metaphase cells in each bone marrow sample. The criteria for cytogenetic responses are as follows:

- **Complete Cytogenetic Response (CCyR):** 0% Ph-chromosome-positive cells in metaphase in bone marrow
- **Partial Cytogenetic Response (PCyR):** 1 to 35% Ph-chromosome-positive cells in metaphase in bone marrow
- **Minor Cytogenetic Response:** 36 to 65% Ph-chromosome-positive cells in metaphase in bone marrow
- **Minimal Cytogenetic Response:** 66 to 95% Ph-chromosome-positive cells in metaphase in bone marrow
- **No Cytogenetic Response:** 96 to 100% Ph-chromosome-positive cells in metaphase in bone marrow

3.1.3.2 Secondary Efficacy Endpoints

In the study CA180017, the secondary efficacy endpoints included MCyR rate at any time prior to cross over, CHR rates, duration of MCyR and CHR, time to MCyR and CHR prior to crossover for both arms. Duration of overall hematologic response, duration of major hematological response, time to overall hematologic response, time to major hematologic response, major cytogenetic response rate, major molecular response rates, and quality of life measures were secondary endpoints in other 4 pivotal single arm studies CA18005, CA18006, CA180013 and CA180015. Per protocol, the duration of overall hematologic response would be computed only for subjects whose best response was a major or minor hematologic response. Also, the duration of major hematologic response would also be computed for subjects whose

best response was a major hematologic response. Subjects who neither progress nor die were censored on the date of their last hematologic assessment.

Per sponsor, minor hematologic response rate in the imatinib resistant group would be computed. Response rates for imatinib intolerant subjects would also be estimated. Per protocol, definitions of MCyR rate, duration of major cytogenetic response, duration of major hematologic response, duration of overall hematologic response and time to cytogenetic response were as follows.

Major cytogenetic response (MCyR) rate, defined as the proportion of all treated subjects with best response of complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).

Duration of major cytogenetic response, measured from the time measurement criteria are first met for CCyR or PCyR (whichever status is recorded first) until the date of progression (Section 3.3.6) or death. Subjects who neither progress nor die will be censored on the date of their last cytogenetic assessment. The duration of major cytogenetic response will be computed for subjects whose best response is either CCyR or PCyR.

Duration of major hematologic response, measured from the first day major hematologic response criteria are met, provided they are confirmed 28 days later, until the date of progression or death. It will be computed for subjects whose best response is major hematologic response.

Duration of overall hematologic response, measured from the first day hematologic response criteria are met, provided they are confirmed 28 days later, until the date of progression or death. It will be computed only for subjects whose best response is a major or minor hematologic response. (CA180005, ca180006)

Time to major cytogenetic response, is defined as the time from first dose of BMS-354825 until measurement criteria are first met for CCyR or PCyR (whichever status is recorded first). Time to major cytogenetic response is computed only for subjects whose best response is either CCyR or PCyR.

Complete hematologic response (CHR) rate, defined as the proportion of all treated subjects who achieve a confirmed complete hematologic response (CHR). All hematologic responses as defined below must be maintained for at least 4 weeks after they are first documented. All hematologic responses can begin only 14 days after dosing start date.

In Study CA180013, a subject with chronic phase CML would be determined to have a CHR if he/she met all of the following criteria:

1) WBC ≤ Institutional upper limit of normal
2) Platelets < 450,000/mm^3
3) No blasts or promyelocytes in peripheral blood
4) < 5% Myelocytes plus metamyelocytes in peripheral blood
5) Peripheral blood basophils δ Institutional upper limits of normal
6) No extramedullary involvement (including no hepatomegaly or splenomegaly)

Please refer to the FDA clinical reviews for more detail of the definitions of hematologic and cytogenetic responses.

Reviewer Comments:

[1] The sponsor provided some results of progression-free survival. However, the sponsor did not pre-specify (PFS) as the primary endpoint or secondary endpoint in any protocol. Furthermore, PFS is not interpretable in single arm studies. The descriptive results of PFS can be only used as supportive interpretation.

3.1.4 SAMPLE SIZE CONSIDERATIONS

Per protocol, no comparison between the two treatment arms would be made in Study CA180017. A minimum of 150 subjects would be required to complete this study. A total of 150 subjects would be assigned to the dasatinib arm and the imatinib arm in a 2-to-1 ratio. With a minimum of 100 randomized subjects to the dasatinib arm, the maximum width of the exact 95% confidence interval (CI) will be 20%. With a minimum accrual of 50 randomized subjects to that arm, the maximum width of the exact 95% confidence interval (CI) will be 29%.

For the single-arm study CA180005 and CA180006, with 60 imatinib-resistant patients, the maximum width of the exact two-sided 95% confidence interval will be 25% when the hematologic response rate is in the expected 5% to 30% range.

A minimum of 30 treated subjects in each group (30 lymphoid blast CML and 30 Ph+ ALL) in study CA180015 will provide 35% as the maximum width of the exact two-sided 95% confidence interval when the hematologic response rate is in the expected 5% to 30% range.

For single arm study CA180005, a minimum of sixty subjects with imatinib-resistant disease will be required to complete this study. Accrual may continue beyond this number in order to further characterize efficacy and safety.

Reviewer's Comments:

[1] By the time of this NDA submission, all 5 pivotal studies were ongoing. In this submission, there were 107, 74, 186, 78 and 36 patients enrolled and treated in study CA180005, CA180006, CA1800013, CA180015 and CA180017, respectively.

3.1.5 ANALYSIS METHODS

Per sponsor, efficacy responses in all 5 studies were programmatically determined from hematologic laboratory values, bone marrow biopsy values, bone marrow cytology and cytogenetics and the presence or absence of extramedullary disease. Response rates and 95% confidence intervals (CIs) were estimated. A two-sided Clopper-Pearson 95% exact confidence interval was also calculated for the CHR and major molecular response rates. Kaplan-Meier estimates and 95% CIs were provided for the time to and duration of response (MaHR and OHR). A two-sided 95% confidence interval for median duration of hematologic response was computed using the method of Brookmeyer and Crowley. All analyses were presented for all treated subjects.

3.1.6 SPONSOR'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the sponsor's major results for the 5 pivotal studies and provides the statistical reviewer's comments and some findings.

3.1.6.1 Data Sets

Per sponsor, the 5 pivotal studies were still ongoing by the time this application was submitted. Data collected from any subject who received at least a single dose of dasatinib, with a minimum of 6-months of follow-up, were included in this NDA submission. For study CA180017, the efficacy results were based on the data obtained on the first 36 subjects (22 dasatinib, 14 imatinib) who were randomized by 30-Jun-2005. All 36 subjects were treated and had at least 3 months of follow-up data by 25-Oct-2005, the data cutoff date for this interim report. By the data cut-off dates for this NDA submission, there were 107, 74, 186, and 78 patients in the 4 single arm pivotal studies CA18005, CA180006, CA180013 and CA180015 respectively.

3.1.6.2 Disposition of Patients

Study CA180017 accrual closed on 21-Sep-2005 with 166 subjects enrolled. The first 36 subjects randomized by 30-Jun-2005 (22 to dasatinib, 14 to imatinib) received treatment, had at least 12 weeks of follow-up data, and were included in the analysis submitted for this NDA. As of 25-Oct-2005 (the data cutoff date for the interim analysis), 20 (91%) dasatinib and 3 (21%) imatinib subjects were still on initial treatment. Two (9%) dasatinib subjects and 11 (79%) imatinib subjects discontinued first allocated study treatment and crossed over to the alternative treatment.

The following Table 4 and Table 5 show the sponsor's and FDA's summary of patient disposition for the 4 single-arm pivotal studies.

Table 4: Sponsor's Summary of Patient Disposition at Cut-off Date (All Treated Subjects)

		Number of Patients (%)		
Study	**Patient Disposition**	**Intolerant**	**Resistant**	**Total**
CA180005	**On treatment**	8 (100.0)	79 (79.8)	87 (81.3)
	Off treatment	0	20 (20.2)	20 (18.7)
	Adverse event unrelated to study drug	0	1	1
	Death	0	4	4
	Disease progression	0	9	9
	Other	0	1	1
	Study drug toxicity	0	2	2
	Subject request	0	3	3
CA180006	**On treatment**	3 (50.0)	32 (47.1)	35 (47.3)
	Off treatment	3 (50.0)	36 (52.9)	39 (52.7)
	Adverse event unrelated to study drug	0	2	2
	Death	1	6	7
	Disease progression	1	21	22
	Other	1	2	3
	Study drug toxicity	0	4	4
	Non-compliance	0	1	1

CA1800013	**On treatment**	55 (93.2)	109 (85.8)	164 (88.2)
	Off treatment	4 (6.8)	18 (14.2)	22 (11.8)
	Adverse event unrelated to study drug	1	2	3
	Death	0	2	2
	Disease progression	0	4	4
	Other	0	1	1
	Study drug toxicity	2	7	9
	Subject request	1	2	3
CA1800015	**Lymphoid Blast (N=42)**			
	On treatment	0	11 (29.7)	11 (26.2)
	Off treatment	5 (100)	26 (70.3)	31 (73.8)
	Deterioration w/o progression	1	2	2
	Death	1	8	9
	Disease progression	1	31	17
	Other	1	6	5
	Study drug toxicity	2	7	1
	Ph+ All (N=36)			
	On treatment	2 (100)	11 (32.4.7)	13 (36.1)
	Off treatment	0	23 (67.6)	23 (63.9)
	Deterioration w/o progression	0	1	1
	Death	0	3	3
	Disease progression	0	15	15
	Other	0	2	2
	Study drug toxicity	0	2	2

[Source: Sponsor's Study Reports]

Table 5: Patient Disposition at Cut-off Date (All Treated Subjects) (FDA's Analysis)

		Number of Patients (%)		
Study	**Patient Disposition**	**Intolerant**	**Resistant**	**Total**
CA180005	**Accelerated (N = 107)**			
	On treatment	8 (100.0)	**74 (74.7)**	**82 (76.6)**
	Off treatment	0	**25 (25.3)**	**25 (24.4)**
	Adverse event unrelated to study drug	0	1	1
	Death	0	4	4
	Disease progression	0	**10**	**10**
	Other	0	**3**	**3**
	Study drug toxicity	0	**4**	**4**
	Subject request	0	3	3
CA180006	**Myeloid Blast (N = 74)**			
	On treatment	3 (50.0)	**29 (42.7)**	**32 (43.24)**
	Off treatment	3 (50.0)	**39 (57.3)**	**42 (56.76)**
	Adverse event unrelated to study drug	0	2	2
	Death	1	6	7
	Disease progression	1	21	22
	Other	1	**4**	**5**

	Study drug toxicity	0	**5**	**5**
	Non-compliance	0	1	1
	Chronic (N = 186)			
	On treatment	55 (93.2)	**105 (82.7)**	**160 (86.0)**
	Off treatment	4 (6.8)	**22 (11.3)**	**26 (14.0)**
	Adverse event unrelated to study drug	1	2	3
CA1800013	**Death**	0	2	2
	Disease progression	0	**6**	**6**
	Other	0	1	1
	Study drug toxicity	2	**9**	**11**
	Subject request	1	2	3
	Lymphoid Blast (N=42)			
	On treatment	0	**7 (18.9)**	**7 (16.7)**
	Off treatment	**5 (100.0)**	**30 (81.1)**	**35 (83.3)**
	Deterioration w/o progression	1	1	3
	Death	1	8	9
	Disease progression	1	20	32
	Other	1	4	7
CA180015	**Study drug toxicity**	2	0	9
	Ph+ All (N=36)			
	On treatment	2 (100.0)	**10 (29.4)**	**12 (33.3)**
	Off treatment	0	**24 (71.6)**	**24 (66.6)**
	Deterioration w/o progression	0	1	1
	Death	0	0	3
	Disease progression	0	**16**	**16**
	Other	0	2	2
	Study drug toxicity	0	2	2

Reviewer's Comment:

[1] This reviewer has verified the sponsor's results of disposition of subjects in Table 4 based on the originally submitted data. Table 5 displays the results of disposition of subjects with updated numbers in bold. The results in Table 5 were based on the updated data provided by the sponsor.

3.1.6.3 Demographic and Baseline Characteristics

Following tables show the demographic and baseline characteristics for the 481 patients in the 5 pivotal studies CA180005, CA180006, CA1800013, CA180015 and CA180017.

Table 6: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180005 (All Treated Population)

	Intolerant N=8	Resistant N=99	Total N=107
Age			
N	8	99	107
Mean	64.8	55.0	55.7
Median	67.0	57.0	57.0
Min - Max	54.0 - 74.0	23.0 - 86.0	23.0 - 86.0
Standard Deviation	6.9	13.2	13.1
Age Categorization (%)			
21-45	0	23 (23.2)	23 (21.5)
46-65	3 (37.5)	55 (55.6)	58 (54.2)
66-75	5 (62.5)	18 (18.2)	23 (21.5)
> 75	0	3 (3.0)	3 (2.8)
Gender (%)			
Male	2 (25.0)	53 (53.5)	55 (51.4)
Female	6 (75.0)	46 (46.5)	52 (48.6)
Race (%)			
White	8 (100.0)	84 (84.8)	92 (86.0)
Black/African American	0	5 (5.1)	5 (4.7)
Asian	0	10 (10.1)	10 (9.3)
Performance Status (ECOG)(%)			
0	3 (37.5)	47 (47.5)	50 (46.7)
1	4 (50.0)	38 (38.4)	42 (39.3)
2	1 (12.5)	14 (14.1)	15 (14.0)

[Source: Sponsor's Study (CA180005) Report Table 5.3]

Table 7: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180006 (All Treated Population)

	Intolerant N=6	Resistant N=68	Total N=74
Age			
N	6	68	74
Mean	58.0	51.8	52.3
Median	60.5	54.5	55.0
Min - Max	40.0 - 69.0	21.0 - 71.0	21.0 - 71.0
Standard Deviation	9.9	13.4	13.2
Age Categorization (%)			
21-45	1 (16.7)	21 (30.9)	22 (29.7)
46-65	4 (66.7)	32 (47.1)	36 (48.6)
66-75	1 (16.7)	15 (22.1)	16 (21.6)
Gender (%)			
Male	2 (33.3)	39 (57.4)	41 (55.4)
Female	4 (66.7)	29 (42.6)	33 (44.6)
Race (%)			

White	6 (100.0)	50 (73.5)	56 (75.7)
Black/African American	0	7 (10.3)	7 (9.5)
Asian	0	11 (16.2)	11 (14.9)
Performance Status (ECOG) (%)			
0	1 (16.7)	12 (17.6)	13 (17.6)
1	3 (50.0)	27 (39.7)	30 (40.5)
2	2 (33.3)	26 (38.2)	28 (37.8)
3	0	1 (1.5)	1 (1.4)
Not Reported	0	2 (2.9)	2 (2.7)

[Source: Sponsor's Study (CA180006) Report Table 5.3]

Table 8: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180013 (All Treated Population)

	Intolerant N=59	**Resistant** N=127	**Total** N=186
Age			
N	59	127	186
Mean	56.0	56.7	56.5
Median	59.0	59.0	59.0
Min - Max	24.0 - 79.0	24.0 - 79.0	24.0 - 79.0
Standard Deviation	12.1	12.6	12.4
Age Categorization (%)			
21-45	12 (20.3)	31 (24.4)	43 (23.1)
46-65	35 (59.3)	59 (46.5)	94 (50.5)
66-75	10 (16.9)	33 (26.0)	43 (23.1)
> 75	2 (3.4)	4 (3.1)	6 (3.2)
Gender (%)			
Male	26 (44.1)	60 (47.2)	86 (46.2)
Female	33 (55.9)	67 (52.8)	100 (53.8)
Race (%)			
White	56 (94.9)	117 (92.1)	173 (93.0)
Black/African American	1 (1.7)	7 (5.5)	8 (4.3)
Asian	1 (1.7)	2 (1.6)	3 (1.6)
Other	1 (1.7)	1 (0.8)	2 (1.1)
Performance Status (ECOG) (%)			
0	42 (71.2)	94 (74.0)	136 (73.1)
1	17 (28.8)	31 (24.4)	48 (25.8)
2	0	2 (1.6)	2 (1.1)

[Source: Sponsor's Study (CA180013) Report Table 5.3]

Table 9: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180015 (All Treated Population)

	Intolerant N=5	Resistant N=37	Total N=42
Age			
N	5	37	42
Mean	51.8	46.2	46.9
Median	58.0	47.0	47.0
Min - Max	26.0 - 72.0	19.0 - 72.0	19.0 - 72.0
Standard Deviation	17.5	15.1	15.3
Age Categorization (%)			
< 21	0	1 (2.7)	1 (2.4)
21-45	2 (40.0)	17 (45.9)	19 (45.2)
46-65	2 (40.0)	16 (43.2)	18 (42.9)
66-75	1 (20.0)	3 (8.1)	4 (9.5)
Gender (%)			
Male	4 (80.0)	18 (48.6)	22 (52.4)
Female	1 (20.0)	19 (51.4)	20 (47.6)
Race (%)			
White	5 (100.0)	35 (94.6)	40 (95.2)
Black/African American	0	1 (2.7)	1 (2.4)
Asian	0	1 (2.7)	1 (2.4)
Performance Status (ECOG) (%)			
0	2 (40.0)	11 (29.7)	13 (31.0)
1	3 (60.0)	15 (40.5)	18 (42.9)
2	0	7 (18.9)	7 (16.7)
Not Reported	0	4 (10.8)	4 (9.5)

[Source: Sponsor's Study (CA180015) Report Table 5.3]

Table 10: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180017 (All Treated Population)

	Intolerant N=22	Resistant N=14	Total N=36
Age			
N	22	14	36
Mean	53	52	52
Median	57	56	57
Min - Max	24 - 76	28 - 69	24 - 76
Standard Deviation	15.7	14.9	15.2
Age Categorization (%)			
21-45	6 (27.3)	4 (28.6)	10 (27.8)
46-65	10 (45.5)	6 (42.9)	16 (44.4)
66-75	5 (22.7)	4 (28.6)	9 (25.0)
> 75	1 (4.5)	0	1 (2.8)
Gender (%)			
Male	11 (50.0)	1 (7.1)	12 (33.3)

Female	11 (50.0)	13 (92.9)	24 (66.7)
Race (%)			
White	20 (90.9)	13 (92.9)	33 (91.7)
Black/African American	1 (4.5)	1 (7.1)	2 (5.6)
Asian	1 (4.5)	0	1 (2.8)
Performance Status (ECOG) (%)			
0	14 (63.6)	8 (57.1)	22 (61.1)

[Source: Sponsor's Study (CA180017) Report Table 5.3]

Table 11: Summary of Demographic and Baseline Characteristics in Study CA180017 (FDA's Analysis)

	Intolerant N=22	Resistant N=14	Total N=36
Age			
N	22	14	36
Mean	53	52	52
Median	57	56	57
Min - Max	24 - 76	28 - 69	24 - 76
Standard Deviation	15.7	14.9	15.2
Age Categorization (%)			
21-45	6 (27.3)	4 (28.6)	10 (27.8)
46-65	10 (45.5)	6 (42.9)	16 (44.4)
66-75	5 (22.7)	4 (28.6)	9 (25.0)
> 75	1 (4.5)	0	1 (2.8)
Gender (%)			
Male	11 (50.0)	1 (7.1)	12 (33.3)
Female	11 (50.0)	13 (92.9)	24 (66.7)
Race (%)			
White	20 (90.9)	13 (92.9)	33 (91.7)
Black/African American	1 (4.5)	1 (7.1)	2 (5.6)
Asian	1 (4.5)	0	1 (2.8)
Performance Status (ECOG) (%)			
0	14 (63.6)	8 (57.1)	22 (61.1)
1	8	5	13
Not Reported	0	1	1

Reviewer Comments:

[1] This reviewer verified above tables which show patients' baseline and characteristic in the 5 pivotal studies.

[2] As seen in Table 7-Table 11, majority of the patients were resistant in the 4 single arm studies.

[3] Demographic and baseline characteristics of the first 36 subjects appeared balanced between the two treatment groups in study CA180017.

3.1.6.4 Primary Endpoints

3.1.6.4.1 Major Cytogenetic Response

The major cytogenetic response (MCyR) at 12 weeks is the primary endpoint in study CA180017. Per sponsor, the efficacy results were based on the first 36 randomized patients (22 in the dasatinib arm and 14 in the imatinib arm) who had the 12-week assessment. Per protocol, MCyR rate was defined as the proportion of all treated subjects with best response of complete cytogenetic response (CCyR) plus the rate of partial cytogenetic response (PCyR). In study CA180017, subjects randomized to imatinib were crossover if one of the following criteria was met:

- The subject was intolerant of imatinib as defined in the protocol. Dose reduction to 600 mg/d allowed if subject was not previously treated at that dose.
- The subject developed progression (confirmed if necessary)
- The subject did not achieve a MCyR or ≥ 30% absolute reduction in Ph+ metaphases by 12 weeks on therapy

Table 12 and Table 13 show the sponsor's and FDA's summary of efficacy results in study CA180017.

Table 12: Sponsor's efficacy Results in CA180017 (All Treated Subjects)

	Dasatinib N=22	**Imatinib N=14**
Major Cytogenetic Response at 12wks (n[%])	10 (45.5)	3 (21.4)
95% CI of MCyR rate	(24.4, 67.8)	(4.7 , 50.8)
Difference of MCyR at 12 weeks (%)	24.0	
95% CI	(-9.9 , 51.2)	
Complete Hematologic Response (n[%])	21 (95.5)	13 (92.9)
95% CI	(77.2 , 99.9)	(66.1 ,99.8)

[Source: Sponsor's study report]

Table 13: Summary Efficacy Results in CA180017 (FDA's Analysis)

	Dasatinib N=22		**Imatinib N=14**	
	Dasatinib	**Dasatinib /Imatinib**	**Imatinib**	**Imatinib /Dasatinib**
	N=20	**N=2**	**N=3**	**N=11**
MCyR (n[%])	10 (50)	0	2 (66)	1
CCyR (n[%])	7 (35)	0	1 (33)	1
CHR (n[%])	20 (100)	1	3 (100)	13

MCyR rate also is the primary endpoint in study CA180013. Cytogenetic response was evaluated with bone marrow aspirates every 12 weeks throughout treatment in study CA180013.

Table 14: Sponsor's Efficacy Results in CA180013

	Intolerant N = 59	Resistant N = 127	Total N = 186
Cytogenetic Response			
MCyR (n [%])	43 (73)	40 (32)	83 (45)
CCyR (n [%])	33 (56)	28 (22)	61 (33)
Hematologic Response			
CHR (n [%])	57 (97)	111 (87)	168 (90)
Duration of Response (months)			
CHR (range)	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
MCyR (range)	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7
Median Duration of Therapy (months)	5.6	5.6	5.6

[Source: Summary-clin-efficacy-cml-ph+all.pdf Table 2.2]

Table 15: Summary of Efficacy Results in CA180013 (FDA's Analysis)

	Number of Subjects (%) Intolerant N=59	Resistant N=127	Total N=186
Major Cytogenetic Response (n[%])	43 (72.9)	40 (31.5)	83 (44.6)
95% CI of MaHR Rate	(59.7, 83.6)	(23.5, 40.3)	(37.3, 52.1)
Complete Hematologic Response (n [%])	57 (96.6)	111(87.4)	168 (90.3)
95% CI of CHR Rate	(88.3, 99.6)	(80.3, 92.6)	(85.1, 94.1)
Overall Hematologic Response (n [%])	57 (96.6)	111 (87.4)	168 (90.3)
95% CI of OHR Rate	(88.3, 99.6)	(80.3,92.6)	(85.1, 94.1)
Median Duration of Response (months)			
CHR	5.3	5.4	5.3
MCyR	2.8	2.8	2.8

Reviewer Comments:

[1] This reviewer has verified the sponsor's results in Table 12 and Table 14.
[2] The Table 15 provides the FDA's results of 95% CIs for MCyR, CHR and OHR. Rates.
[3] From Table 12, in the study CA180017, the 95% confidence interval of the difference of MCyR at 12 weeks in does not exclude 0. It means that it does not exclude the possibility of dasatinib having the same treatment effect as the imatinib or even worse than imatinib. However, it is too early to draw any conclusion from the result which was based on such a small number of subjects.
[4] Notice in study CA180017, crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. Table 12 and 13 show the sponsor's and FDA's results. The sponsor's results show the results for results for the subjects in both treatment groups regardless of the subject's crossover status while FDA's results show the results of pre-crossover and post-crossover between two treatment groups.

3.1.6.4.2 Major Hematologic Response and Overall Hematologic Response

The rates of major hematologic response (MaHR) and overall hematologic response (OHR) were co-primary endpoints for study CA180005, CA18006 and CA180015. MaHR was defined as the best response of complete hematologic response (CHR) or no evidence of leukemia (NEL). Overall hematologic response (OHR) was defined as best response of major or minor hematologic response. The rates of MaHR and OHR were assessed in all treated population.

Table 16: Sponsor's Results of Co-primary endpoints in Study CA180005

	Resistant N = 99	**Intolerant N = 8**	**Total N = 107**
Major Hematologic Response (%)	58 (58.5)	5 (62.5)	63 (58.9)
95% CI of MaHR Rate	48.2 - 68.4	24.5 - 91.4	49.0 - 68.3
Overall Hematologic Response (%)	80 (80.8)	6 (75.0)	86 (80.3)
95% CI of OHR Rate	71.7 - 88.0	34.9 - 96.8	71.6 - 87.4

[*Source: Study report]*

Table 17: Sponsor's Summary of Co-primary endpoints in Study CA180005

	Intolerant N = 8	**Resistant N = 99**	**Total N = 107**
Hematologic Response Rate			
OHR (n [%])	6 (75)	80 (81)	86 (80)
MaHR (n [%])	5 (63)	58 (59)	63 (59)

CHR (n [%])	2 (25)	33 (33)	35 (33)
NEL (n [%])	3 (38)	25 (25)	28 (26)
MiHR (n [%])	1 (13)	22 (22)	23 (21)
Cytogenetic Response Rate			
MCyR (n [%])	1 (13)	32 (32)	33 (31)
CCyR (n [%])	0	23 (23)	23 (21)
Median Duration of Therapy (months)	6.0	5.5	5.5

[Source: Sponsor's Clinical Summary of Efficacy]

Table 18: Summary of Co-primary endpoints in Study CA180005

(FDA's Analysis)

	Resistant N = 99	**Intolerant N = 8**	**Total N = 107**
Major Hematologic Response (n [%])	58 (58.5)	5 (62.5)	63 (58.9)
95% CI of MaHR Rate	48.2 - 68.4	24.5 - 91.4	49.0 - 68.3
CHR	33	2	35 (32.7)
NEL	25	3	28 (26)
MiHR	22	1	23 (21)
Overall Hematologic Response (n [%])	80 (80.8)	6 (75.0)	86 (80.3)
95% CI of OHR Rate	71.7 - 88.0	34.9 - 96.8	71.6 - 87.4

Table 19: Sponsor's Summary of Co-primary endpoints in Study CA180006

(All Treated Population)

	Number of Subjects (%)		
	Imatinib- intolerant (N=6)	**Imatinib-resistant N=68**	**Total N=74**
Hematologic Response Rate			
OHR (n [%])	3 (50)	36 (53)	39 (53)
MaHR (n [%])	1 (17)	23 (34)	24 (32)
CHR (n [%])	1 (17)	17 (25)	18 (24)
NEL (n [%])	0	6 (9)	6 (8)
MiHR (n [%])	2 (33)	13 (19)	15 (20)

Cytogenetic Response Rate			
MCyR (n [%])	2 (33)	20 (29)	22 (30)
CCyR (n [%])	2 (33)	18 (27)	20 (27)
Median Duration of Therapy (months)	4.9	3.5	3.5

[Source: Sponsor's Clinical Summary of Efficacy]

Table 20: Summary of Co-primary endpoints in Study CA180006 (FDA's Analysis)

	Number of Subjects (%)		
	Imatinib- intolerant N=6	**Imatinib-resistant N=68**	**Total N=74**
Major Hematologic Response (n[%])	1 (16.7)	23 (30.9)	24 (32.4)
95% CI of MaHR Rate	0.4 - 64	20.2 - 43.3	22.0-44.3
CHR	1	17	18 (24)
NEL	0	6	6 (8)
MiHR	2	13	15 (20)
Overall Hematologic Response (n[%])	3 (50.0)	36 (52.9)	39 (52.7)
95% CI of OHR Rate	11.8 - 88.2	40.4 - 65.2	40.8 -64.4

[Source: sponsor's study report]

Table 21: Sponsor's Summary of Co-primary endpoints in Study CA180015 (All Treated Population)

	Lymphoid Blast CML			**Ph+ ALL**		
	Intolerant N = 5	**Resistant N = 37**	**Total N = 42**	**Intolerant N = 2**	**Resistant N = 34**	**Total N = 36**
Hematologic Response Rate						
OHR (n [%])	1 (20)	14 (38)	15 (36)	2 (100)	15 (44)	17 (47)
MaHR (n [%])	1 (20)	12 (32)	13 (31)	2 (100)	13 (38)	15 (42)
CHR (n [%])	1 (20)	10 (27)	11 (26)	1 (50)	10 (29)	11 (31)
NEL (n [%])	0	2 (5)	2 (5)	1 (50)	3 (9)	4 (11)
MiHR (n [%])	0	2 (5)	2 (5)	0	2 (6)	2 (6)

[Source: Sponsor's Clinical Summary of Efficacy]

Table 22: FDA's Summary of Co-primary endpoints for Lymphoid Blast CML in Study CA180015 (All Treated Population)

	Number of Subjects (%)		
	Intolerant*	**Resistant**	**Total**
	N = 5	**N = 37**	**N = 42**
Major Hematologic Response (Rate)	1 (20.0)	12 (32)	13 (31)
95% CI of MaHR Rate	NA	**18.0 - 49.8**	**17.6 - 47.1**
Overall Hematologic Response	1 (20.0)	14 (37.8)	15 (35.7)
95% CI of OHR Rate	NA	**22.5 - 55.2**	**21.6 - 52.0**

**95% CIs not provided for imatinib-intolerant subjects as N ≤ 5*

Table 23: FDA's Summary of Co-primary endpoints for Ph+ all in Study CA180015 (All Treated Population)

	Number of Subjects (%)		
	Intolerant*	**Resistant**	**Total**
	N = 2	**N = 34**	**N = 36**
Major Hematologic Response (%)	2 (100.0)	13 (38.2)	15 (41.7)
95% CI of MaHR Rate	NA	**22.1 - 56.4**	**25.5 - 59.2**
Overall Hematologic Response (%)	2 (100.0)	15 (44.1)	17 (47.2)
95% CI of OHR Rate	NA	**27.1 - 62.1**	**30.4 - 64.5**

**95% CIs not provided for imatinib-intolerant subjects as N ≤ 5*

Reviewer Comments:

[1] This reviewer has verified above three Tables about the co-primary endpoints in study CA180005, CA180006 and CA180015.
[2] The Table 18, 20, 22, 23 display the FDA's results of 95% CIs for MCyR, CHR and OHR rates based on the sponsor's updated data.

3.1.6.5 Secondary Endpoints

3.1.6.5.1 Complete Cytogenetic Response.

In the study CA180017, CHR rate was one of the secondary efficacy endpoints. Duration of overall hematologic response, duration of major hematological response, time to overall hematologic response, time to major hematologic response, major cytogenetic response rate were

secondary endpoints in other 4 pivotal single arm studies CA18005, CA18006, CA180013 and CA180015.

The following tables summarize the sponsor's results of the secondary endpoints complete hematologic response rate and complete cytogenetic response.

Table 24: Sponsor's Results of the Secondary Endpoint in Study CA180017

(All Treated Population)

	Dasatinib N=22	**Imatinib N=14**
Complete Hematologic Response [n [%])	21 (95.5)	13 (92.9)
95% exact CI of CHR rate	77.2 - 99.9	66.1 - 99.8

[Source: Sponsor's study Report]

3.1.6.5.2 Major Cytogenetic Response

Table 25: Sponsor's Results of the Major Cytogenetic Response (Rate with 95% CI)

(All Treated Population)

Study	**Population**		
CA180005	**Resistant N=99**	**Intolerant N=8**	**Total N=107**
	28 (28) 20 - 38	0 (0) 0 - 37	28 (26) 18 - 36
CA180006	**Resistant N=99**	**Intolerant N=8**	**Total N=107**
	19 (27.9) 17.7 - 40.1	2 (33.3) 4.3 - 77.7	21 (28.4) 18.5 -40.1
CA180013	**Resistant N=127**	**Intolerant N=59**	**Total N=186**
	38 (64.4) 50.9 -76.4	35 (27.6) 20.0-36.2	73 (39.2) 32.2-46.7
CA180015	**Resistant N=37**	**Intolerant N=5**	**Total N=42**

	18 (48.6) 31.9 - 65.6	3 (60.0) NA	21 (50.0) 34.2 - 65.8
	Resistant **N=34**	**Intolerant** **N=2**	**Total** **N=36**
CA180015			
	19 (48.6) 31.9 - 65.6	2 (100) NA	21 (58) 40.1 - 74.5

[Source: Sponsor's study Report]

3.1.6.5.3 Duration of responses

Per sponsor, durable responses were reported in some treated subjects in the studies. Following Table 26 and Table 27 show the sponsor's and FDA's results of durations of responses in the pivotal studies.

Table 26: Sponsor's Results of Durations of Response

	Range of Duration of Response (Months)	Intolerant	Resistant	Total
	MaHR			
CA180005	OHR	1.4 - 8.5	0.9 - 9.5	0.9 - 9.5
CA180006	MaHR	5.7-5.7	1.2 - 7.8	1.2 - 7.8
	CHR	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
CA180013	MCyR	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7

[Source: Sponsor's study Report]

Reviewer's Comment:

[1] The results of durations of responses in Table 26 were verified. In study CA180005 and CA180006, 98% to 100% of patients who had MaHR and MCyR were still in responses by the date of data-cutoff; hence the duration of responses could not be estimated.

[2] Since no statistical comparison was conducted, whether the durations of the responses are durable should be determined by the clinical judgment.

[3] The results of FDA's analysis in Table 28 were based on the data adjudicated by the clinical reviewer for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. As a result of the adjudication, there are two more patients who progressed in lymphoid blast groups. Following table and figure show the sponsor's and FDA's results on duration of MaHR in

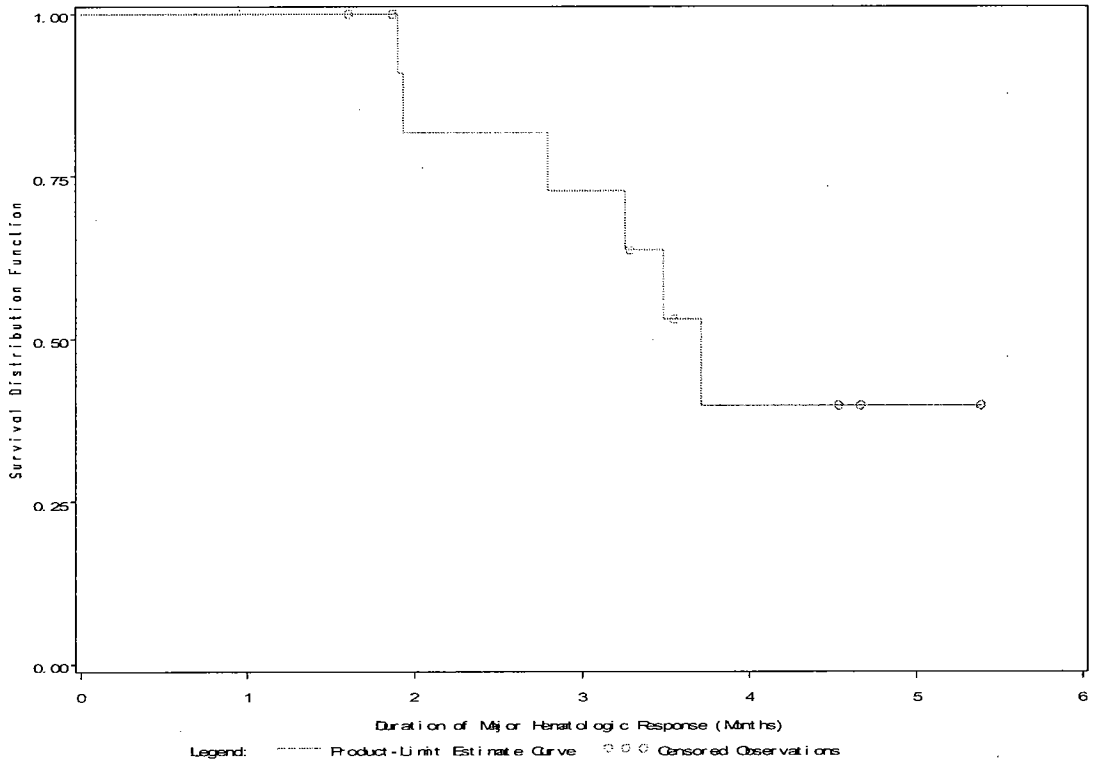
study CA180015. In a single arm study, the results of any time to event endpoints such as duration of MaHR can only considered as descriptive.

Table 27: Summary of the Results on Duration of MaHR in Study CA180015.

	Lymphoid Blast CML (n=42)	PH+ all (n=36)
Sponsor's Results		
# Patient who reached MaHR	13	15
# Patients progressed	6	3
Median duration time (95% CI)	3.71 (2.79, *)	*
FDA Results		
#Patient who reached MaHR	13	15
# Patients progressed	6	5
Median duration time (95% CI)	3.71 (2.79, *)	4.83 (2.89, *)

**: Values could not be reached or estimated.*

Figure 1: Reviewer's Kaplan-Meier Plot of Duration of Major Hematologic Response for Lymphoid Blast CML in Study CA180015



3.2 EVALUATION OF SAFETY

Please refer to FDA clinical reviews provided by Drs. Edvardas Kaminskas, Vicky Goodman and Michael Brave for safety evaluation of dasatinib.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of the primary endpoints: cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) in the 4 pivotal single-arm phase 2 studies.

4.1 GENDER, RACE, AGE AND REGION

The following table shows this reviewer's summary of subgroup analysis. The subgroups include the subgroups of patients by gender, age, race and region. In the 4 single arm studies, about 76 percent to 95 percent of patients were Caucasian. The following subgroup results appeared consistent with the respective overall population.

Table 28: Hematologic Response and Cytogenetic Response for the patients whose age less than 65 (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=126)	CA180005 Accelerated (n = 80)	CA180006 Myeloid Blast (n = 57)	CA180015 Lymphoid Blast (N = 36)	CA180015 Ph+ ALL (N = 30)
Hematologic Response Rate (%)					
OHR(n[%]) (95% CI)	NA	65 (81) (71 - 89)	29 (51) (37 - 64)	14 (39) (23 - 56)	14 (47) (28 - 66)
MaHR (n[%]) (95% CI)	NA	46 (49 - 68)	16 (22 - 44)	12 ( ) (18 - 47)	13 ( ) (26 - 59)
CHR (n[%]) (95% CI)	116 (92)	27 (33.8)	12 (21)	10(28)	10 (33)
NEL (n[%])	NA	19 (23.8)	4(7)	2(6)	3(10)
MiHR (n[%])	NA	19 (23.8)	13 (23)	2 (6)	1(3)
Cytogenetic Response Rate (%)					
MCyR (n[%]) (95% CI)	57 (45) (36 - 54)	23 (29) (19 - 40)	17 (30) (18 - 43)	20 (56) (38 - 72)	19 (63) (44 - 80)
CCyR (n[%])	44(34)	15 (18.8)	15(26)	17(47)	19 (63)

The results in Shaded boxes are the results of primary endpoints

Table 29: Summary of Hematologic Response and Cytogenetic Response for the patients whose age Great or Equal to 65 (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=60)	CA180005 Accelerated (n = 27)	CA180006 Myeloid Blast (n = 17)	CA180015 Lymphoid Blast (N = 6)	CA180015 Ph+ ALL (N = 6)
Hematologic Response Rate (%)					
OHR(n[%])	NA	21 (77)	10	1(17)	3(50)
MaHR (n[%])	NA	17 (63)	8	1(17)	2(33)
CHR (n[%])	52 (87)	8 (29.6)	6(35)	1(17)	1(17)
NEL (n[%])	NA	9 (33.3)	2(12)	0	1(17)
MiHR (n[%])	NA	4	2 (12)	0	1(17)
Cytogenetic Response Rate (%)					
MCyR (n[%])	26 (43)	10 (37)	5(29)	1(17)	2(33)
CCyR (n[%])	17(28)	8 (29.6)	5(29)	1(17)	2(33)

The results in Shaded boxes are the results of primary endpoints

Table 30: Summary of Hematologic Response and Cytogenetic Response for Male patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=86)	CA180005 Accelerated (n = 55)	CA180006 Myeloid Blast (n = 41)	CA180015 Lymphoid Blast (N = 22)	CA180015 Ph+ ALL (N = 23)
Hematologic Response Rate (%)					
OHR(n[%])	NA	43 (78)	26 (63)	10 (45)	11 (48)
MaHR (n[%])	NA	27(49)	15(37)	9 (41)	9 (39)
CHR (n[%])	80 (93)	11 (20)	11 (27)	7(32)	6(26)
NEL (n[%])	NA	16 (29)	4(10)	2(9)	3(13)
MiHR (n[%])	NA	16 (29)	11 (27)	1 (5)	2(9)
Cytogenetic Response Rate (%)					
MCyR (n[%])	39 (45)	17 (31)	16 (39)	20 (56)	19 (63)
CCyR (n[%])	30(35)	10 (18)	14(34)	17(47)	19 (63)

The results in Shaded boxes are the results of primary endpoints

Table 31: Summary of Hematologic Response and Cytogenetic Response for Female patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=100)	CA180005 Accelerated (n = 52)	CA180006 Myeloid Blast (n = 33)	CA180015 Lymphoid Blast (N = 20)	CA180015 Ph+ ALL (N = 13)
Hematologic Response Rate (%)					
OHR(n[%])	NA	42 ( )	13 (39)	5(25)	6 (5)
MaHR (n[%])	NA	36 ( )	9(27)	4 (20)	6 (5)
CHR (n[%])	88 (88)	24 (46)	7 (21)	4 (20)	5 (38)
NEL (n[%])	NA	12 (23)	2(6)	0	1(8)
MiHR (n[%])	NA	7(13)	4 (12)	1 (5)	0
Cytogenetic Response Rate (%)					
MCyR (n[%])	44 (44)	16 (31)	6 (18)	7 (35)	7 (54)
CCyR (n[%])	31(31)	13(25)	6(18)	6(30)	7 (54)

The results in Shaded boxes are the results of primary endpoints

APPEARS THIS WAY
ON ORIGINAL

Table 32: Hematologic Response and Cytogenetic Response for Caucasian patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=173)	CA180005 Accelerated (n = 92)	CA180006 Myeloid Blast (n = 56)	CA180015 Lymphoid Blast (N = 40)	CA180015 Ph+ ALL (N = 35)
Hematologic Response Rate (%)					
OHR(n[%])	NA	43 (78)	33 (59)	10 (45)	16 (46)
MaHR (n[%])	NA	27(49)	22(39)	9 (41)	14 (40)
CHR (n[%])	156 (90)	32 (34)	17 (30)	11(28)	10(29)
NEL (n[%])	NA	25 (27)	5(9)	2(5)	4(11)
MiHR (n[%])	NA	17 (18)	11 (20)	1 (3)	2(6)
Cytogenetic Response Rate (%)					
MCyR (n[%])	77 (45)	29 (31)	16 (39)	20 (50)	20 (57)
CCyR (n[%])	57(33)	21 (23)	14(34)	17(43)	20 (57)

The results in Shaded boxes are the results of primary endpoints

APPEARS THIS WAY
ON ORIGINAL

Table 33: Hematologic Response and Cytogenetic Response for Non-Caucasian patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=86)	CA180005 Accelerated (n = 15)	CA180006 Myeloid Blast (n = 18)	CA180015 Lymphoid Blast (N = 2)	CA180015 Ph+ ALL (N = 1)
Hematologic Response Rate (%)					
OHR(n[%])	NAc	12 (80)	6 (34)	1 (50)	1(100)
MaHR (n[%])	NA	6(40)	2(12)	0	1(100)
CHR (n[%])	12 (92)	3 (20)	1 (6)	0	1(100)
NEL (n[%])	NA	3 (20)	1(6)	0	0
MiHR (n[%])	NA	6 (40)	4 (22)	1 (50)	0
Cytogenetic Response Rate (%)					
MCyR (n[%])	6(46)	4 (26)	3 (18)	1(50)	1 (100)
CCyR (n[%])	4(31)	2 (13)	2(12)	1(50)	1 (100)

The results in Shaded boxes are the results of primary endpoints

Reviewer's Comment:

[1] The results of primary endpoints, cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) in subgroups of patients with age great than or equal to 65, age less than 65, female patients, male patients, Caucasian patients, non-Caucasian are consistent with the respective overall population.

5 SUMMARY AND CONCLUSIONS

5.1 SPONSOR'S EFFICACY CONCLUSIONS

This application includes 5 pivotal phase II studies and 1 supportive phase I study. The sponsor claimed that dasatinib was effective in subjects with all phases of CML and Ph+ ALL, resulting in durable hematologic and cytogenetic responses. The effectiveness of dasatinib was based on

the rates of hematologic and cytogenetic responses with the durations of responses. Per sponsor, hematologic and cytogenetic responses were achieved in both imatinib resistant and imatinib-intolerant subjects in these 5 studies. After median treatment duration 2.8 months to 5.6 months, the subjects in these 5 studies who achieved a major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) range from 30% to 58%, 31% to 59 % and 36% to 80%, respectively. Moreover, the sponsor reported that the durations of hematologic and cytogenetic responses were durable. The median duration of MCyR was 2.8 months for chronic CML patients, and the median durations of MaHR and OHR range from 4.4 to 4.7 months and from 4.7 to 4.8 months for accelerated phase CML patients and myeloid blast phase CML patients, respectively. In the only one randomized trial CA180017, results at the 12-week assessment from the first 36 randomized patients (22 in the dasatinib arm and 14 in the imatinib arm) show that a CHR was achieved in >90% of patients in both arms, a MCyR occurred in 45% of patients receiving dasatinib and 21% of patients receiving imatinib, a complete cytogenetic response (CCyR) occurred in 32% of patients receiving dasatinib and 7% of patients receiving imatinib. Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. No statistical comparison was conducted in the 5 pivotal studies and therefore no statistical inference can be drawn from these studies.

5.2 ODAC DISCUSSION

The June 2006 Oncologic Drugs Advisory Committee (ODAC) meeting was held in Atlanta, Georgia on June 2, 2006. The New Drug Application (NDA) for dasatinib was discussed in this ODAC meeting. During the FDA presentation, FDA asked the ODAC to discuss whether a lower initial dose of dasatinib for chronic phase chronic myeloid leukemia patients was appropriate, since FDA review team found out that low douse (70 mg b.i.d. is an effective dose) also resulted in responses, and it would suggest that a 50 mg BID dose, rather than the 70 mg dose studied in the primary efficacy trials might reduce toxicity without sacrificing efficacy.

During June 2 meeting in Atlanta, the FDA asked the ODAC five questions. The following are 4 of them (Tables provided with the questions will not be provided here).

1. The Agency has accepted duration responses in hematologic malignancies for approval for both chronic leukemias (accelerated approval) and acute leukemias (regular approval). The FDA granted Gleevec® (imatinib) accelerated approval for chronic, accelerated, and blast crisis phase of CML based on durable major cytogenetic responses and major hematologic responses.

   Based on the magnitude and duration of responses (Table 1 and Table 2), has the sponsor provided sufficient evidence of dasatinib's effectiveness for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

   Voting Result: Unamously yes.

   For accelerated approval—imatinib-resistant populations (except Philadelphia-positive ALL)

2. The major toxicities observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent, but serious, adverse events include cardiac toxicity and intracranial bleeding. Based on the phase 2 data, does the risk/benefit profile support dasatinib's approval for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

   Voting Result: Unamously yes.

   For accelerated approval—imatinib-intolerant populations (except Philadelphia-positive ALL)

3. Imatinib intolerant was defined as either 1) imatinib-related toxicity leading to imatinib discontinuation, or 2) inability to tolerate imatinib. The number of intolerant patients enrolled per study (except for the chronic phase CML studies) was less than 10%. Based on the data presented in Table 3, has the sponsor provided evidence of an effect on a surrogate endpoint (major cytogenetic response) for Chronic phase CML patients intolerant to Gleevec? Based on the data presented below (Table 3) , has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients intolerant to imatinib in either Accelerated, Myeloid blast, or Lymphoid blast phases?

   Voting Result: 13 yes and 1 abstained.

   For approval— Philadelphia-positive ALL

4. As stated above, the FDA has approved drugs to treat acute leukemia based on durable complete responses. The sponsor has presented data (major hematological responses) for Philadelphia-positive acute lymphoblast leukemia patients who have experienced disease progression on imatinib and other therapies. Based on the data presented in the above tables, has dasatinib demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or intolerant Philadelphia-positive ALL population?

   Voting Result: 13 yes and 1 abstained.

Finally, FDA asked the ODAC to discuss future study designs which will be required to a commitment to perform a confirmatory clinical trial to demonstrate clinical benefit if an accelerated approval is granted. These trials could be either front-line or relapsed disease settings.

5.3 CONCLUSIONS AND RECOMMENDATIONS

In this NDA submission, efficacy data were collected from 5 pivotal studies (Phase II multicenter studies) and one supportive Phase I dose escalation trial. Among the 5 pivotal studies, 4 were single arm phase II studies and 1 study was randomized non-comparative study. The 5 pivotal studies were still ongoing when the sponsor submitted this NDA. This review verified the sponsor's major efficacy results and performed some additional analyses, including subgroups analysis for subgroups of patients who were less than 65 years old, greater or equal to 65 years old, all male, all female, and Caucasian. The results of subgroups were consistent to the respective overall population. Since no statistical comparison was conducted in the 5 pivotal studies, it will be determined by the clinical judgment whether the durations of responses are durable and whether its effectiveness is adequate for accelerate approval and the proposed disease indications.

6 APPENDICES

APPENDIX 1 – Patient ID's whose data were adjudicated by the FDA efficacy medical reviewer

Table 34: List of IDs for Patients whose data were adjudicated in Study CA180015

Patient ID
CA180015-044-15015
CA180015-044-15059

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

/s/

Xiaoping Jiang
6/23/2006 02:23:14 PM
BIOMETRICS

Rajeshwari Sridhara
6/23/2006 02:42:30 PM
BIOMETRICS

Aloka Chakravarty
6/23/2006 02:48:52 PM
BIOMETRICS

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:	21-986 / N000
Drug Name:	Dasatinib (BMS-354825)
Indications:	1) Adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib. 2) Adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.
Applicant:	Bristol-Myers Squibb Company
Date(s):	Submission Date: December 28, 2005 PDUFA Date: June 28, 2006
Review Priority:	Priority.
Biometrics Division:	Division of Biometrics V (HFD-711)
Statistical Reviewer:	Xiaoping (Janet) Jiang, Ph.D.
Concurring Reviewers:	Team Leader: Raji Sridhara, Ph.D. Division Director: Aloka Chakravarty, Ph.D.
Medical Division:	Division of Oncology Drug Product (HFD-150)
Clinical Team:	Reviewers: Edvardas Kaminskas, M.D. Vicki Goodman, M.D. Michael Brave, M.D. Team Leader: Ann Farrell, M.D.
Project Managers:	Christy Cottrell Amy Baird

Keywords: Superiority, log-rank test.

Table of Contents

Table of tables

Table of Figures

1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The sponsor submitted this application to seek an accelerated approval for dasatinib. This application includes 5 pivotal phase II studies and 1 supportive phase I study. The effectiveness of dasatinib is based on the rates of hematologic and cytogenetic responses. No statistical comparison was conducted in these 5 pivotal studies and therefore no statistical inference will be drawn from those studies. The sponsor claimed that dasatinib was effective in subjects with all phases of CML and Ph+ ALL, resulting in durable hematologic and cytogenetic responses. Per sponsor, hematologic and cytogenetic responses were achieved in both imatinib resistant and imatinib-intolerant subjects in these 5 studies. After median treatment duration 2.8 months to 5.6 months, the subjects in these 5 studies who achieved a major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) range from 30% to 58%, 31% to 59 % and 36% to 80%, respectively. Moreover, by the time of data cutoff for this NDA submission, the duration of MCyR ranged from 0 to 4.7 months for chronic CML patients, and the durations of MaHR ranged from 0.5 to 9.5 months and from 1.2 to 7.8 months for accelerated phase CML patients and myeloid blast phase CML patients, respectively. Whether its effectiveness is adequate for accelerate approval and the proposed disease indications will be determined by clinical judgment. This application was presented at the Oncology Drugs Advisory Committee (ODAC) on June 02, 2006 at Atlanta, Georgia. The committee unamously voted in favor of warranting accelerated approval in CML patients resistant or intolerant to imatinib in Chronic, Accelerated, Myeloid blast, or Lymphoid blast phases (only one member abstained for patients intolerant to imatinib). The majority of the committee members voted in favor of warranting regular approval in Philadelphia-positive ALL patients resistant or intolerant to imatinib. See more details about the ODAC discussion in Section 5.2.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this NDA submission, efficacy and safety data were collected from 5 pivotal studies (Phase II multicenter studies) and one supportive Phase I dose escalation trial. These six studies were conducted to determine the efficacy and safety of dasatinib in patients with chronic, accelerated and blast chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of treatment with imatinib. Subjects in 5 Phase 2 studies were treated with dasatinib at 70 mg twice daily (BID), once in the morning and once in the evening. Among all 5 phase II studies, one was randomized phase II study and other 4 were single arm phase II studies. Study CA180017 was a randomized, non-comparative study of dasatinib (70 mg BID) and high-dose imatinib (400 mg BID) in chronic CML subjects who were resistant to imatinib. While only 36 subjects were randomized in study CA180017 prior to the randomization cut-off date (30-Jun-2005) for this application, this study was designed to provide important data on the efficacy of dasatinib and of escalated-dose imatinib after failure to respond to the approved doses of imatinib. The single-arm study CA180013 enrolled subjects

who were resistant to or intolerant of imatinib at any dose. The other 3 single-arm studies (CA180005, CA180006, and CA180015) were performed to evaluate the activity and safety of dasatinib in advanced stage CML and Ph+ ALL. The dasatinib studies enrolled subjects with all phases of Ph+ leukemia. Most subjects had a long history of leukemia and were heavily pretreated. These 5 pivotal studies were conducted at multicenter worldwide ranging from 18 to 41 centers. Per sponsor, these 5 pivotal studies are still ongoing.

The data cut-off date for this submission was May 12, 2005 for study CA180005, CA180006 and CA180013. May 23, 2005 and June 30, 2005 were the data-cut off dates. By the data cut-off dates for this application, a total of 481 patients were enrolled and treated in these 5 studies. Of those 481 patients, 107 subjects had accelerated phase chronic myeloid leukemia (CML) resistant to or imatinib mesylate in study CA180005, 74 subjects had myeloid blast phase chronic myeloid leukemia resistant to or intolerant of imatinib mesylate in study CA180006, 186 subjects had chronic phase Philadelphia chromosome positive chronic myeloid leukemia who have disease that is resistant to high dose imatinib mesylate (Gleevec®) or who are intolerant of imatinib in study CA180013, 78 subjects had lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate in study CA180015.

The primary endpoints in these studies were major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR).

In this review, this statistical reviewer will only focus on the efficacy results of the 5 pivotal studies.

1.3 STATISTICAL ISSUES AND FINDINGS

In this NDA, 4 single arm phase 2 studies and 1 randomized non-comparative phase 2 study were conducted to establish efficacy of dasatinib in patients with chronic, accelerated and blast chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) resistant to or intolerant of treatment with imatinib. The primary efficacy endpoints were major cytogenetic response (MCyR) in study CA180013 and CA180017. Major hematologic response (MaHR) rate and overall hematologic response (OHR) were co-primary endpoints in study CA180005, CA180006 and CA180015.

Statistical Issues:

No statistical comparison was conducted in 5 pivotal studies including one randomized pivotal study. Per sponsor, these 5 studies still are ongoing.

There is no substantial statistical issue in this NDA except the following:

- From the results of study CA180017, the point estimate of the difference of treatment effect between dasatinib and imatinib is 24.0% with 95% confidence interval (CI) for the difference of treatment effect between dasatinib and imatinib is (-9.9%, 51.2%). This CI does not exclude 0. It means that it does not exclude the possibility of dasatinib having the same treatment effect as the imatinib or even worse than imatinib. However, it is pre-

mature to have any conclusion based on the results obtained from data with limited number of subjects (36 subjects).

Findings

- Following Table A and Table B show that 31% to 90% of subjects across all phases of CML or Ph+ ALL achieved a hematologic response (CHR for chronic CML and MaHR for advanced CML or Ph+ ALL). In particular, CHR for chronic CML reached 90% with 95% CI [85, 94], and 31% to 59% of subjects across all phases of CML or Ph+ ALL achieved a major cytogenetic response.

Table A: Sponsor's Efficacy Results in Phase 2, Single-arm Studies

(All treated Population)

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph+ ALL (N = 36)
Hematologic Response Rate (%)[a]					
OHR (95% CI)	NAc	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	90	33	24	26	31
NEL	NA	26	8	5	11
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)[b]					
MCyR (95% CI)	45 (37 - 52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	33	21	27	43	58

[a] *≥ 6-month follow-up. Hematologic response criteria (all confirmed responses were maintained at least 4 weeks)*

[b] *≥ 6-month follow-up. Cytogenetic response criteria:* ***CCyR*** *(0% Ph+ metaphases) or PCyR (> 0 % -35%).*

MCyR *= CCyR + PCyR.*

The results in Shaded boxes are the results of primary endpoints

Table B: Hematologic and Cytogentic Response Results in All treated Population from 4 Single-arm Phase 2 Studies (FDA's Analysis)

	CA180013 Chronic (N = 186)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph+ ALL (N = 36)
Hematologic Response Rate (%)[a]					
OHR (95% CI)	NA	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	90 (85-94)	33 (24-42)	24 (15-36)	26 (15-36)	31 (16-48)
NEL	NA	26 (18-36)	8 (3-17)	5 (0.6-16)	11 (3.1-26)
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 -19)
Cytogenetic Response Rate (%)[b]					
MCyR (95% CI)	45 (37-52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	33(26-40)	21 (14-30)	27 (17-39)	43 (28-59)	58 (41-74)

[a] *≥ 6-month follow-up. Hematologic response criteria (all confirmed responses were maintained at least 4 weeks)*
[b] *≥ 6-month follow-up. Cytogenetic response criteria:* ***CCyR*** *(0% Ph+ metaphases) or PCyR (> 0 % -35%).*
MCyR *= CCyR + PCyR.*
The results in Shaded boxes are the results of primary endpoints

- The sponsor claimed that dasatinib was effective resulting in durable hematologic and cytogenetic responses. Except for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate, 98% to 100% of patients with other phases of CML who had MaHR and MCyR were still in responses by the date of data-cutoff, hence the duration of responses could not be estimated. The following Table C shows the sponsor's results of duration of responses.

Table C: Sponsor's Results of Durations of Hematologic and Cytogenetic Response in All treated Population from 4 Single-arm Phase 2 Studies

Study	Range of Duration of Response (Months)	Intolerant	Resistant	Total
	MaHR	3.1- 8.5	0.5 - 9.5	0.5 - 9.5
CA180005	**OHR**	1.4 - 8.5	0.9 - 9.5	0.9 - 9.5
CA180006	**MaHR**	5.7-5.7	1.2 - 7.8	1.2 - 7.8
	CHR	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
CA180013	**MCyR**	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7

- In study CA180017, Results at the 12-week assessment from the first 36 randomized patients are included in this submission. As shown in the Table D, the results of these 36 subjects (22 in the dasatinib arm and 14 in the imatinib arm) show that a CHR was achieved in >90% of patients in both arms, a MCyR occurred in 45% of patients receiving dasatinib and 21% of patients receiving imatinib, a complete cytogenetic response (CCyR) occurred in 32% of patients receiving dasatinib and 7% of patients receiving imatinib. Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. However, it is too early to draw any inference conclusion based on the limited number of patients.

- Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients in study CA180017. The Following Table D and Table E show the sponsor's and FDA's results. The sponsor's results show the results for the subjects in both treatment groups regardless of the subject's crossover status while FDA's results show the results of pre-crossover and post-crossover between the two treatment groups. Please see section 3.1.6.4.1 for more detail of criteria of crossover.

Table D: Sponsor's Results of Efficacy in Subjects with Chronic CML Resistant to Imatinib (Study CA180017)

	Dasatinib N=22	**Imatinib** N=14
Median duration of treatment (months)	3.7	2.7
MCyR,[a] n (%)	10 (45)	3 (21)
CCyR,[a] n(%)	7 (32)	1 (7)
CHR,[b] n(%)	21 (95)	13 (93)

[a] ***CCyR*** *(0% Ph+ metaphases) or partial cytogenetic response (PCyR) (> 0 % - 35%).* ***MCyR*** *= CCyR + PCyR.* [b] ***CHR:*** *complete hematologic response*
[Source: sponsor's Clinic-overview TABLE 4.3.1*]*

Table E: Efficacy of Dasatinib and Imatinib in Subjects with Chronic CML Resistant to Imatinib in Study CA180017 (FDA's Analysis)

	Dasatinib N=22		**Imatinib N=14**	
	Dasatinib N=20	**Dasatinib /Imtinib** N=2	**Imatinib** N=3	**Imatinib /Dasatinib** N=11
MCyR,[a] n (%)	10 (50)	0	2 (66)	1
CCyR,[a] n(%)	7 (35)	0	1 (33)	1
CHR,[b] n(%)	20 (100)	1	3 (100)	10

[a] ***CCyR*** *(0% Ph+ metaphases) or partial cytogenetic response (PCyR) (> 0 % - 35%).* ***MCyR*** *= CCyR + PCyR.* [b] ***CHR:*** *complete hematologic response*

- This statistical reviewer performed an analysis on duration of major hematologic response based on the data adjudicated by the clinical reviewer for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. Table E shows the results of the sponsor and FDA analyses of duration of MaHR in study CA180015. There are two more patients who progressed in lymphoid blast groups according to the data adjudicated by the clinical reviewer. In a single arm study, the results of any time to event endpoints such as duration of MaHR can be only considered as descriptive.

Table F: Summary of the Results on Duration of MaHR in Study CA180015

Sponsor's Results		
	Lymphoid Blast CML (n=42)	**PH+ all (n=36)**
# Patient who reached MaHR	13	15
# Patients progressed	6	3
Median duration time (95% CI)	3.71 (2.79, *)	*

FDA Results		
#Patient who reached MaHR	13	15
# Patients progressed	6	5
Median duration time (95% CI)	3.71 (2.79, *)	4.83 (2.89, *)

**: Values could not be reached or estimated.*

- This reviewer performed several subgroup exploratory analyses on the primary endpoints MCyR, MaHR and OHR. Table F summarizes the results of these subgroup analyses, in the subgroups of patients who were less than 65 years old, all male, all female, and Caucasian. These results of subgroups are similar to the respective overall population.

Table G: Hematologic Response and Cytogenetic Response in Subgroups (FDA's Analysis)

	CA180013 Chronic (N=186)	**CA180005 Accelerated (N = 107)**	**CA180006 Myeloid Blast (N = 74)**	**CA180015 Lymphoid Blast (N = 42)**	**CA180015 Ph+ ALL (N = 36)**
Patients whose age<65 years					
# Patients	126	80	57	36	30
OHR(n[%])	NA	65 (81)	29 (51)	14 (39)	14 (47)
MaHR (n[%])	NA	46 (58)	16 (28)	12 (33)	13 (43)
MCyR (n[%])	57 (45)	23 (29)	17 (30)	20 (56)	19 (63)

Patients whose age>=65 years					
# Patients	60	27	17	6	6
OHR(n[%])	NA	21 (77)	10	1(17)	3(50)
MaHR (n[%])	NA	17 (63)	8	1(17)	2(33)
MCyR (n[%])	26 (43)	10 (37)	5(29)	1(17)	2(33)
Male Patients					
# Patients	86	55	41	22	23
OHR(n[%])	NA	43 (78)	26 (63)	10 (45)	11 (48)
MaHR (n[%])	NA	27(49)	15(37)	9 (41)	9 (39)
MCyR (n[%])	39 (45)	17 (31)	16 (39)	14(64)	14(61)
Female Patients					
# Patients	100	52	33	20	13
OHR(n[%])	NA	42 (81)	13 (39)	5(25)	6 (5)
MaHR (n[%])	NA	36 (69)	9(27)	4 (20)	6 (5)
MCyR (n[%])	44 (44)	16 (31)	6 (18)	7 (35)	7 (54)
Caucasian Patients					
# Patients	173	92	56	40	35
OHR(n[%])	NA	43 (78)	33 (59)	14 (35)	16 (46)
MaHR (n[%])	NA	27(49)	22(39)	13 (33)	14 (40)
MCyR (n[%])	77 (45)	29 (31)	16 (39)	20 (50)	20 (57)

2 INTRODUCTION

2.1 OVERVIEW

Dasatinib (BMS-354825) is a potent oral inhibitor of multiple oncogenic kinases. It is currently under development for treatment in subjects with all phases of chronic myeloid leukemia (CML), Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), and solid tumors. In

this application, safety and efficacy data are provided to support the indications for CML and Ph+ ALL in patients who are resistant or intolerant to treatment with imatinib mesylate (imatinib, Gleevec®). The sponsor claimed the effectiveness of dasatinib based on the rates and durability of hematologic response and cytogenetic response.

In this NDA submission, interim efficacy data, with a minimum of 6-months of follow-up, were provided by the sponsor for each of 5 pivotal studies. Per sponsor, all Phase 2 studies are ongoing; the patients would be treated and followed in these studies for up to 24 months to confirm the efficacy reported in this application. The sponsor submitted this NDA to seek an accelerated approval on the indications: *"1) Treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy including imatinib; 2) Treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy."* dasatinib tablets are available for oral administration in strengths of 20 mg, 50 mg, and 70 mg of dasatinib. With conventional treatment, CML is a fatal disease with a median survival of 4 years for patients with chronic CML and ≤6 months for patients in blast phase. Stem cell transplant, available to a limited subset of patients with CML (e.g. young, newly diagnosed patients with chronic CML), is the only curative therapy.

Among 5 phase II pivotal studies for this NDA submission, 4 of them (CA180005, CA180006, CA180013, and CA180015) were single-arm studies. Only CA180017 was randomized, open-label study. Since CA180017 was the last study to start and close enrollment, interim efficacy data were provided with only 36 chronic patients who were randomized in CA180017 prior to the randomization cutoff for this application.

In the randomized study CA180017, patients who were resistant to imatinib ≤600 mg per day were randomized in a 2:1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID. Crossover to the alternate therapy was permitted in the event of disease progression or intolerable toxicity. No imatinib-intolerant patients were enrolled. Results at the 12-week assessment from the first 36 randomized patients are included in this submission.

By the time of data cutoff for the analyses, there were 186 chronic, 107 accelerated, 74 Myeloid blast patients, 78 lymphoid Blast CML and Ph+ All patients. Major cytogenetic response (MCyR) was the primary endpoint for both study CA180017 and study CA180013, and major hematologic response (MaHR) and overall hematologic response (OHR) were the primary endpoints for study CA180005, study CA180006 and study CA180015. Complete hematologic response (CHR) is one of secondary endpoints for all 5 pivotal studies.

The Sponsor submitted the protocol for studying dasatinib under IND No. 66,971, which was originally submitted on March 4, 2003.

2.2 DATA SOURCES

Data used for this review were from the electronic submission received in December 2005. The network path was "\\Cdsesub1\n021986\N000\2005-12-28" in the EDR.

3 STATISTICAL EVALUATION

This review focuses on major efficacy results of 4 single arm phase II studies CA180005, CA180006, CA180013, and CA180015 and the randomized phase II study CA180017. Section 3.1 includes efficacy evaluation for these 5 pivotal studies.

3.1 EVALUATION OF EFFICACY

This section provides the brief description of Study CA180017, CA180013, CA180005, CA180006 and CA180015 based on the sponsor's study reports. Any difference between the sponsor's study reports and the protocols are also discussed in this section.

3.1.1 STUDY OBJECTIVES

The primary objective of study CA180017 was to estimate the major cytogenetic response (MCyR) rates of BMS-354825 and imatinib at 800 mg daily at 12 weeks in subjects with chronic phase Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) who had disease that was resistant to imatinib.

The secondary objectives of the study CA180017 were as follows:

- To estimate the MCyR at any time (prior to crossover) in both treatment arms
- To assess the durability of major cytogenetic response and time to MCyR prior to cross over in both treatment arms
- To estimate complete hematologic response (CHR) rate prior to crossover in both treatment arms
- To assess the durability of CHR and time to CHR prior to crossover in both treatment arms
- To estimate major molecular response rates by measuring BCR-ABL transcripts in blood during treatment using quantitative RT-PCR prior to crossover
- To estimate post-crossover efficacy endpoints in subjects who cross over
- To assess the health-related quality of life in both treatment arms prior to crossover using the FACT-G
- To assess further the safety and tolerability of BMS-354825
- To collect blood samples for pharmacokinetic analysis of BMS-354825 given BID that will contribute to population pharmacokinetic modeling.

The primary objectives of the 4 single arm studies are as shown in following Table 1.

Table 1: Summary of the Primary Objectives in the 4 Single Arm Studies

Study	Primary Objective	#Patients Enrolled and Treated
CA180005	To estimate the major and overall hematologic response rates to dasatinib in accelerated phase chronic myeloid leukemia (CML) subjects with primary or acquired resistance to imatinib mesylate.	107
CA180006	To estimate the major and overall hematologic response rates to BMS-354825 in myeloid blast phase CML subjects with primary or acquired resistance to imatinib mesylate.	74
CA180013	To estimate the major cytogenetic response (MCyR) rate to dasatinib in subjects with chronic phase chronic myeloid leukemia (CML) who had disease that was resistant to imatinib.	186
CA180015	To estimate the major hematologic response (MaHR) rate and overall hematologic response (OHR) rate to dasatinib in lymphoid blast phase CML subjects and Ph+ ALL subjects with primary or acquired resistance to imatinib.	78

3.1.2 STUDY DESIGN

The study CA180017 was designed as an open-label, randomized, non-comparative Phase 2 study of dasatinib and imatinib in subjects with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. By the data cutoff date, 36 eligible subjects were randomized in a 2:1 ratio to receive either dasatinib 70 mg BID or imatinib 800 mg/day (400 mg BID) with continuous daily treatment. These 36 subjects had at least 12 weeks of follow-up data. Randomization was stratified by site and cytogenetic response on prior imatinib therapy (any response, i.e. complete, partial, minor, and minimal, versus no cytogenetic response). Dasatinib dose modifications were allowed in case of disease progression or lack of response, or to manage drug toxicity. No dose escalation was allowed for imatinib. Dosing of imatinib was at 400 mg PO BID, with continuous daily dosing. Subjects was treated until confirmed progression or intolerable toxicity, at which time subjects would cross over to the BMS-354825 treatment arm after a one-week washout of imatinib. If at 12 weeks the subject did not achieve MCyR or $\geq$ 30% absolute reduction in Ph+ metaphases, then the subject would be crossed over to the BMS-354825 arm of the study after a one-week washout of imatinib. No dose escalation was allowed; one dose reduction to 600 mg/d was allowed if the subject had not previously been treated at that dose level. Subjects randomized to imatinib would crossover if one of the following criteria was met: 1) The subject was intolerant of 800 mg imatinib (or 600 mg if subject is dose reduced), 2) The subject developed progression (confirmed if necessary), or 3) The subject did not achieve a MCyR or 30% absolute reduction in Ph+ metaphases by 12 weeks on therapy. Cytogenetic assessment was to be performed every 12 weeks and at the time of crossover. Hematologic assessment was to be performed weekly up to 12 weeks and every 2 weeks thereafter.

Following table summarizes the 4 single arm pivotal studies.

Table 2: Summary of 4 Open Label Single Arm Phase II Studies

Study	Treatment	Population
CA180005	Dasatinib 70 mg BID, dose escalation to 100 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
CA180006	Dasatinib 70 mg BID, dose escalation to 100 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
CA180013	Dasatinib 70 mg BID, dose escalation to 90 mg BID (lack of response) or dose reduction to 50 mg BID and 40 mg BID (toxicity)	Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib Mesylate (Gleevec®) or who are Intolerant of Imatinib
CA180015	Dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed as specified in the protocol for the management of disease progression or toxicity.	Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

Please refer to FDA clinical reviews provided by Drs. Edvardas Kaminskas, Vicky Goodman and Michael Brave for more detail of inclusion and exclusion criterion for the study populations in the 5 pivotal studies.

3.1.3 EFFICACY ENDPOINTS

3.1.3.1 Primary Efficacy Endpoint

The primary endpoint in study CA180017 was major cytogenetic response (MCyR) at 12 weeks. MCyR rate at 12 weeks is defined as the proportion of all randomized subjects at 12 weeks with best response of complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). Subjects that cross over prior to week 12 were classified as non-responders. MCyR rate was calculated for each arm as randomized.

The primary endpoints in other 4 single arm pivotal studies are displayed in following table.

Table 3: Summary of 4 Open Label Single Arm Phase II Studies

Study	Primary Endpoint
CA180005	major hematologic response (MaHR) and overall hematologic response (OHR)
CA180006	major hematologic response (MaHR) and overall hematologic response (OHR)
CA180013	major hematologic response (MaHR)
CA180015	major hematologic response (MaHR) and overall hematologic response (OHR)

As displayed in Table 3, major hematologic response (MaHR) and overall hematologic response (OHR) in the imatinib resistant group are the co-primary endpoints in study CA180005, CA180006 and CA180015. MaHR rate is defined as the proportion of all treated subjects with best response of complete hematologic response (CHR) or no evidence of leukemia (NEL). Overall hematologic response (OHR) rate is defined as the proportion of treated subjects with best response of major or minor hematologic response. The hematologic responses were evaluated with regular blood draws and the cytogenetic responses were evaluated with regular bone marrow biopsies.

In study CA180013, Cytogenetic responses are based on the prevalence of Ph+ metaphases among at least 20 metaphase cells in each bone marrow sample. The criteria for cytogenetic responses are as follows:

- **Complete Cytogenetic Response (CCyR):** 0% Ph-chromosome-positive cells in metaphase in bone marrow
- **Partial Cytogenetic Response (PCyR):** 1 to 35% Ph-chromosome-positive cells in metaphase in bone marrow
- **Minor Cytogenetic Response:** 36 to 65% Ph-chromosome-positive cells in metaphase in bone marrow
- **Minimal Cytogenetic Response:** 66 to 95% Ph-chromosome-positive cells in metaphase in bone marrow
- **No Cytogenetic Response:** 96 to 100% Ph-chromosome-positive cells in metaphase in bone marrow

3.1.3.2 Secondary Efficacy Endpoints

In the study CA180017, the secondary efficacy endpoints included MCyR rate at any time prior to cross over, CHR rates, duration of MCyR and CHR, time to MCyR and CHR prior to crossover for both arms. Duration of overall hematologic response, duration of major hematological response, time to overall hematologic response, time to major hematologic response, major cytogenetic response rate, major molecular response rates, and quality of life measures were secondary endpoints in other 4 pivotal single arm studies CA18005, CA18006, CA180013 and CA180015. Per protocol, the duration of overall hematologic response would be computed only for subjects whose best response was a major or minor hematologic response. Also, the duration of major hematologic response would also be computed for subjects whose

best response was a major hematologic response. Subjects who neither progress nor die were censored on the date of their last hematologic assessment.

Per sponsor, minor hematologic response rate in the imatinib resistant group would be computed. Response rates for imatinib intolerant subjects would also be estimated. Per protocol, definitions of MCyR rate, duration of major cytogenetic response, duration of major hematologic response, duration of overall hematologic response and time to cytogenetic response were as follows.

Major cytogenetic response (MCyR) rate, defined as the proportion of all treated subjects with best response of complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR).

Duration of major cytogenetic response, measured from the time measurement criteria are first met for CCyR or PCyR (whichever status is recorded first) until the date of progression (Section 3.3.6) or death. Subjects who neither progress nor die will be censored on the date of their last cytogenetic assessment. The duration of major cytogenetic response will be computed for subjects whose best response is either CCyR or PCyR.

Duration of major hematologic response, measured from the first day major hematologic response criteria are met, provided they are confirmed 28 days later, until the date of progression or death. It will be computed for subjects whose best response is major hematologic response.

Duration of overall hematologic response, measured from the first day hematologic response criteria are met, provided they are confirmed 28 days later, until the date of progression or death. It will be computed only for subjects whose best response is a major or minor hematologic response. (CA180005, ca180006)

Time to major cytogenetic response, is defined as the time from first dose of BMS-354825 until measurement criteria are first met for CCyR or PCyR (whichever status is recorded first). Time to major cytogenetic response is computed only for subjects whose best response is either CCyR or PCyR.

Complete hematologic response (CHR) rate, defined as the proportion of all treated subjects who achieve a confirmed complete hematologic response (CHR). All hematologic responses as defined below must be maintained for at least 4 weeks after they are first documented. All hematologic responses can begin only 14 days after dosing start date.

In Study CA180013, a subject with chronic phase CML would be determined to have a CHR if he/she met all of the following criteria:

1) WBC ≤ Institutional upper limit of normal
2) Platelets < 450,000/mm^3
3) No blasts or promyelocytes in peripheral blood
4) < 5% Myelocytes plus metamyelocytes in peripheral blood
5) Peripheral blood basophils δ Institutional upper limits of normal
6) No extramedullary involvement (including no hepatomegaly or splenomegaly)

Please refer to the FDA clinical reviews for more detail of the definitions of hematologic and cytogenetic responses.

Reviewer Comments:

[1] The sponsor provided some results of progression-free survival. However, the sponsor did not pre-specify (PFS) as the primary endpoint or secondary endpoint in any protocol. Furthermore, PFS is not interpretable in single arm studies. The descriptive results of PFS can be only used as supportive interpretation.

3.1.4 SAMPLE SIZE CONSIDERATIONS

Per protocol, no comparison between the two treatment arms would be made in Study CA180017. A minimum of 150 subjects would be required to complete this study. A total of 150 subjects would be assigned to the dasatinib arm and the imatinib arm in a 2-to-1 ratio. With a minimum of 100 randomized subjects to the dasatinib arm, the maximum width of the exact 95% confidence interval (CI) will be 20%. With a minimum accrual of 50 randomized subjects to that arm, the maximum width of the exact 95% confidence interval (CI) will be 29%.

For the single-arm study CA180005 and CA180006, with 60 imatinib-resistant patients, the maximum width of the exact two-sided 95% confidence interval will be 25% when the hematologic response rate is in the expected 5% to 30% range.

A minimum of 30 treated subjects in each group (30 lymphoid blast CML and 30 Ph+ ALL) in study CA180015 will provide 35% as the maximum width of the exact two-sided 95% confidence interval when the hematologic response rate is in the expected 5% to 30% range.

For single arm study CA180005, a minimum of sixty subjects with imatinib-resistant disease will be required to complete this study. Accrual may continue beyond this number in order to further characterize efficacy and safety.

Reviewer's Comments:

[1] By the time of this NDA submission, all 5 pivotal studies were ongoing. In this submission, there were 107, 74, 186, 78 and 36 patients enrolled and treated in study CA180005, CA180006, CA1800013, CA180015 and CA180017, respectively.

3.1.5 ANALYSIS METHODS

Per sponsor, efficacy responses in all 5 studies were programmatically determined from hematologic laboratory values, bone marrow biopsy values, bone marrow cytology and cytogenetics and the presence or absence of extramedullary disease. Response rates and 95% confidence intervals (CIs) were estimated. A two-sided Clopper-Pearson 95% exact confidence interval was also calculated for the CHR and major molecular response rates. Kaplan-Meier estimates and 95% CIs were provided for the time to and duration of response (MaHR and OHR). A two-sided 95% confidence interval for median duration of hematologic response was computed using the method of Brookmeyer and Crowley. All analyses were presented for all treated subjects.

3.1.6 SPONSOR'S RESULTS AND STATISTICAL REVIEWER'S COMMENTS/FINDINGS

This section summarizes the sponsor's major results for the 5 pivotal studies and provides the statistical reviewer's comments and some findings.

3.1.6.1 Data Sets

Per sponsor, the 5 pivotal studies were still ongoing by the time this application was submitted. Data collected from any subject who received at least a single dose of dasatinib, with a minimum of 6-months of follow-up, were included in this NDA submission. For study CA180017, the efficacy results were based on the data obtained on the first 36 subjects (22 dasatinib, 14 imatinib) who were randomized by 30-Jun-2005. All 36 subjects were treated and had at least 3 months of follow-up data by 25-Oct-2005, the data cutoff date for this interim report. By the data cut-off dates for this NDA submission, there were 107, 74, 186, and 78 patients in the 4 single arm pivotal studies CA18005, CA180006, CA180013 and CA180015 respectively.

3.1.6.2 Disposition of Patients

Study CA180017 accrual closed on 21-Sep-2005 with 166 subjects enrolled. The first 36 subjects randomized by 30-Jun-2005 (22 to dasatinib, 14 to imatinib) received treatment, had at least 12 weeks of follow-up data, and were included in the analysis submitted for this NDA. As of 25-Oct-2005 (the data cutoff date for the interim analysis), 20 (91%) dasatinib and 3 (21%) imatinib subjects were still on initial treatment. Two (9%) dasatinib subjects and 11 (79%) imatinib subjects discontinued first allocated study treatment and crossed over to the alternative treatment.

The following Table 4 and Table 5 show the sponsor's and FDA's summary of patient disposition for the 4 single-arm pivotal studies.

Table 4: Sponsor's Summary of Patient Disposition at Cut-off Date (All Treated Subjects)

		Number of Patients (%)		
Study	**Patient Disposition**	**Intolerant**	**Resistant**	**Total**
CA180005	**On treatment**	8 (100.0)	79 (79.8)	87 (81.3)
	Off treatment	0	20 (20.2)	20 (18.7)
	Adverse event unrelated to study drug	0	1	1
	Death	0	4	4
	Disease progression	0	9	9
	Other	0	1	1
	Study drug toxicity	0	2	2
	Subject request	0	3	3
CA180006	**On treatment**	3 (50.0)	32 (47.1)	35 (47.3)
	Off treatment	3 (50.0)	36 (52.9)	39 (52.7)
	Adverse event unrelated to study drug	0	2	2
	Death	1	6	7
	Disease progression	1	21	22
	Other	1	2	3
	Study drug toxicity	0	4	4
	Non-compliance	0	1	1

CA1800013	**On treatment**	55 (93.2)	109 (85.8)	164 (88.2)
	Off treatment	4 (6.8)	18 (14.2)	22 (11.8)
	Adverse event unrelated to study drug	1	2	3
	Death	0	2	2
	Disease progression	0	4	4
	Other	0	1	1
	Study drug toxicity	2	7	9
	Subject request	1	2	3
CA1800015	**Lymphoid Blast (N=42)**			
	On treatment	0	11 (29.7)	11 (26.2)
	Off treatment	5 (100)	26 (70.3)	31 (73.8)
	Deterioration w/o progression	1	2	2
	Death	1	8	9
	Disease progression	1	31	17
	Other	1	6	5
	Study drug toxicity	2	7	1
	Ph+ All (N=36)			
	On treatment	2 (100)	11 (32.4.7)	13 (36.1)
	Off treatment	0	23 (67.6)	23 (63.9)
	Deterioration w/o progression	0	1	1
	Death	0	3	3
	Disease progression	0	15	15
	Other	0	2	2
	Study drug toxicity	0	2	2

[Source: Sponsor's Study Reports]

Table 5: Patient Disposition at Cut-off Date (All Treated Subjects) (FDA's Analysis)

		Number of Patients (%)		
Study	**Patient Disposition**	**Intolerant**	**Resistant**	**Total**
CA180005	**Accelerated (N = 107)**			
	On treatment	8 (100.0)	**74 (74.7)**	**82 (76.6)**
	Off treatment	0	**25 (25.3)**	**25 (24.4)**
	Adverse event unrelated to study drug	0	1	1
	Death	0	4	4
	Disease progression	0	**10**	**10**
	Other	0	**3**	**3**
	Study drug toxicity	0	**4**	**4**
	Subject request	0	3	3
CA180006	**Myeloid Blast (N = 74)**			
	On treatment	3 (50.0)	**29 (42.7)**	**32 (43.24)**
	Off treatment	3 (50.0)	**39 (57.3)**	**42 (56.76)**
	Adverse event unrelated to study drug	0	2	2
	Death	1	6	7
	Disease progression	1	21	22
	Other	1	**4**	**5**

	Study drug toxicity	0	**5**	**5**
	Non-compliance	0	1	1
	Chronic (N = 186)			
	On treatment	55 (93.2)	**105 (82.7)**	**160 (86.0)**
	Off treatment	4 (6.8)	**22 (11.3)**	**26 (14.0)**
	Adverse event unrelated to study drug	1	2	3
CA1800013	**Death**	0	2	2
	Disease progression	0	**6**	**6**
	Other	0	1	1
	Study drug toxicity	2	**9**	**11**
	Subject request	1	2	3
	Lymphoid Blast (N=42)			
	On treatment	0	**7 (18.9)**	**7 (16.7)**
	Off treatment	**5 (100.0)**	**30 (81.1)**	**35 (83.3)**
	Deterioration w/o progression	1	1	3
	Death	1	8	9
	Disease progression	1	20	32
	Other	1	4	7
CA180015	**Study drug toxicity**	2	0	9
	Ph+ All (N=36)			
	On treatment	2 (100.0)	**10 (29.4)**	**12 (33.3)**
	Off treatment	0	**24 (71.6)**	**24 (66.6)**
	Deterioration w/o progression	0	1	1
	Death	0	0	3
	Disease progression	0	**16**	**16**
	Other	0	2	2
	Study drug toxicity	0	2	2

Reviewer's Comment:

[1] This reviewer has verified the sponsor's results of disposition of subjects in Table 4 based on the originally submitted data. Table 5 displays the results of disposition of subjects with updated numbers in bold. The results in Table 5 were based on the updated data provided by the sponsor.

3.1.6.3 Demographic and Baseline Characteristics

Following tables show the demographic and baseline characteristics for the 481 patients in the 5 pivotal studies CA180005, CA180006, CA1800013, CA180015 and CA180017.

Table 6: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180005 (All Treated Population)

	Intolerant N=8	Resistant N=99	Total N=107
Age			
N	8	99	107
Mean	64.8	55.0	55.7
Median	67.0	57.0	57.0
Min - Max	54.0 - 74.0	23.0 - 86.0	23.0 - 86.0
Standard Deviation	6.9	13.2	13.1
Age Categorization (%)			
21-45	0	23 (23.2)	23 (21.5)
46-65	3 (37.5)	55 (55.6)	58 (54.2)
66-75	5 (62.5)	18 (18.2)	23 (21.5)
> 75	0	3 (3.0)	3 (2.8)
Gender (%)			
Male	2 (25.0)	53 (53.5)	55 (51.4)
Female	6 (75.0)	46 (46.5)	52 (48.6)
Race (%)			
White	8 (100.0)	84 (84.8)	92 (86.0)
Black/African American	0	5 (5.1)	5 (4.7)
Asian	0	10 (10.1)	10 (9.3)
Performance Status (ECOG)(%)			
0	3 (37.5)	47 (47.5)	50 (46.7)
1	4 (50.0)	38 (38.4)	42 (39.3)
2	1 (12.5)	14 (14.1)	15 (14.0)

[Source: Sponsor's Study (CA180005) Report Table 5.3]

Table 7: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180006 (All Treated Population)

	Intolerant N=6	Resistant N=68	Total N=74
Age			
N	6	68	74
Mean	58.0	51.8	52.3
Median	60.5	54.5	55.0
Min - Max	40.0 - 69.0	21.0 - 71.0	21.0 - 71.0
Standard Deviation	9.9	13.4	13.2
Age Categorization (%)			
21-45	1 (16.7)	21 (30.9)	22 (29.7)
46-65	4 (66.7)	32 (47.1)	36 (48.6)
66-75	1 (16.7)	15 (22.1)	16 (21.6)
Gender (%)			
Male	2 (33.3)	39 (57.4)	41 (55.4)
Female	4 (66.7)	29 (42.6)	33 (44.6)
Race (%)			

White	6 (100.0)	50 (73.5)	56 (75.7)
Black/African American	0	7 (10.3)	7 (9.5)
Asian	0	11 (16.2)	11 (14.9)
Performance Status (ECOG) (%)			
0	1 (16.7)	12 (17.6)	13 (17.6)
1	3 (50.0)	27 (39.7)	30 (40.5)
2	2 (33.3)	26 (38.2)	28 (37.8)
3	0	1 (1.5)	1 (1.4)
Not Reported	0	2 (2.9)	2 (2.7)

[Source: Sponsor's Study (CA180006) Report Table 5.3]

Table 8: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180013 (All Treated Population)

	Intolerant N=59	**Resistant** N=127	**Total** N=186
Age			
N	59	127	186
Mean	56.0	56.7	56.5
Median	59.0	59.0	59.0
Min - Max	24.0 - 79.0	24.0 - 79.0	24.0 - 79.0
Standard Deviation	12.1	12.6	12.4
Age Categorization (%)			
21-45	12 (20.3)	31 (24.4)	43 (23.1)
46-65	35 (59.3)	59 (46.5)	94 (50.5)
66-75	10 (16.9)	33 (26.0)	43 (23.1)
> 75	2 (3.4)	4 (3.1)	6 (3.2)
Gender (%)			
Male	26 (44.1)	60 (47.2)	86 (46.2)
Female	33 (55.9)	67 (52.8)	100 (53.8)
Race (%)			
White	56 (94.9)	117 (92.1)	173 (93.0)
Black/African American	1 (1.7)	7 (5.5)	8 (4.3)
Asian	1 (1.7)	2 (1.6)	3 (1.6)
Other	1 (1.7)	1 (0.8)	2 (1.1)
Performance Status (ECOG) (%)			
0	42 (71.2)	94 (74.0)	136 (73.1)
1	17 (28.8)	31 (24.4)	48 (25.8)
2	0	2 (1.6)	2 (1.1)

[Source: Sponsor's Study (CA180013) Report Table 5.3]

Table 9: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180015 (All Treated Population)

	Intolerant N=5	Resistant N=37	Total N=42
Age			
N	5	37	42
Mean	51.8	46.2	46.9
Median	58.0	47.0	47.0
Min - Max	26.0 - 72.0	19.0 - 72.0	19.0 - 72.0
Standard Deviation	17.5	15.1	15.3
Age Categorization (%)			
< 21	0	1 (2.7)	1 (2.4)
21-45	2 (40.0)	17 (45.9)	19 (45.2)
46-65	2 (40.0)	16 (43.2)	18 (42.9)
66-75	1 (20.0)	3 (8.1)	4 (9.5)
Gender (%)			
Male	4 (80.0)	18 (48.6)	22 (52.4)
Female	1 (20.0)	19 (51.4)	20 (47.6)
Race (%)			
White	5 (100.0)	35 (94.6)	40 (95.2)
Black/African American	0	1 (2.7)	1 (2.4)
Asian	0	1 (2.7)	1 (2.4)
Performance Status (ECOG) (%)			
0	2 (40.0)	11 (29.7)	13 (31.0)
1	3 (60.0)	15 (40.5)	18 (42.9)
2	0	7 (18.9)	7 (16.7)
Not Reported	0	4 (10.8)	4 (9.5)

[Source: Sponsor's Study (CA180015) Report Table 5.3]

Table 10: Sponsor's Summary of Demographic and Baseline Characteristics in Study CA180017 (All Treated Population)

	Intolerant N=22	Resistant N=14	Total N=36
Age			
N	22	14	36
Mean	53	52	52
Median	57	56	57
Min - Max	24 - 76	28 - 69	24 - 76
Standard Deviation	15.7	14.9	15.2
Age Categorization (%)			
21-45	6 (27.3)	4 (28.6)	10 (27.8)
46-65	10 (45.5)	6 (42.9)	16 (44.4)
66-75	5 (22.7)	4 (28.6)	9 (25.0)
> 75	1 (4.5)	0	1 (2.8)
Gender (%)			
Male	11 (50.0)	1 (7.1)	12 (33.3)

Female	11 (50.0)	13 (92.9)	24 (66.7)
Race (%)			
White	20 (90.9)	13 (92.9)	33 (91.7)
Black/African American	1 (4.5)	1 (7.1)	2 (5.6)
Asian	1 (4.5)	0	1 (2.8)
Performance Status (ECOG) (%)			
0	14 (63.6)	8 (57.1)	22 (61.1)

[Source: Sponsor's Study (CA180017) Report Table 5.3]

Table 11: Summary of Demographic and Baseline Characteristics in Study CA180017 (FDA's Analysis)

	Intolerant N=22	Resistant N=14	Total N=36
Age			
N	22	14	36
Mean	53	52	52
Median	57	56	57
Min - Max	24 - 76	28 - 69	24 - 76
Standard Deviation	15.7	14.9	15.2
Age Categorization (%)			
21-45	6 (27.3)	4 (28.6)	10 (27.8)
46-65	10 (45.5)	6 (42.9)	16 (44.4)
66-75	5 (22.7)	4 (28.6)	9 (25.0)
> 75	1 (4.5)	0	1 (2.8)
Gender (%)			
Male	11 (50.0)	1 (7.1)	12 (33.3)
Female	11 (50.0)	13 (92.9)	24 (66.7)
Race (%)			
White	20 (90.9)	13 (92.9)	33 (91.7)
Black/African American	1 (4.5)	1 (7.1)	2 (5.6)
Asian	1 (4.5)	0	1 (2.8)
Performance Status (ECOG) (%)			
0	14 (63.6)	8 (57.1)	22 (61.1)
1	8	5	13
Not Reported	0	1	1

Reviewer Comments:

[1] This reviewer verified above tables which show patients' baseline and characteristic in the 5 pivotal studies.

[2] As seen in Table 7-Table 11, majority of the patients were resistant in the 4 single arm studies.

[3] Demographic and baseline characteristics of the first 36 subjects appeared balanced between the two treatment groups in study CA180017.

3.1.6.4 Primary Endpoints

3.1.6.4.1 Major Cytogenetic Response

The major cytogenetic response (MCyR) at 12 weeks is the primary endpoint in study CA180017. Per sponsor, the efficacy results were based on the first 36 randomized patients (22 in the dasatinib arm and 14 in the imatinib arm) who had the 12-week assessment. Per protocol, MCyR rate was defined as the proportion of all treated subjects with best response of complete cytogenetic response (CCyR) plus the rate of partial cytogenetic response (PCyR). In study CA180017, subjects randomized to imatinib were crossover if one of the following criteria was met:

- The subject was intolerant of imatinib as defined in the protocol. Dose reduction to 600 mg/d allowed if subject was not previously treated at that dose.
- The subject developed progression (confirmed if necessary)
- The subject did not achieve a MCyR or ≥ 30% absolute reduction in Ph+ metaphases by 12 weeks on therapy

Table 12 and Table 13 show the sponsor's and FDA's summary of efficacy results in study CA180017.

Table 12: Sponsor's efficacy Results in CA180017 (All Treated Subjects)

	Dasatinib N=22	Imatinib N=14
Major Cytogenetic Response at 12wks (n[%])	10 (45.5)	3 (21.4)
95% CI of MCyR rate	(24.4, 67.8)	(4.7 , 50.8)
Difference of MCyR at 12 weeks (%)	24.0	
95% CI	(-9.9 , 51.2)	
Complete Hematologic Response (n[%])	21 (95.5)	13 (92.9)
95% CI	(77.2 , 99.9)	(66.1 ,99.8)

[Source: Sponsor's study report]

Table 13: Summary Efficacy Results in CA180017 (FDA's Analysis)

	Dasatinib N=22		Imatinib N=14	
	Dasatinib	**Dasatinib /Imatinib**	**Imatinib**	**Imatinib /Dasatinib**
	N=20	**N=2**	**N=3**	**N=11**
MCyR (n[%])	10 (50)	0	2 (66)	1
CCyR (n[%])	7 (35)	0	1 (33)	1
CHR (n[%])	20 (100)	1	3 (100)	13

MCyR rate also is the primary endpoint in study CA180013. Cytogenetic response was evaluated with bone marrow aspirates every 12 weeks throughout treatment in study CA180013.

Table 14: Sponsor's Efficacy Results in CA180013

	Intolerant N = 59	Resistant N = 127	Total N = 186
Cytogenetic Response			
MCyR (n [%])	43 (73)	40 (32)	83 (45)
CCyR (n [%])	33 (56)	28 (22)	61 (33)
Hematologic Response			
CHR (n [%])	57 (97)	111 (87)	168 (90)
Duration of Response (months)			
CHR (range)	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
MCyR (range)	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7
Median Duration of Therapy (months)	5.6	5.6	5.6

[Source: Summary-clin-efficacy-cml-ph+all.pdf Table 2.2]

Table 15: Summary of Efficacy Results in CA180013 (FDA's Analysis)

	Number of Subjects (%)		
	Intolerant N=59	Resistant N=127	Total N=186
Major Cytogenetic Response (n[%])	43 (72.9)	40 (31.5)	83 (44.6)
95% CI of MaHR Rate	(59.7, 83.6)	(23.5, 40.3)	(37.3, 52.1)
Complete Hematologic Response (n [%])	57 (96.6)	111(87.4)	168 (90.3)
95% CI of CHR Rate	(88.3, 99.6)	(80.3, 92.6)	(85.1, 94.1)
Overall Hematologic Response (n [%])	57 (96.6)	111 (87.4)	168 (90.3)
95% CI of OHR Rate	(88.3, 99.6)	(80.3,92.6)	(85.1, 94.1)
Median Duration of Response (months)			
CHR	5.3	5.4	5.3
MCyR	2.8	2.8	2.8

Reviewer Comments:

[1] This reviewer has verified the sponsor's results in Table 12 and Table 14.
[2] The Table 15 provides the FDA's results of 95% CIs for MCyR, CHR and OHR. Rates.
[3] From Table 12, in the study CA180017, the 95% confidence interval of the difference of MCyR at 12 weeks in does not exclude 0. It means that it does not exclude the possibility of dasatinib having the same treatment effect as the imatinib or even worse than imatinib. However, it is too early to draw any conclusion from the result which was based on such a small number of subjects.
[4] Notice in study CA180017, crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. Table 12 and 13 show the sponsor's and FDA's results. The sponsor's results show the results for results for the subjects in both treatment groups regardless of the subject's crossover status while FDA's results show the results of pre-crossover and post-crossover between two treatment groups.

3.1.6.4.2 Major Hematologic Response and Overall Hematologic Response

The rates of major hematologic response (MaHR) and overall hematologic response (OHR) were co-primary endpoints for study CA180005, CA18006 and CA180015. MaHR was defined as the best response of complete hematologic response (CHR) or no evidence of leukemia (NEL). Overall hematologic response (OHR) was defined as best response of major or minor hematologic response. The rates of MaHR and OHR were assessed in all treated population.

Table 16: Sponsor's Results of Co-primary endpoints in Study CA180005

	Resistant N = 99	**Intolerant N = 8**	**Total N = 107**
Major Hematologic Response (%)	58 (58.5)	5 (62.5)	63 (58.9)
95% CI of MaHR Rate	48.2 - 68.4	24.5 - 91.4	49.0 - 68.3
Overall Hematologic Response (%)	80 (80.8)	6 (75.0)	86 (80.3)
95% CI of OHR Rate	71.7 - 88.0	34.9 - 96.8	71.6 - 87.4

[Source: Study report]

Table 17: Sponsor's Summary of Co-primary endpoints in Study CA180005

	Intolerant N = 8	**Resistant N = 99**	**Total N = 107**
Hematologic Response Rate			
OHR (n [%])	6 (75)	80 (81)	86 (80)
MaHR (n [%])	5 (63)	58 (59)	63 (59)

CHR (n [%])	2 (25)	33 (33)	35 (33)
NEL (n [%])	3 (38)	25 (25)	28 (26)
MiHR (n [%])	1 (13)	22 (22)	23 (21)
Cytogenetic Response Rate			
MCyR (n [%])	1 (13)	32 (32)	33 (31)
CCyR (n [%])	0	23 (23)	23 (21)
Median Duration of Therapy (months)	6.0	5.5	5.5

[Source: Sponsor's Clinical Summary of Efficacy]

Table 18: Summary of Co-primary endpoints in Study CA180005

(FDA's Analysis)

	Resistant N = 99	**Intolerant N = 8**	**Total N = 107**
Major Hematologic Response (n [%])	58 (58.5)	5 (62.5)	63 (58.9)
95% CI of MaHR Rate	48.2 - 68.4	24.5 - 91.4	49.0 - 68.3
CHR	33	2	35 (32.7)
NEL	25	3	28 (26)
MiHR	22	1	23 (21)
Overall Hematologic Response (n [%])	80 (80.8)	6 (75.0)	86 (80.3)
95% CI of OHR Rate	71.7 - 88.0	34.9 - 96.8	71.6 - 87.4

Table 19: Sponsor's Summary of Co-primary endpoints in Study CA180006

(All Treated Population)

	Number of Subjects (%)		
	Imatinib- intolerant (N=6)	**Imatinib-resistant N=68**	**Total N=74**
Hematologic Response Rate			
OHR (n [%])	3 (50)	36 (53)	39 (53)
MaHR (n [%])	1 (17)	23 (34)	24 (32)
CHR (n [%])	1 (17)	17 (25)	18 (24)
NEL (n [%])	0	6 (9)	6 (8)
MiHR (n [%])	2 (33)	13 (19)	15 (20)

Cytogenetic Response Rate			
MCyR (n [%])	2 (33)	20 (29)	22 (30)
CCyR (n [%])	2 (33)	18 (27)	20 (27)
Median Duration of Therapy (months)	4.9	3.5	3.5

[Source: Sponsor's Clinical Summary of Efficacy]

Table 20: Summary of Co-primary endpoints in Study CA180006 (FDA's Analysis)

	Number of Subjects (%)		
	Imatinib- intolerant N=6	**Imatinib-resistant N=68**	**Total N=74**
Major Hematologic Response (n[%])	1 (16.7)	23 (30.9)	24 (32.4)
95% CI of MaHR Rate	0.4 - 64	20.2 - 43.3	22.0-44.3
CHR	1	17	18 (24)
NEL	0	6	6 (8)
MiHR	2	13	15 (20)
Overall Hematologic Response (n[%])	3 (50.0)	36 (52.9)	39 (52.7)
95% CI of OHR Rate	11.8 - 88.2	40.4 - 65.2	40.8 -64.4

[Source: sponsor's study report]

Table 21: Sponsor's Summary of Co-primary endpoints in Study CA180015 (All Treated Population)

	Lymphoid Blast CML			**Ph+ ALL**		
	Intolerant N = 5	**Resistant N = 37**	**Total N = 42**	**Intolerant N = 2**	**Resistant N = 34**	**Total N = 36**
Hematologic Response Rate						
OHR (n [%])	1 (20)	14 (38)	15 (36)	2 (100)	15 (44)	17 (47)
MaHR (n [%])	1 (20)	12 (32)	13 (31)	2 (100)	13 (38)	15 (42)
CHR (n [%])	1 (20)	10 (27)	11 (26)	1 (50)	10 (29)	11 (31)
NEL (n [%])	0	2 (5)	2 (5)	1 (50)	3 (9)	4 (11)
MiHR (n [%])	0	2 (5)	2 (5)	0	2 (6)	2 (6)

[Source: Sponsor's Clinical Summary of Efficacy]

Table 22: FDA's Summary of Co-primary endpoints for Lymphoid Blast CML in Study CA180015 (All Treated Population)

	Number of Subjects (%)		
	Intolerant*	**Resistant**	**Total**
	N = 5	**N = 37**	**N = 42**
Major Hematologic Response (Rate)	1 (20.0)	12 (32)	13 (31)
95% CI of MaHR Rate	NA	**18.0 - 49.8**	**17.6 - 47.1**
Overall Hematologic Response	1 (20.0)	14 (37.8)	15 (35.7)
95% CI of OHR Rate	NA	**22.5 - 55.2**	**21.6 - 52.0**

**95% CIs not provided for imatinib-intolerant subjects as N ≤ 5*

Table 23: FDA's Summary of Co-primary endpoints for Ph+ all in Study CA180015 (All Treated Population)

	Number of Subjects (%)		
	Intolerant*	**Resistant**	**Total**
	N = 2	**N = 34**	**N = 36**
Major Hematologic Response (%)	2 (100.0)	13 (38.2)	15 (41.7)
95% CI of MaHR Rate	NA	**22.1 - 56.4**	**25.5 - 59.2**
Overall Hematologic Response (%)	2 (100.0)	15 (44.1)	17 (47.2)
95% CI of OHR Rate	NA	**27.1 - 62.1**	**30.4 - 64.5**

**95% CIs not provided for imatinib-intolerant subjects as N ≤ 5*

Reviewer Comments:

[1] This reviewer has verified above three Tables about the co-primary endpoints in study CA180005, CA180006 and CA180015.
[2] The Table 18, 20, 22, 23 display the FDA's results of 95% CIs for MCyR, CHR and OHR rates based on the sponsor's updated data.

3.1.6.5 Secondary Endpoints

3.1.6.5.1 Complete Cytogenetic Response.

In the study CA180017, CHR rate was one of the secondary efficacy endpoints. Duration of overall hematologic response, duration of major hematological response, time to overall hematologic response, time to major hematologic response, major cytogenetic response rate were

secondary endpoints in other 4 pivotal single arm studies CA18005, CA18006, CA180013 and CA180015.

The following tables summarize the sponsor's results of the secondary endpoints complete hematologic response rate and complete cytogenetic response.

Table 24: Sponsor's Results of the Secondary Endpoint in Study CA180017

(All Treated Population)

	Dasatinib N=22	**Imatinib N=14**
Complete Hematologic Response [n [%])	21 (95.5)	13 (92.9)
95% exact CI of CHR rate	77.2 - 99.9	66.1 - 99.8

[Source: Sponsor's study Report]

3.1.6.5.2 Major Cytogenetic Response

Table 25: Sponsor's Results of the Major Cytogenetic Response (Rate with 95% CI)

(All Treated Population)

Study	**Population**		
CA180005	**Resistant N=99**	**Intolerant N=8**	**Total N=107**
	28 (28) 20 - 38	0 (0) 0 - 37	28 (26) 18 - 36
CA180006	**Resistant N=99**	**Intolerant N=8**	**Total N=107**
	19 (27.9) 17.7 - 40.1	2 (33.3) 4.3 - 77.7	21 (28.4) 18.5 -40.1
CA180013	**Resistant N=127**	**Intolerant N=59**	**Total N=186**
	38 (64.4) 50.9 -76.4	35 (27.6) 20.0-36.2	73 (39.2) 32.2-46.7
CA180015	**Resistant N=37**	**Intolerant N=5**	**Total N=42**

	18 (48.6) 31.9 - 65.6	3 (60.0) NA	21 (50.0) 34.2 - 65.8
	Resistant **N=34**	**Intolerant** **N=2**	**Total** **N=36**
CA180015			
	19 (48.6) 31.9 - 65.6	2 (100) NA	21 (58) 40.1 - 74.5

[Source: Sponsor's study Report]

3.1.6.5.3 Duration of responses

Per sponsor, durable responses were reported in some treated subjects in the studies. Following Table 26 and Table 27 show the sponsor's and FDA's results of durations of responses in the pivotal studies.

Table 26: Sponsor's Results of Durations of Response

	Range of Duration of Response (Months)	Intolerant	Resistant	Total
	MaHR			
CA180005	OHR	1.4 - 8.5	0.9 - 9.5	0.9 - 9.5
CA180006	MaHR	5.7-5.7	1.2 - 7.8	1.2 - 7.8
	CHR	2.9 - 6.9	1.1 - 7.6	1.1 - 7.6
CA180013	MCyR	0.0 - 4.7	0.0 - 3.7	0.0 - 4.7

[Source: Sponsor's study Report]

Reviewer's Comment:

[1] The results of durations of responses in Table 26 were verified. In study CA180005 and CA180006, 98% to 100% of patients who had MaHR and MCyR were still in responses by the date of data-cutoff; hence the duration of responses could not be estimated.

[2] Since no statistical comparison was conducted, whether the durations of the responses are durable should be determined by the clinical judgment.

[3] The results of FDA's analysis in Table 28 were based on the data adjudicated by the clinical reviewer for subjects with lymphoid blast phase chronic myeloid leukemia or Philadelphia chromosome positive acute lymphoblastic leukemia resistant to or intolerant of imatinib mesylate. As a result of the adjudication, there are two more patients who progressed in lymphoid blast groups. Following table and figure show the sponsor's and FDA's results on duration of MaHR in

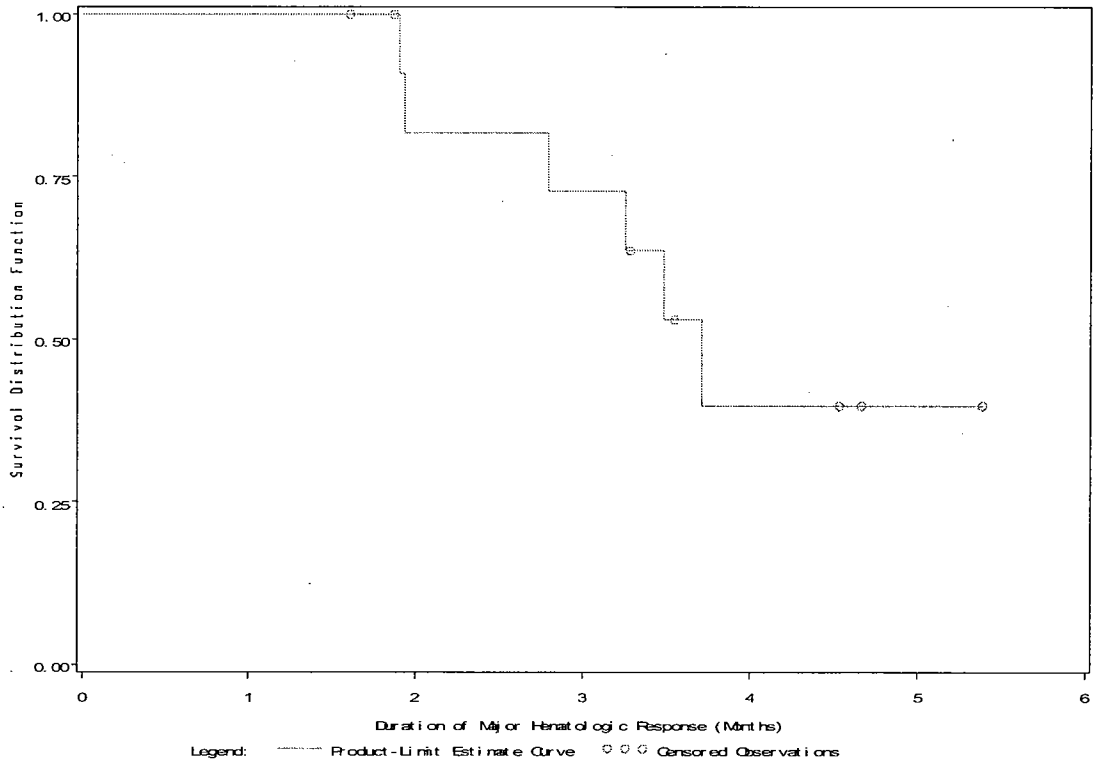
study CA180015. In a single arm study, the results of any time to event endpoints such as duration of MaHR can only considered as descriptive.

Table 27: Summary of the Results on Duration of MaHR in Study CA180015.

	Lymphoid Blast CML (n=42)	PH+ all (n=36)
Sponsor's Results		
# Patient who reached MaHR	13	15
# Patients progressed	6	3
Median duration time (95% CI)	3.71 (2.79, *)	*
FDA Results		
#Patient who reached MaHR	13	15
# Patients progressed	6	5
Median duration time (95% CI)	3.71 (2.79, *)	4.83 (2.89, *)

**: Values could not be reached or estimated.*

Figure 1: Reviewer's Kaplan-Meier Plot of Duration of Major Hematologic Response for Lymphoid Blast CML in Study CA180015



3.2 EVALUATION OF SAFETY

Please refer to FDA clinical reviews provided by Drs. Edvardas Kaminskas, Vicky Goodman and Michael Brave for safety evaluation of dasatinib.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will be focused on the reviewer's results of the exploratory subgroup analyses of the primary endpoints: cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) in the 4 pivotal single-arm phase 2 studies.

4.1 GENDER, RACE, AGE AND REGION

The following table shows this reviewer's summary of subgroup analysis. The subgroups include the subgroups of patients by gender, age, race and region. In the 4 single arm studies, about 76 percent to 95 percent of patients were Caucasian. The following subgroup results appeared consistent with the respective overall population.

Table 28: Hematologic Response and Cytogenetic Response for the patients whose age less than 65 (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=126)	CA180005 Accelerated (n = 80)	CA180006 Myeloid Blast (n = 57)	CA180015 Lymphoid Blast (N = 36)	CA180015 Ph+ ALL (N = 30)
Hematologic Response Rate (%)					
OHR(n[%]) (95% CI)	NA	65 (81) (71 - 89)	29 (51) (37 - 64)	14 (39) (23 - 56)	14 (47) (28 - 66)
MaHR (n[%]) (95% CI)	NA	46 (49 - 68)	16 (22 - 44)	12 ( ) (18 - 47)	13 ( ) (26 - 59)
CHR (n[%]) (95% CI)	116 (92)	27 (33.8)	12 (21)	10(28)	10 (33)
NEL (n[%])	NA	19 (23.8)	4(7)	2(6)	3(10)
MiHR (n[%])	NA	19 (23.8)	13 (23)	2 (6)	1(3)
Cytogenetic Response Rate (%)					
MCyR (n[%]) (95% CI)	57 (45) (36 - 54)	23 (29) (19 - 40)	17 (30) (18 - 43)	20 (56) (38 - 72)	19 (63) (44 - 80)
CCyR (n[%])	44(34)	15 (18.8)	15(26)	17(47)	19 (63)

The results in Shaded boxes are the results of primary endpoints

Table 29: Summary of Hematologic Response and Cytogenetic Response for the patients whose age Great or Equal to 65 (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=60)	CA180005 Accelerated (n = 27)	CA180006 Myeloid Blast (n = 17)	CA180015 Lymphoid Blast (N = 6)	CA180015 Ph+ ALL (N = 6)
Hematologic Response Rate (%)					
OHR(n[%])	NA	21 (77)	10	1(17)	3(50)
MaHR (n[%])	NA	17 (63)	8	1(17)	2(33)
CHR (n[%])	52 (87)	8 (29.6)	6(35)	1(17)	1(17)
NEL (n[%])	NA	9 (33.3)	2(12)	0	1(17)
MiHR (n[%])	NA	4	2 (12)	0	1(17)
Cytogenetic Response Rate (%)					
MCyR (n[%])	26 (43)	10 (37)	5(29)	1(17)	2(33)
CCyR (n[%])	17(28)	8 (29.6)	5(29)	1(17)	2(33)

The results in Shaded boxes are the results of primary endpoints

Table 30: Summary of Hematologic Response and Cytogenetic Response for Male patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=86)	CA180005 Accelerated (n = 55)	CA180006 Myeloid Blast (n = 41)	CA180015 Lymphoid Blast (N = 22)	CA180015 Ph+ ALL (N = 23)
Hematologic Response Rate (%)					
OHR(n[%])	NA	43 (78)	26 (63)	10 (45)	11 (48)
MaHR (n[%])	NA	27(49)	15(37)	9 (41)	9 (39)
CHR (n[%])	80 (93)	11 (20)	11 (27)	7(32)	6(26)
NEL (n[%])	NA	16 (29)	4(10)	2(9)	3(13)
MiHR (n[%])	NA	16 (29)	11 (27)	1 (5)	2(9)
Cytogenetic Response Rate (%)					
MCyR (n[%])	39 (45)	17 (31)	16 (39)	20 (56)	19 (63)
CCyR (n[%])	30(35)	10 (18)	14(34)	17(47)	19 (63)

The results in Shaded boxes are the results of primary endpoints

Table 31: Summary of Hematologic Response and Cytogenetic Response for Female patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=100)	CA180005 Accelerated (n = 52)	CA180006 Myeloid Blast (n = 33)	CA180015 Lymphoid Blast (N = 20)	CA180015 Ph+ ALL (N = 13)
Hematologic Response Rate (%)					
OHR(n[%])	NA	42 ( )	13 (39)	5(25)	6 (5)
MaHR (n[%])	NA	36 ( )	9(27)	4 (20)	6 (5)
CHR (n[%])	88 (88)	24 (46)	7 (21)	4 (20)	5 (38)
NEL (n[%])	NA	12 (23)	2(6)	0	1(8)
MiHR (n[%])	NA	7(13)	4 (12)	1 (5)	0
Cytogenetic Response Rate (%)					
MCyR (n[%])	44 (44)	16 (31)	6 (18)	7 (35)	7 (54)
CCyR (n[%])	31(31)	13(25)	6(18)	6(30)	7 (54)

The results in Shaded boxes are the results of primary endpoints

Appears This Way
On Original

Table 32: Hematologic Response and Cytogenetic Response for Caucasian patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=173)	CA180005 Accelerated (n = 92)	CA180006 Myeloid Blast (n = 56)	CA180015 Lymphoid Blast (N = 40)	CA180015 Ph+ ALL (N = 35)
Hematologic Response Rate (%)					
OHR(n[%])	NA	43 (78)	33 (59)	10 (45)	16 (46)
MaHR (n[%])	NA	27(49)	22(39)	9 (41)	14 (40)
CHR (n[%])	156 (90)	32 (34)	17 (30)	11(28)	10(29)
NEL (n[%])	NA	25 (27)	5(9)	2(5)	4(11)
MiHR (n[%])	NA	17 (18)	11 (20)	1 (3)	2(6)
Cytogenetic Response Rate (%)					
MCyR (n[%])	77 (45)	29 (31)	16 (39)	20 (50)	20 (57)
CCyR (n[%])	57(33)	21 (23)	14(34)	17(43)	20 (57)

The results in Shaded boxes are the results of primary endpoints

Table 33: Hematologic Response and Cytogenetic Response for Non-Caucasian patients (FDA's Analysis)

Study Population (Sample Size)	CA180013 Chronic (n=86)	CA180005 Accelerated (n = 15)	CA180006 Myeloid Blast (n = 18)	CA180015 Lymphoid Blast (N = 2)	CA180015 Ph+ ALL (N = 1)
Hematologic Response Rate (%)					
OHR(n[%])	NAc	12 (80)	6 (34)	1 (50)	1(100)
MaHR (n[%])	NA	6(40)	2(12)	0	1(100)
CHR (n[%])	12 (92)	3 (20)	1 (6)	0	1(100)
NEL (n[%])	NA	3 (20)	1(6)	0	0
MiHR (n[%])	NA	6 (40)	4 (22)	1 (50)	0
Cytogenetic Response Rate (%)					
MCyR (n[%])	6(46)	4 (26)	3 (18)	1(50)	1 (100)
CCyR (n[%])	4(31)	2 (13)	2(12)	1(50)	1 (100)

The results in Shaded boxes are the results of primary endpoints

Reviewer's Comment:

[1] The results of primary endpoints, cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) in subgroups of patients with age great than or equal to 65, age less than 65, female patients, male patients, Caucasian patients, non-Caucasian are consistent with the respective overall population.

5 SUMMARY AND CONCLUSIONS

5.1 SPONSOR'S EFFICACY CONCLUSIONS

This application includes 5 pivotal phase II studies and 1 supportive phase I study. The sponsor claimed that dasatinib was effective in subjects with all phases of CML and Ph+ ALL, resulting in durable hematologic and cytogenetic responses. The effectiveness of dasatinib was based on

the rates of hematologic and cytogenetic responses with the durations of responses. Per sponsor, hematologic and cytogenetic responses were achieved in both imatinib resistant and imatinib-intolerant subjects in these 5 studies. After median treatment duration 2.8 months to 5.6 months, the subjects in these 5 studies who achieved a major cytogenetic response (MCyR), major hematologic response (MaHR) and overall hematologic response (OHR) range from 30% to 58%, 31% to 59 % and 36% to 80%, respectively. Moreover, the sponsor reported that the durations of hematologic and cytogenetic responses were durable. The median duration of MCyR was 2.8 months for chronic CML patients, and the median durations of MaHR and OHR range from 4.4 to 4.7 months and from 4.7 to 4.8 months for accelerated phase CML patients and myeloid blast phase CML patients, respectively. In the only one randomized trial CA180017, results at the 12-week assessment from the first 36 randomized patients (22 in the dasatinib arm and 14 in the imatinib arm) show that a CHR was achieved in >90% of patients in both arms, a MCyR occurred in 45% of patients receiving dasatinib and 21% of patients receiving imatinib, a complete cytogenetic response (CCyR) occurred in 32% of patients receiving dasatinib and 7% of patients receiving imatinib. Crossover to alternate therapy occurred in 9% of dasatinib patients and 79% of imatinib patients. No statistical comparison was conducted in the 5 pivotal studies and therefore no statistical inference can be drawn from these studies.

5.2 ODAC DISCUSSION

The June 2006 Oncologic Drugs Advisory Committee (ODAC) meeting was held in Atlanta, Georgia on June 2, 2006. The New Drug Application (NDA) for dasatinib was discussed in this ODAC meeting. During the FDA presentation, FDA asked the ODAC to discuss whether a lower initial dose of dasatinib for chronic phase chronic myeloid leukemia patients was appropriate, since FDA review team found out that low douse (70 mg b.i.d. is an effective dose) also resulted in responses, and it would suggest that a 50 mg BID dose, rather than the 70 mg dose studied in the primary efficacy trials might reduce toxicity without sacrificing efficacy.

During June 2 meeting in Atlanta, the FDA asked the ODAC five questions. The following are 4 of them (Tables provided with the questions will not be provided here).

1. The Agency has accepted duration responses in hematologic malignancies for approval for both chronic leukemias (accelerated approval) and acute leukemias (regular approval). The FDA granted Gleevec® (imatinib) accelerated approval for chronic, accelerated, and blast crisis phase of CML based on durable major cytogenetic responses and major hematologic responses.

   Based on the magnitude and duration of responses (Table 1 and Table 2), has the sponsor provided sufficient evidence of dasatinib's effectiveness for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

   Voting Result: Unamously yes.

   For accelerated approval—imatinib-resistant populations (except Philadelphia-positive ALL)

2. The major toxicities observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent, but serious, adverse events include cardiac toxicity and intracranial bleeding. Based on the phase 2 data, does the risk/benefit profile support dasatinib's approval for the following: Chronic phase CML? Accelerated phase CML? Myeloid blast CML? Lymphoid blast CML?

   Voting Result: Unamously yes.

   For accelerated approval—imatinib-intolerant populations (except Philadelphia-positive ALL)

3. Imatinib intolerant was defined as either 1) imatinib-related toxicity leading to imatinib discontinuation, or 2) inability to tolerate imatinib. The number of intolerant patients enrolled per study (except for the chronic phase CML studies) was less than 10%. Based on the data presented in Table 3, has the sponsor provided evidence of an effect on a surrogate endpoint (major cytogenetic response) for Chronic phase CML patients intolerant to Gleevec? Based on the data presented below (Table 3) , has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients intolerant to imatinib in either Accelerated, Myeloid blast, or Lymphoid blast phases?

   Voting Result: 13 yes and 1 abstained.

   For approval— Philadelphia-positive ALL

4. As stated above, the FDA has approved drugs to treat acute leukemia based on durable complete responses. The sponsor has presented data (major hematological responses) for Philadelphia-positive acute lymphoblast leukemia patients who have experienced disease progression on imatinib and other therapies. Based on the data presented in the above tables, has dasatinib demonstrated sufficient evidence to warrant regular approval in either the imatinib-resistant or intolerant Philadelphia-positive ALL population?

   Voting Result: 13 yes and 1 abstained.

Finally, FDA asked the ODAC to discuss future study designs which will be required to a commitment to perform a confirmatory clinical trial to demonstrate clinical benefit if an accelerated approval is granted. These trials could be either front-line or relapsed disease settings.

5.3 CONCLUSIONS AND RECOMMENDATIONS

In this NDA submission, efficacy data were collected from 5 pivotal studies (Phase II multicenter studies) and one supportive Phase I dose escalation trial. Among the 5 pivotal studies, 4 were single arm phase II studies and 1 study was randomized non-comparative study. The 5 pivotal studies were still ongoing when the sponsor submitted this NDA. This review verified the sponsor's major efficacy results and performed some additional analyses, including subgroups analysis for subgroups of patients who were less than 65 years old, greater or equal to 65 years old, all male, all female, and Caucasian. The results of subgroups were consistent to the respective overall population. Since no statistical comparison was conducted in the 5 pivotal studies, it will be determined by the clinical judgment whether the durations of responses are durable and whether its effectiveness is adequate for accelerate approval and the proposed disease indications.

6 APPENDICES

APPENDIX 1 – Patient ID's whose data were adjudicated by the FDA efficacy medical reviewer

Table 34: List of IDs for Patients whose data were adjudicated in Study CA180015

Patient ID
CA180015-044-15015
CA180015-044-15059

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

/s/

Xiaoping Jiang
6/12/2006 03:22:17 PM
BIOMETRICS

Rajeshwari Sridhara
6/12/2006 04:28:40 PM
BIOMETRICS

Aloka Chakravarty
6/16/2006 03:20:06 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986 & 22-072

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)