DIVISION OF DRUG ONCOLOGY PRODUCTS

Briefing Document for Oncology Drug Advisory Committee

NDA:	21-986, N-000
Applicant:	Bristol-Myers Squibb
Established Drug Name:	Dasatinib (BMS-354825)

Proposed Indications:

1) Treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib.

2) Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

Formulation: Tablets for oral administration

Date Submitted:	December 28, 2005
Advisory Committee meeting:	June 2, 2006
Medical Reviewers:	Michael Brave, M.D., Vicki Goodman, M.D., Edvardas Kaminskas, M.D., and Ann T. Farrell, M.D.
Statistical Reviewer:	Janet Jiang, Ph.D.
Clinical Pharmacology Reviewers:	Angela Men, Ph.D. and Julie M. Bullock, Pharm.D.

Summary

The applicant, Bristol-Myers-Squibb, has submitted a New Drug Application (NDA) for dasatinib, an orally administered small molecule inhibitor of multiple kinases including BCR-ABL. The applicant proposes that dasatinib is indicated for use in the treatment of adults with:

1) Chronic (CP), accelerated (AP), or blast phase (BP) chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate

2) Philadelphia chromosome-positive (Ph^+) acute lymphoblastic leukemia (ALL) and lymphoid blast (LB) chronic myeloid leukemia with resistance or intolerance to prior therapy.

The evidence for the efficacy and safety of dasatinib is derived primarily from one single arm, phase 1and four phase 2 trials in patients who have failed therapy with 600 mg/daily or more of imatinib or who were intolerant to imatinib and usually had received less than 600mg/daily. Patients were considered intolerant of imatinib if they discontinued imatinib due to non-hematologic toxicity of any grade. An additional study randomized imatinib resistant patients to either high-dose imatinib or dasatinib; due to its small size and short duration of follow-up, this study provides only supportive data.

Except for the CP CML studies, the studies mostly enrolled patients who were resistant to imatinib. In general the patients defined as intolerant were more likely to have been diagnosed with CML for a shorter period of time, have received imatinib for a shorter period of time and at lower doses than patients defined as resistant. The presence of specific genetic mutations that are thought to confer resistance was not required for enrollment in any of the studies.

The phase 1 study did not determine a maximum tolerated dose (MTD); therefore the applicant chose the recommended dose for phase 2 based on efficacy observed. However, in the phase 1 study, efficacy was observed at doses lower than the recommended phase 2 dose.

The primary response endpoint definition differed depending upon the disease category. In CP CML studies, major cytogenetic response (MCyR) was a primary endpoint. The (MCyR) rate after 12 weeks of treatment in these studies was 45% (95% CI, 37% to 52%). In all other studies major hematologic response (MaHR) was a primary endpoint. The MaHR rate after 12 weeks of treatment ranged from approximately 30% to 60% in those studies. Because these studies are ongoing, durations of hematologic and cytogenetic responses to dasatinib treatment are not known at this time.

Dasatinib's major safety issues are: myelosuppression, fluid retention, hemorrhage, and QT prolongation. Forty-five percent of patients experienced fluid retention other than congestive heart failure with nineteen percent experiencing pericardial or pleural

effusion. The major grade 3 or 4 safety issues observed were hematologic (neutropenia, thrombocytopenia, and anemia), constitutional (pyrexia, asthenia, fatigue), pulmonary (dyspnea and pleural effusion) and gastrointestinal (nausea, diarrhea, abdominal pain). Five percent of patients experienced grade 3 or 4 pleural effusion. Five central nervous system hemorrhages were fatal. QT prolongation was seen in 2-3% of patients; however, prolongation rarely resulted in discontinuation.

Dasatinib treatment results in hematologic and cytogenetic responses in patients with all phases of CML and of Ph^+ ALL who are resistant to imatinib mesylate. An effective starting dose of orally administered dasatinib is 70 mg BID; however, lower doses of dasatinib, such as 50 mg BID and 105 mg QD, may be as effective as 70 mg BID and may result in less frequent dose interruptions, dose reductions, and drug discontinuations due to toxicity.

Agency issues with the application include:

- whether a lower starting dose may be appropriate to reduce the toxicity
- whether sufficient data have been provided to recommend dasatinib for the imatinib intolerant population

Clinical Review

1.0 Background

1.1 Chronic Myeloid Leukemia (CML) and Imatinib Resistance

CML is a clonal disease of the hematopoietic stem cell, characterized by a reciprocal chromosomal translocation t(9;22)(q34;q11) which forms the Philadelphia chromosome and creates a novel fusion gene BCR-ABL. CML is diagnosed in approximately 4,300 patients each year in the United States and accounts for 14% of adult leukemia. The median age at presentation is 45 to 55 years, with a third of patients older than 60 years.

CML has three phases: chronic, accelerated, and blastic. Patients with CML may manifest biphasic or triphasic disease. Chronic phase (CP) CML is characterized by 15% or fewer blasts and promyelocytes in the peripheral blood and bone marrow. Accelerated phase (AP) and blast phase (BP) CML are characterized by 16-30% and >30% blasts in either the peripheral blood or bone marrow, respectively. In addition, patients in the accelerated or blast phase may have extramedullary disease.

Most patients are diagnosed in CP. The clinical onset of CP CML is often insidious because patients are usually asymptomatic at the time of diagnosis, whereas patients with AP or BP may present with fatigue, malaise, weight loss or have symptoms related to splenic enlargement. Less frequently patients with advanced disease present with myelosuppression (e.g. infections, thrombosis, or bleeding) or leukostasis, (e.g., cerebrovascular accidents).

The median survival is 4 to 6 years for all patients with CML, with a range of less than 1 year to more than 10 years. However, once patients develop BP disease, survival is less than 1 year and usually only a few months.

In 2001, the US Food and Drug Administration approved imatinib mesylate for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Approval was based on hematologic and cytogenetic responses in three single-arm trials in over 1,000 CML patients. The two-year follow-up data from those studies showing continued high rate of durable responses led to the conversion of this imatinib indication from accelerated to regular approval.

Imatinib resistance is defined as hematologic or cytogenetic. Primary hematologic resistance can be defined as an incomplete hematologic response after 3 months of therapy and occurs in approximately 5% of patients with newly diagnosed CML. Primary cytogenetic resistance can be defined as failure to achieve either a major cytogenetic response (MCyR) after 6 months of therapy or a complete cytogenetic response (CCyR) after 12 months of therapy. Patients who lose their previously established response have either secondary (acquired) hematologic and/or cytogenetic resistance. Development of imatinib resistance is relatively unusual in early CP CML patients. Approximately 16% of patients with CP (disease duration not greater than 6 months) developed secondary resistance or disease progression after 42 months of follow-up.

1.2 Currently available treatment of imatinib-resistant CML

No therapy has been approved for the treatment of any phase imatinib-resistant or intolerant CML. Patients with imatinib-resistant CML receive a variety of therapies including experimental therapies.

1.2.1 Allogeneic hematopoietic stem cell transplantation (HSCT)

The only proven potentially curative treatment of CML is allogeneic HSCT. Patients who receive a transplant from a matched sibling donor may become long-term survivors with no evidence of BCR-ABL. However, not all patients with CML are eligible for a transplant due to a variety of factors (e.g., age, donor availability). In addition, allogeneic HSCT is associated with treatment-related morbidity and mortality.

1.2.2 Interferon-α

Interferon-α is an antiproliferative and immunomodulatory protein product which is approved for Ph^+ CP-CML patients who are minimally pretreated (within 1 year of diagnosis). In the Randomized Study of Interferon and STI-571 (IRIS) study, 11 patients who failed first-line therapy with imatinib (6 for disease progression, 4 for intolerance, and 1 for failure to achieve a MCyR at 12 months) crossed over to interferon-α plus cytarabine. Three of these 11 patients (27%) attained complete hematologic response (CHR) and none attained MCyR.

1.2.3 Imatinib dose escalation

Published results suggest that patients with CP CML whose disease manifests relapse or resistance to initial therapy at 400 mg may achieve a complete or partial hematologic or cytogenetic response with higher doses of imatinib (600-800 mg). Although a substantial fraction of patients appear to respond to escalations of imatinib, these responses are rarely durable. In addition, patients may have significant difficulty tolerating higher doses.

1.1.4 Hydroxyurea

Hydroxyurea is an antineoplastic agent approved for the treatment of resistant CML. No information is available about effectiveness in patients with imatinib-resistant CML.

1.1.5 Cytarabine

Cytarabine is a nucleoside analogue approved for use in the treatment of ALL and BP CML. No clinical data are available regarding its use in patients with imatinib-resistant CML.

2.0 Dasatinib

2.1 Mechanism of action

Dasatinib is a small molecule that competes with ATP for the ATP-binding site in the kinase domain of selected protein tyrosine kinases (PTKs). Dasatinib inhibits five PTK families: SRC family; BCR-ABL; c-KIT ; EPHA2 and PDGFβ receptor. Dasatinib appears more potent than imatinib against BCR-ABL (IC_{50} 3 nM versus 790 nM) and cytotoxic against BCR-ABL dependent CML and B-precursor ALL cell lines.

2.1 Pharmacology/Toxicology

Dasatinib was nonmutagenic in a bacterial reverse mutation assay. Dasatinib inhibited the hERG current by 6.1 %, 36.5 %, and 76.8 % at 3, 10, and 30 μM, respectively (IC_{50} 14.3 μM) suggesting the possibility that QTc prolongation may be seen with clinical use.

2.2 Pharmacokinetics

Dasatinib is available as 20 mg, 50 mg, and 70 mg immediate release film-coated tablets. Following oral administration, peak concentrations occur between 0.5 to 3 hours after dosing. Dasatinib exhibits linear pharmacokinetics suggesting a dose proportional increase in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The half-life is approximately 5-6 hours. No significant accumulation occurs after multiple dosing for 8 days.

Dasatinib metabolism occurs mainly by CYP3A4 activity. Based on a radiolabel study, over 85% of the radioactivity was eliminated in the feces, suggesting minimal renal

excretion of dasatinib. Plasma protein binding of dasatinib is 96%.

In vitro studies in human liver microsomes indicate that dasatinib is not an inducer but may be a weak inhibitor of CYP3A4. Dasatinib administration with rifampin (CYP3A4 inducer) resulted in significant decreases in dasatinib C_{max} and AUC; therefore co-administration of dasatinib with CYP3A4 inducers should be avoided.

Due to the pH dependant absorption of dasatinib, a study investigating the effect of gastric pH modulators with Maalox and famotidine was conducted. The results from this study indicate that administration of dasatinib with OTC antacids should be separated by at least 2 hours to avoid decreases in dasatinib exposure.

2.3 Pharmacodynamics

Exposure-response analyses were performed to characterize the relationships between trough levels of dasatinib and effectiveness (cytogenetic response, hematologic response) and trough levels of dasatinib and incidence of severe toxicity (grade 3/4) in patients with CP CML and Ph^+ ALL patients using logistic regression. Data from 5 phase 2 studies in chronic phase (CA180013 and CA180017) and advanced phase patients (CA180005, CA180006, CA180015) were included. Based on the limited data available, no significant correlation between C_{trough} of dasatinib and endpoints of effectiveness and safety could be discerned. Further data is being collected in ongoing Phase 2 studies, and a population PK model is being developed which could help identify a better relationship between exposure and effectiveness and safety.

3.0 Efficacy

3.1 Summary of Clinical Studies in Leukemia Patients

The Sponsor submitted the results of one Phase 1 dose-ranging study, four phase 2 single-arm, multi-center studies, and one small, non-comparative open-label randomized study. These studies enrolled patients who failed therapy with 600 mg/daily or more of imatinib or who were intolerant to imatinib and usually had received less than 600mg/daily. Patients were considered intolerant of imatinib if they discontinued imatinib due to non-hematologic toxicity of any grade. The Phase 1 study included patients with all phases of CML and Ph^+ ALL; the five Phase 2 studies enrolled patients by phase of disease, as shown in Table 1 below.

Table 1. Studies Supporting the Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Phase **Study No.**	**Population**	**No. of patients treated**
Phase 2, Two-arm, randomized **CA 180017**	Chronic phase CML [IM-R* only]	36
Phase 2, Single-arm **CA 180013**	Chronic phase CML [IM-R* or IM-I*]	186
Phase 2, Single-arm **CA 180005**	Accelerated phase CML [IM-R* or IM-I*]	107
Phase 2, Single-arm **CA 180006**	Myeloid blast (MB) phase CML [IM-R* or IM-I*]	74
Phase 2, Single-arm **CA 180015**	Ph^+ ALL or lymphoid blast (LB) CML [IM-R* or IM-I*]	78
Phase 1 CA 180002	Chronic, accelerated, or blast Phase CML and Ph^+ ALL [IM-R* or IM-I*]	84

*IM-R, imatinib resistant; IM-I, imatinib intolerant.

3.2 Dasatinib Dose Escalation Study (CA180002)

Eighty-four patients with a minimum 3 months follow-up are included in the analysis of this study performed to determine dose limiting toxicity (DLT) and MTD. The study is ongoing with 60% of subjects remaining on treatment (90% chronic CML patients, 64% accelerated CML, 26% myeloid blast CML, and 10% lymphoid blast/Ph^+ ALL) at the time of the report.

MTD and Recommended Phase 2 Dose: The criteria for determining MTD were not met in any of the treatment groups. Only 2 of 84 patients had adverse events that met the DLT criteria during the first four weeks of treatment: one had grade 4 thrombocytopenia in the 35 mg BID cohort of chronic phase CML patients, and one myeloid blast (MB) CML patient in the 120 mg BID cohort had grade 3 pleural and grade 4 pericardial effusions. Hence, the recommended Phase 2 dose was based on efficacy rather than safety criteria.

Table 2 below illustrates the median dose required to achieve a cytogenetic or hematologic response for each disease category.

Table 2. CA180002. Median Dasatinib Doses at Which Cytogenetic and Hematologic Responses Were Achieved – All Treated Subjects

Disease (N= number of patients)	**Dose to achieve MCyR Median (range)**	**Dose to achieve CHR Median (range)**
CP CML – QD dosing (N=21)	105 mg QD (30 mg QD – 180 mg QD)	105 mg QD (15 mg QD – 180 mg QD)
CP CML – BID dosing (N= 19)	60 mg BID (35 mg BID – 70 mg BID)	50 mg BID (25 mg BID – 70 mg BID)
AP CML – BID dosing (N=11)	90 mg BID (50 mg BID – 120 mg BID)	70 mg BID (50 mg BID – 120 mg BID)
MB CML – BID dosing ((N= 23)	70 mg BID (50 mg BID – 90 mg BID)	70 mg BID (50 mg BID – 70 mg BID)
LB CML/Ph+ ALL – BID dosing (N=10)	70 mg BID (25 mg BID – 90 mg BID)	70 mg BID (70 mg BID – 90 mg BID)

On the basis of these findings, the Sponsor concluded that the recommended dasatinib dose for Phase 2 studies is 70 mg BID.

Reviewer's Comments on Dose Determination

- *CP CML - There was no evidence of a linear dose-response. Most of the MCyRs occurred in 50 mg BID or 105 mg/day and 70 mg BID cohorts. Higher dose cohorts and lower dose cohorts had fewer responses. Thus, the optimal treatment dose appears to be about 100 – 140 mg/day. Due to treatment interruptions in the 70 mg BID schedule, the optimal delivered dose appears to be about 100 mg/day.*

- *AP CML - The dose escalation scheme for accelerated phase cohort started with higher doses than chronic phase CML cohorts, i.e. 50 mg BID to 120 mg BID. In accelerated phase patients the 50 mg BID cohort had 2 CHRs and 1 MCyR, the 70 mg BID, 90 mg BID, and 120 mg BID had single CHR and MCyR responses. These results suggest that 50 mg BID may be a reasonable starting dose.*

- *MB CML - The dose escalation scheme for the myeloid blast cohort started with higher doses than chronic phase CML cohorts, i.e. 50 mg BID to 120 mg BID. In myeloid blast CML, one patient treated with 50 mg BID (de-escalated from 70 mg BID) and two treated with 70 mg BID had CHRs; no patient in the 90 mg BID and the 120 mg BID cohort achieved a CHR. Two patients treated with 50 mg BID (de-escalated from 70 mg BID), 5 patients with 70 mg BID, and one patient with 90 mg BID achieved a MCyR.*

- *LB CML /Ph+ ALL- In lymphoid blast CML/Ph+ ALL patients, 2/2 achieved CHR at a starting dose of 70 mg BID and 1/5 at the starting dose of 90 mg BID; there were no CHRs among 3 patients treated with 35 mg BID and 50 mg BID doses. MCyR was achieved among 1/1 25 mg BID, 2/2 50 mg BID, 2/2 70 mg BID, and 3/5 90 mg BID starting dose cohorts.*

Based on evidence of CHR and MCyR at doses lower than 70 mg, a starting dose of 50 mg BID or lower may be appropriate in chronic phase disease, with dose escalation as needed based on response and toxicity.

3.3 Trial Design in Single-Arm Phase 2 Studies

Studies CA180013, CA180005, CA180006 and CA10015 were single-arm multi-center trials in patients with CP, AP, MB and combined LB and Ph $^+$ ALL. Patients enrolled on all these trials were either imatinib resistant or imatinib intolerant. Imatinib resistance was defined as 1) progression of CP CML on imatinib ≥ 400 mg/day, or 2) progression of AP CML on imatinib ≥ 600 mg/day, or 3) MB or LB CML after at least 4 weeks of treatment with imatinib ≥ 600 mg/day. Imatinib intolerance was defined as 1) imatinib-related toxicity that led to imatinib discontinuation, or 2) ability to tolerate imatinib at only ≤ 400 mg/day. The presence of specific genetic mutations that are thought to confer resistance was not required for enrollment in any of the studies.

The starting dose was 70 mg BID on all phase 2 studies, with dose reductions allowed for toxicity and dose escalation allowed for lack of response.

Efficacy results are based on six-month follow-up data. Primary endpoints are as described in Tables 3 and 4. In brief, MCyR is the primary endpoint for the CP study CA180013, and MaHR and OHR are the co-primary endpoints of the three studies in advanced disease. For regulatory purposes, MCyR and MaHR are the endpoints under consideration.

Table 3. Primary and Secondary Endpoints in Chronic Phase CML (CP CML) Studies (CA180002, CA180017 and CA180013)

Endpoints	**Cytogenic parameters**	**Hematologic parameters**
Primary endpoint	Major cytogenic response (MCyR)	-----
Secondary endpoints	Durability of MCyR Time to MCyR	Complete hematologic response (CHR) Durability of CHR Time to CHR

Table 4. Primary and Secondary Endpoints in AP CML, MB CML, LB CML, and Ph$^+$ ALL Studies (CA180002, CA180005, CA180006, and CA180015)

Endpoints	**Cytogenetic parameters**	**Hematologic parameters**
Primary endpoint	-----	Major hematologic response (MaHR) Overall hematologic response (OHR)
Secondary endpoints	Major cytogenic response (MCyR)	Complete hematologic response (CHR) No evidence of leukemia (NEL) Minor hematologic response (MiHR) Durability of OHR and MaHR Time to OHR and MaHR

Endpoint Definitions:

Cytogenetic

MCyR: Complete cytogenetic response (CCyR) (0% Ph^+ metaphases) + partial cytogenetic response (PCyR) (>0% - 35% Ph^+ metaphases) rates after 12 weeks of treatment.

Hematologic

MaHR: CHR + NEL.

> CHR: WBC ≤ ULN, ANC ≥ 1000/mm³, platelets ≥ 100,000/mm³, no blasts or promyelocytes in peripheral blood (PB), bone marrow (BM) blasts ≤ 5%, < 5% myelocytes + promyelocytes in PB, PB basophils < 20%, no extramedullary involvement. A confirmed CHR is one that is maintained for 4 weeks.
>
> NEL: meets criteria above for CHR except: ANC 500-1000/mm^3 and/or platelets 20,000-100,000/mm^3.

MiHR: < 15% blasts in PB and in BM, < 30% blasts + promyelocytes in PB and BM, < 20% basophils in PB, no extramedullary disease other than spleen and liver. MiHR is the return to chronic phase.

OHR: best response of MaHR + MiHR.

3.4 Demographic and Prior Treatment Characteristics

Demographic characteristics are summarized by phase of disease in Table 5. Prior treatment history and reason for discontinuation of imatinib are summarized by disease status in Table 6. The male: female ratio was nearly 1:1 in all populations except Ph^+ ALL, where it was nearly 2:1. Most patients on all studies were white. Patients with lymphoid blast CML and Ph^+ ALL were slightly younger than patients in other studies. As might be expected, subjects with earlier stage disease had better performance status.

Most patients with CML had received prior interferon, and over half had received prior chemotherapy. Almost all of the patients with Ph^+ ALL had received prior chemotherapy, and many had also undergone bone marrow transplant. Length of prior imatinib therapy was longest in chronic and accelerated phase subjects and shortest among Ph^+ ALL subjects. Most patients had received imatinib doses of at least 400-600 mg/day and had discontinued imatinib due to disease progression.

Table 5. Baseline Demographics in the Four Single-Arm Phase 2 Studies

Baseline Parameter	**Chronic Phase N=186**	**Accelerated Phase N=107**	**Myeloid Blast N=74**	**Lymphoid Blast N=42**	**Ph^+ ALL N=36**
Gender (%)					
Male	46	51	55	52	64
Female	54	49	45	48	38
Age (years), median (range)	59 (24-79)	57 (23-86)	55 (21-71)	47 (19-72)	46 (15-85)
Race, (%)					
White	93	85	76	95	97
Black	4	5	10	2	0
Asian	2	10	15	2	3
ECOG performance status, (%)					
0	73	47	18	31	22
1	26	39	41	43	44
2	0	14	38	17	31
unknown	0	0	3	10	3

Table 6. Prior Therapy for CML/ Ph^+ ALL

	Chronic Phase N=186	**Accelerated Phase N=107**	**Myeloid Blast N= 74**	**Lymphoid Blast N=42**	**Ph+ ALL N=36**
Median time from initial CML diagnosis (months)	64	91	49	28	20
Prior Therapy other than Imatinib					
Prior bone marrow transplant (%)	9	18	12	33	42
Prior chemotherapy (%)	43	67	66	79	92
Prior Interferon (%)	70	75	55	48	8
Prior hydroxyurea or anagrelide (%)	86	96	88	79	14
Length of Imatinib Therapy (%)					
< 1 year	20	8	15	48	44
1-3 years	26	24	38	29	53
> 3 years	54	68	47	24	3
Highest Imatinib Dose (%)					
>600 mg	52	59	49	52	47
400-600 mg	48	41	51	45	53
<400 mg	0	0	0	2	0
Best Hematologic Response to Imatinib (%)					
Complete	86	83	84	67	75
No Evidence of Leukemia	0	6	5	7	0
No Response	10	9	7	16	8
Unable to Determine	4	2	4	10	17
Best Cytogenetic Response to Imatinib (%)					
Complete	17	10	32	33	42
Partial	16	22	14	10	8
Other	66	65	53	57	50
Reason for Discontinuation of Imatinib					
Resistance	68	93	92	88	94
Intolerance	32	7	8	12	6

3.5 Efficacy Data

The median duration of treatment is described by disease status in Table 7.

Table 7. Duration of Treatment

	Chronic Phase	Accelerated Phase	Myeloid Blast	Lymphoid Blast	Ph $^{+}$ ALL
Duration of therapy (months), median (range)	5.6 (0.03-8.3)	5.5 (0.2-10.1)	3.5 (0.03-9.2)	2.8 (0.1-6.4)	3.2 (0.2-8.1)

A summary of cytogenetic and hematologic response data is presented in Table 8. Forty-five percent of CP subjects achieved a MCyR, the primary endpoint in that population; ninety percent achieved CHR. In the advanced disease studies, MaHR and OHR were co-primary endpoints. MaHR was achieved in 59% of AP patients, 32% in MB, 31% in LB and 42% in Ph^+ ALL.

Table 8. Summary of Cytogenetic and Hematologic Responses – Percentages of Subjects with Responses – All Treated Subjects in the Single-Arm Phase 2 Studies

	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 (%)					
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 (95% CI)	90 (85-94)	33 (24-42)	24 (15-36)	26 (3-17)	31 (16-48)
NEL (95% CI)	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 (%)					
MCyR (95% CI)	45 (37 -52)	31 (22-41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)

Time to response and duration of response:

- In CP CML, the median time to CHR was 15 days and to MCyR, 85 days.
- In AP CML, the median time to MaHR was 57 days.
- In MB CML, the median time to MaHR was 57 days.
- In LB CML, the median time to achieve MaHR was 33 days. In Ph^+ ALL, the median time to MaHR was 54 days.
- Most of cytogenetic and hematologic responses occurred during the first 3 months of treatment with dasatinib; only few responses occurred during the second 3 months of follow-up.

- Median duration of MaHR was 3.7 months in LB subjects (95% CI 2.8, upper limit not reached) with 6/13 responders progressing and 4.8 months in Ph^+ ALL patients (95% CI 2.9 months, upper limit not reached) with 5/15 patients progressing per the FDA reviewer's analysis.
- Duration of responses could not be reliably estimated during this period of follow-up in subjects with CP, AP and MB disease.

Duration of response data for the four phase 2 single-arm trials are summarized with Kaplan-Meier curves in Figures 1-5 below.

Figure 1. Duration of Complete Hematologic Response in CP CML (Sponsor's Figure 3.2A [6 month Efficacy Update]).

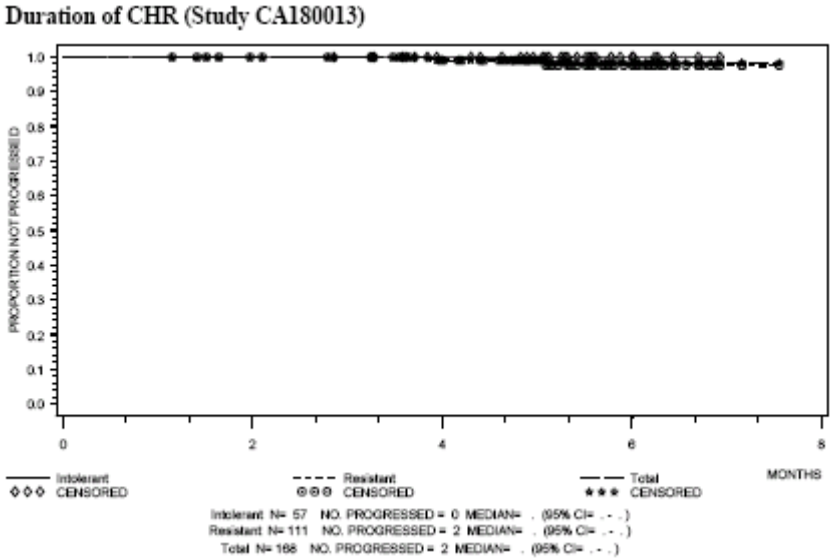


Figure 2. Duration of Major Hematologic Response in Accelerated Phase CML (Sponsor's Figure 4.2A [6 month Efficacy Update]).

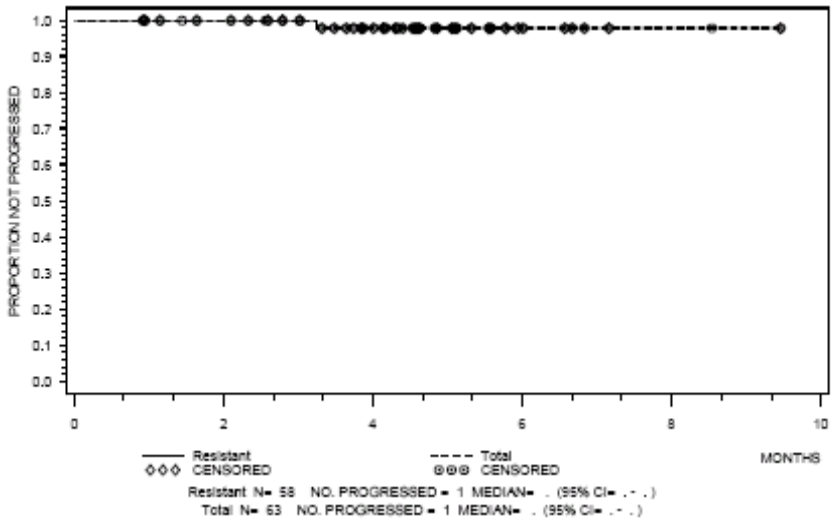


Figure 3. Duration of Major Hematologic Response in MB CML (Sponsor's Figure 5.2A [6 month Efficacy Update]).

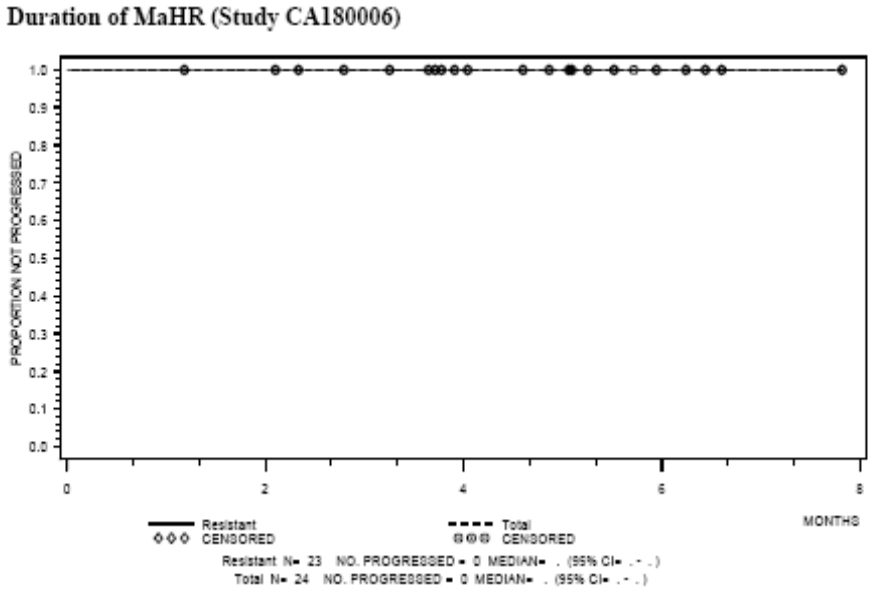


Figure 4. Duration of Major Hematologic Response in LB CML (Sponsor's Figure 6.2A [6 month Efficacy Update]).

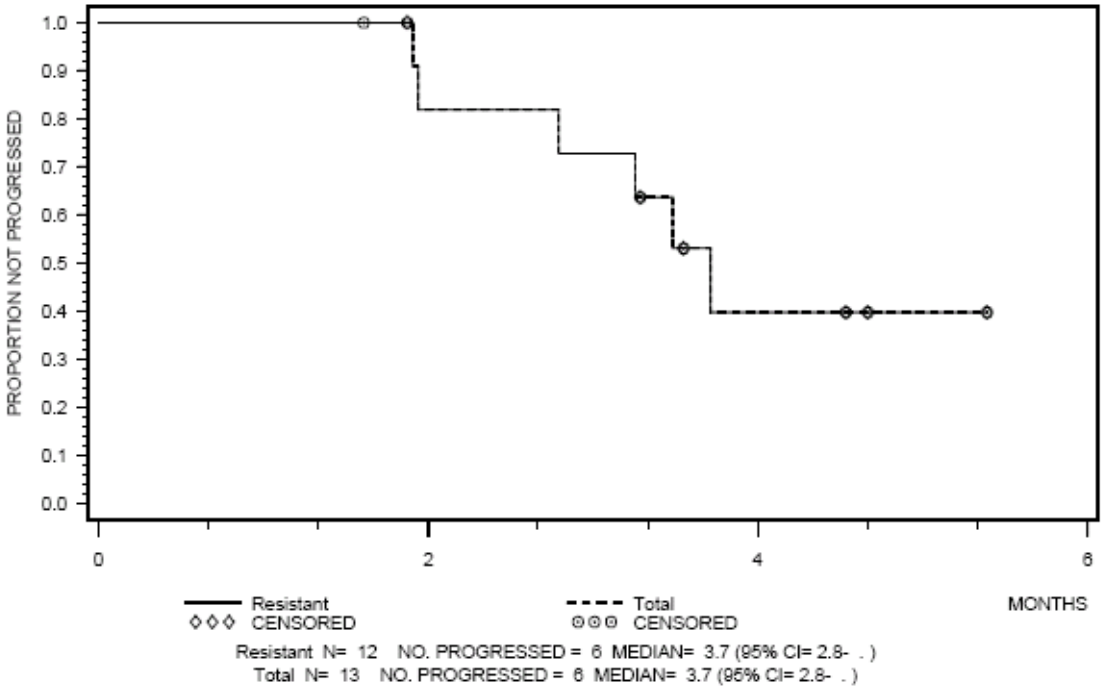
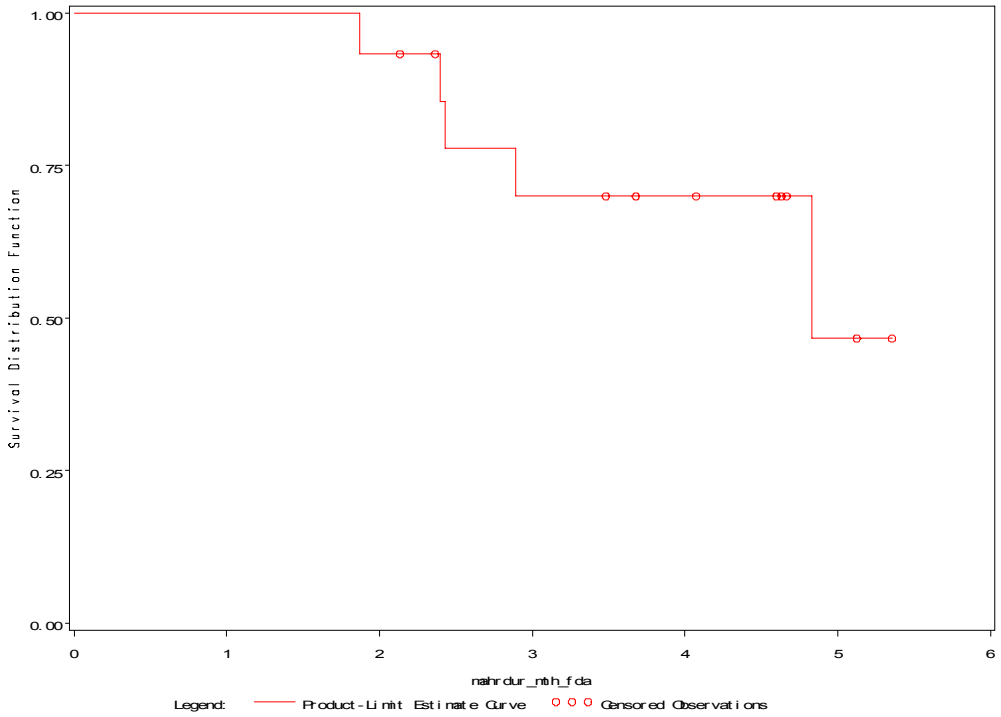


Figure 5. Duration of Major Hematologic Response in Ph$^+$ ALL (FDA adjudicated data)



3.6 Imatinib intolerant and imatinib-resistant populations

Except for Study CA180013 which enrolled 27% patients with imatinib-intolerant CP CML, the enrollment of imatinib intolerant patients in all other studies was 10% or less. The imatinib intolerant population achieved higher cytogenetic and hematologic response rates than the imatinib-resistant CML population. The numbers of imatinib intolerant subjects were small in the other studies and appear insufficient to draw valid conclusions. This analysis is shown in Table 9 below.

Table 9. Summary of MCyR and CHR Responses in Imatinib Intolerant and Imatinib-Resistant Subjects in All Studies – All Treated Subjects

Disease phase	**Intolerant N = 94**		**Resistant N = 457**	
	MCyR	**CHR**	**MCyR**	**CHR**
Chronic	49/67 (73%)	65/67 (97%)	62/181 (34%)	161/181 (89%)
Accelerated	2/12 (17%)	3/12 (25%)	34/106 (32%)	37/106 (35%)
Myeloid Blast	2/7 (29%)	1/7 (14%)	28/90 (31%)	20/90 (22%)
Lymphoid Blast/ Ph+ ALL	6/8 (75%)	3/8 (38%)	44/80 (55%)	23/80 (29%)
Total (all phases)	59/94 (63%)	72/94 (77%)	168/457 (37%)	241/457 (53%)

3.7 Efficacy responses based on age, race and gender

There were no response differences between subjects 65 years of age and younger and subjects over 65, and between females and males. No conclusions can be drawn about response rates in subjects of races other than White, since they represented only about 10% of the total subject population (47 of 443).

3.8 Study CA 180017 (chronic phase CML)

Study CA180017 is a randomized, open-label, multi-center, non-comparative study of dasatinib 70 mg BID and imatinib 400 mg BID in patients with chronic phase CML and imatinib resistance defined as above. Patients were randomized in a 2:1 ratio to receive either dasatinib or imatinib at above doses administered continuously. Thirty-six patients with at least 12 weeks of follow-up are included in this report, 22 randomized to dasatinib and 14 to imatinib.

Dasatinib dose escalations were allowed for disease progression or lack of response, and dose reductions to manage drug toxicity. Imatinib dose escalation was not allowed; dose reduction to 600 mg daily was allowed. Crossover to alternative treatment was permitted for lack of response, disease progression or persistent intolerance. Cytogenetic assessment was to be performed every 12 weeks and at the time of crossover; hematologic assessment was performed weekly up to 12 weeks and biweekly thereafter. The primary efficacy endpoint was MCyR at 12 weeks.

Subjects were well balanced with respect to age, race, ECOG performance status, and prior therapy, except for bone marrow transplant (23% in the dasatinib arm and 0% in the imatinib arm). The male:female ratio was approximately 1:1 in the dasatinib group, while 93% of imatinib patients were female.

At the time of report, 11/14 imatinib arm subjects had crossed over to the dasatinib arm (because of intolerance [6 patients], failure to achieve MCyR [4], and disease progression [1]); 3/14 (21%) remain in the treatment arm. Twenty of 22 patients in the dasatinib arm remain in the treatment arm (91%); 2/22 crossed over to the imatinib arm (because of intolerance [1] and disease progression [1]).

Preliminary efficacy results include a MCyR of 45% in the dasatinib arm and 21% in the imatinib arm.

3.9 Efficacy Conclusions

The following efficacy conclusions include data from all patients treated with dasatinib on the five studies described above.

1. Dasatinib treatment results in hematologic and cytogenetic responses in patients with all phases of CML and of Philadelphia chromosome-positive ALL who are resistant to or intolerant of imatinib mesylate, as shown by the results of one

Phase 1 dose escalation study and of five Phase 2 studies in which 551 patients were enrolled and treated.

2. An effective starting dose of orally administered dasatinib is 70 mg BID, as determined in a Phase 1 dose escalation study. Lower doses of dasatinib, such as 50 mg BID and 105 mg QD, may be as effective as 70 mg BID when tested in chronic phase CML subjects and may result in less frequent dose interruptions and dose reductions. All Phase 2 trials were carried out using continuous 70 mg BID dasatinib dosing.

3. Dasatinib treatment of patients with CP CML (N = 248) resulted in a 45% major cytogenetic response rate (MCyR), the primary efficacy endpoint, and a 91% complete hematologic response rate (CHR), a secondary efficacy endpoint. The median time to MCyR was 85 days, and to CHR, 16 days. Too few progression events have occurred to adequately estimate the duration of the responses. None of the subjects who achieved a MCyR had progressed.

4. Dasatinib treatment of patients with AP CML (N = 118) resulted in a 74% overall hematologic response (OHR) rate and a 54% major hematological response rate (MaHR, complete hematologic response + no evidence of leukemia), the primary efficacy endpoints, and a 31% MCyR, a secondary endpoint. The median time to MaHR was 57 days. Duration of MaHR cannot be estimated at the minimum 6-month follow-up.

5. Dasatinib treatment of patients with MB CML (N = 97) resulted in a 48% OHR and a 29% MaHR, the primary efficacy endpoints, and a 31% MCyR, a secondary endpoint. The median time to MaHR was 57 days. Duration of MaHR cannot be estimated at the minimum 6-month follow-up.

6. Dasatinib treatment of patients with LB CML and patients with Ph^+ ALL (N = 88) resulted in an overall OHR of 38% and a MaHR of 34%, primary efficacy endpoints, and a 57% MCyR, a secondary endpoint. Among lymphoid blast CML patients, the median time to MaHR was 35 days, and to OHR, 33 days. At the 6-month minimum follow-up, 83% of patients had discontinued dasatinib, mainly because of disease progression and deaths. Among Ph^+ ALL patients, the median time to MaHR was 57 days, and to OHR, 35 days. At the 6-month minimum follow-up, 67% of patients discontinued dasatinib, mainly because of disease progression, deaths, and dasatinib toxicity.

7. There were no age- or gender-related response differences.

8. Most cytogenetic and hematologic responses occurred during the first 3 months of dasatinib treatment; few additional responses occurred during the second 3 months of treatment.

9. Cytogenetic and hematologic responses among subjects with all phases of CML and with Ph+ ALL were associated with lower incidence of disease progression. This association was the strongest in the CP CML, AP CML, and MB CML subjects, and weaker among LB CML and Ph^+ ALL subjects.

4. Safety

4.1 Population Database

A total of 489 patients are included in the safety database of patients with all phases of CML and Ph + ALL who were treated at a starting dose of 70 mg BID (the phase 2 dose). This included 214 patients with chronic phase CML, 110 patients with accelerated phase CML, 84 patients with myeloid blast CML, and 81 patients with lymphoid blast CML or Ph+ ALL. Data analyzed were collected on 5 single-arm trials, and one small (n=36) randomized trial in chronic phase patients, where dasatinib was compared to high dose imatinib (400 mg bid).

4.2 Subject Deaths

All deaths within 30 days of drug discontinuation are reported here, regardless of the dasatinib dose. Each subject is listed once. One additional death occurring 33 days after drug discontinuation is also listed here as it was reported to be drug-related. Deaths are summarized in Table 10.

There were 67 subject deaths (12%) among patients receiving dasatinib across all CML/ Ph^+ ALL studies. On-study death occurred in 2% of chronic phase patients, 3% of accelerated phase patients, 31% of myeloid blast patients, and 34% of lymphoid blast/ Ph^+ ALL patients.

Table 10. Subject Deaths on Study or Within 30 days of Discontinuation*

	Reported cause of death			
Disease Status	**PD** only**	**Infection**	**Bleeding**	**Other**
Chronic	1	1	2	1
Accelerated	0	2	0	2
Myeloid Blast	18	6	3	3
Lymphoid Blast/ Ph^+ ALL	11	11	2	4

* one patient with myeloid blast disease died 33 days after discontinuing drug but his death was considered drug related.
**progressive disease.

Causes of death listed as “other” included: renal failure, ARDS/tumor lysis syndrome, “shock”, organ failure (and progressive disease (PD)), global cardiac insufficiency, constrictive pericarditis, respiratory failure (in the setting of PD), hypoxia/pleural effusion, and “damaged general status”.

One death (reportedly due to shock) occurred suddenly and unexpectedly. The patient was a 51-year-old male who began study therapy on 4/13/05. Five days later, he went to the ER with syncope and weakness. He was noted to be short of breath, hypotensive and tachycardic. He had recurrent syncope in the emergency room and became pulseless. Resuscitation efforts were not successful. Electrocardiograms performed at that time revealed normal QT/QTc intervals. Septic shock was considered the likely cause of death in light of a diagnosis of Clostridial bacteremia two weeks earlier.

4.3 Dose reductions and interruptions

Dose reductions, interruptions, and drug discontinuations occurring due to adverse events in the safety population are summarized by disease stage in Table 11 below.

Table 11. Dose Reductions, Interruptions and Drug Discontinuations in Patients Initially Receiving 70 mg bid of Dasatinib

Disease Phase	Dose reduction	Dose interruption	Drug Discontinued
Chronic, n (%)	19 (9%)	118 (55%)	13 (6%)
Accelerated, n (%)	10 (9%)	61 (55%)	5 (5%)
Myeloid Blast, n (%)	8 (10%)	39 (46%)	23 (27%)
Lymphoid Blast/Ph + ALL, n (%)	4 (5%)	32 (40%)	28 (35%)

4.4 Adverse Events

Nearly all patients (99%) had at least one adverse event. Three hundred and twenty-four (66%) patients experienced at least one grade 3/4 adverse event on study. Gastrointestinal symptoms such as diarrhea, nausea and vomiting were common across all phases of disease. Other frequent adverse events across all stages of disease include headache, fatigue, dyspnea, pyrexia, rash and fluid retention events. The most common adverse events pooled across disease phases are summarized in Table 12.

While thrombocytopenia, anemia, and neutropenia are listed in this table because they met the 10% cutoff incidence, reporting of these hematologic abnormalities as adverse events is incomplete. A more accurate picture of bone marrow toxicity is shown in Table 16.

Table 12. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Dasatinib-Treated Subjects with CML and Ph + ALL (n=489)

Adverse Event	All Grades (%)	Grade 3/4 (%)
Diarrhea	229 (47)	25 (5)
Pyrexia	192 (39)	33 (7)
Headache	184 (38)	13 (3)
Fatigue	167 (34)	16 (3)
Nausea	152 (31)	9 (2)
Dyspnea	141 (29)	29 (6)
Rash/Exanthem	140 (29)	7 (1)
Peripheral Edema	125 (26)	1 (0.2)
Abdominal pain	122 (25)	11 (2)
Cough	116 (24)	4 (0.8)
Asthenia	109 (22)	18 (4)
Vomiting	107 (22)	7 (1)
Thrombocytopenia	90 (18)	82 (17)
Pleural Effusion	81 (17)	22 (4)
Anorexia	73 (15)	7 (1)
Weight Decreased	70 (14)	3 (0.6)
Bone pain	66 (13)	10 (2)
Constipation	60 (12)	1 (0.2)
Epistaxis	56 (11)	3 (0.6)
Arthralgia	56 (11)	4 (0.8)
Anemia	55 (11)	34 (7)
Dizziness	55 (11)	1 (0.2)
Myalgia	54 (11)	4 (0.8)
Neutropenia	52 (11)	50 (10)
Febrile Neutropenia	49 (10)	47 (10)
Petechiae	49 (10)	1 (0.2)
Weight Increased	49 (10)	0 (0)
Chills	47 (10)	1 (0.2)

4.5 Cardiac events:

4.51 Congestive heart failure(CHF) /ventricular dysfunction

Patients with significant cardiac histories including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias or QTc prolongation were excluded from dasatinib trials.

Twenty patients (4%) in the safety population experienced cardiac dysfunction events. Twelve were reported as grade 3 and one as grade 4, the remainder were grade 2. There was one death related to cardiac failure: The patient was a 28 year old man heavily pretreated for CML including prior anthracyclines who had baseline “minor” mitral valve insufficiency and pericardial effusion but a normal baseline ejection fraction (50-55%). He began study drug on February 4, 2005. The patient was hospitalized for acute

cholecystitis on February 21, 2005 and discontinued treatment at that time. He also was noted to have febrile pancytopenia. On February 25, his left ventricular ejection fraction was 45% and he was described as having dilated cardiomyopathy and pulmonary arterial hypertension, both felt to be related to study drug. On March 18, 2005 his ejection fraction was 30%. He died due to global cardiac insufficiency and febrile pancytopenia on March 25.

Median time from start of study drug to onset of ventricular dysfunction/cardiac failure in study patients was 19 days (range 3-104).

Fourteen of the 20 events were reported as SAEs. Four events led to drug discontinuation, 9 led to drug interruption, 1 led to dose reduction; dose modification did not occur in 6 events. Cardiac failure events occurred in patients with all phases of CML/ Ph+ ALL.

4.52 QT prolongation

Pre-clinical data suggest that dasatinib may have the potential to cause QT prolongation. Prolonged QT, listed as either an adverse event or based on ECG data, was examined in all the CML trials.

Nine patients (1.8%) had at least one episode of QT prolongation reported as an adverse event while receiving dasatinib. These patients are summarized by worst grade in Table 13.

Reviewer's Table 13. QT prolongation: # Patients by Worst Grade (NCI CTCAE v.3)

	Grade1/2	Grade 3	Grade 4
QT prolongation, n	3	5	1

The grade 4 event (QTc > 500 msec with life-threatening signs/symptoms) was a 70 year old female with a prior history of hypertension and cardiac palpitations who developed symptoms of congestive heart failure six days after the resolution of QT prolongation. ECGs taken near the time of the CHF event and subsequent to the event showed QTc values of 463 msec or less (baseline ≤ 453 msec).

The drug was discontinued as a result of the QT event in one patient, interrupted in four patients and dose reduced in one patient; no action was taken with respect to study drug in 3 patients (all with grade 1 events). One patient with normal baseline QTc developed QTc prolongation after 8 days of dasatinib, with several readings over 500 msec and a 60 msec increase from baseline. Dasatinib was interrupted and restarted 2 days later at 50 mg bid. Subsequent ECGs did not show QTc prolongation.

An additional patient had a machine calculated QTcB (QT corrected by the Bazett method) of 537 msec following his first dose of dasatinib. His treatment was interrupted and resumed a week later at 50 mg bid. At this dose, he had a machine-reported QTcB of 606 msec; treatment was again held and restarted 4 days later at 40 mg bid. No further

events were reported. Subsequent ECG readings by the central lab did not confirm these findings; the highest QTcB value was 498 msec.

Fourteen patients (2.8%) had QTc prolongation as reported by the central ECG laboratory while on-study. Four of these patients had at least one abnormal baseline value; the remaining ten had on-treatment abnormalities only. Two of these patients also had QTc prolongation reported as an adverse event.

One patient was reported to have ventricular tachycardia. This patient, who had no prior cardiac history, experienced syncope. Holter monitoring showed episodic non-sustained ventricular tachycardia (3-5 beat runs). There was no evidence of QTc prolongation.

No episodes of torsades de pointes were reported.

4.53 Myocardial infarction

Six patients (1.2%) experienced myocardial infarction across all studies. All but one of the patients had a prior cardiac history or significant risk factors including hypertension, diabetes, hyperlipidemia, prior history of myocardial infarction and chemotherapy-induced cardiomyopathy. All events were grade 3 (two) or 4 (four). Patients were aged 45-86 years, half were male. The drug was interrupted in four cases; there were no dose reductions or discontinuations.

4.6 Bleeding Events

In addition to the disease-related risk of bleeding events in CML patients, a possible drug-related mechanism of platelet dysfunction was identified in nonclinical studies. *In vitro* data demonstrated that dasatinib inhibits collagen-induced platelet aggregation in human, cynomolgus monkey, and rat platelet-rich plasma, and that dasatinib reduced human whole blood clot strength.

Bleeding events of any type occurred in 34% of patients. Grade 3/4 bleeding events occurred in 10% of patients. Epistaxis was the most common single event, occurring in 11% of patients. Gastrointestinal bleeding events occurred in 10% of dasatinib-treated patients; grade 3/4 events occurred in 6%. Other sites included gingival, conjunctival, CNS, vaginal, urinary tract, eye, and respiratory tract.

4.6.1 CNS Hemorrhage
Six patients experienced CNS hemorrhage while receiving dasatinib. Five of these patients had fatal CNS hemorrhages. These events are summarized in Table 14.

Table 14. Bleeding Events

Bleeding Event	Grade	Disease Phase	Platelet Count	Additional Information
Intracranial hemorrhage	5	Chronic	14,000	
Cerebral hemorrhage	5	Lymphoid Blast	1,000	
Cerebral hemorrhage	5	Myeloid Blast	9,000	
Intracranial hemorrhage	5	Myeloid Blast	21,000 (3days prior)	Platelet count 10,000 at start of study
Cerebral hemorrhage	5	Myeloid Blast	10,000	Pre-treatment platelets 14,000; Head injury d/t fall following first dasatinib dose
Subdural hematoma	3	Ph + ALL	56,000	Resolved after surgical tx; pt. resumed dasatinib

4.7 Fluid Retention Events other than CHF

Overall, 194 (40%) patients experienced edema of any type, and 93 (19%) patients experienced pleural and/or pericardial effusions. The breakdown of the most common event categories and worst grade is summarized in Table 15 below.

Table 15. Fluid Retention Other Than CHF

Event	All Grades	Grade 3/4
Peripheral edema	125 (26%)	1 (0.2%)
Pleural effusion	81 (17%)	22 (5%)
Periorbital edema	34 (7%)	0 (0%)
Face edema	20 (4%)	0 (0)%
Pericardial effusion	18 (4%)	2 (0.4%)
Pulmonary edema	15 (3%)	2 (0.4%)

4.8 Hematologic Laboratory Abnormalities by Disease Status

Many subjects with advanced disease had baseline hematologic laboratory abnormalities. Across all disease phases, the percent of patients experiencing grade 3/4 neutropenia, thrombocytopenia, and anemia worsened with treatment. Grade 3/4 hematologic abnormalities at baseline and on treatment are summarized below for patients enrolled on the single-arm phase 2 studies in chronic phase, accelerated phase, myeloid blast phase and lymphoid blast/Ph+ ALL.

Table 16. Grade 3/4 Hematologic Laboratory Abnormalities in Patients Receiving Dasatinib

Disease Phase	Neutropenia (% of Patients with)	Thrombocytopenia (% of Patients with)	Anemia (% of Patients with)
Chronic			
--At Baseline	2%	2%	2%
--On Treatment	45%	46%	18%
Accelerated			
--At Baseline	7%	23%	5%
--On Treatment	76%	79%	66%
Myeloid Blast			
--At Baseline	24%	45%	15%
--On Treatment	79%	82%	66%
Lymphoid Blast/Ph+ ALL			
--At Baseline	33%	58%	3%
--On Treatment	76%	78%	49%

4.9 Safety Summary

Major toxicities associated with dasatinib use include:

- Gastrointestinal
  Diarrhea, nausea and vomiting were common adverse events in all phases of disease.

- Myelosuppression
  While many patients had baseline hematologic abnormalities, especially in advanced disease, the incidence of grade 3/4 neutropenia, thrombocytopenia and anemia all increased with dasatinib use.

- Fluid retention events
  - Pleural/pericardial effusions reported in 19%
  - Edema (peripheral, periorbital and others) reported in 40%

- Congestive heart failure/ventricular dysfunction
  Four percent of patients on study experienced cardiac dysfunction, with one on-study death due to congestive heart failure.

- Prolongation of QTc interval
  Approximately 2-3% of patients had QTc prolongation reported as an adverse event, reported by the central laboratory reading ECGs, or both. There were no episodes of torsades de pointes reported.

- Bleeding events
  Dasatinib caused platelet dysfunction *in vitro*. Bleeding events were common on dasatinib studies, occurring in approximately one-third of patients. Sites of bleeding included superficial mucosal, gastrointestinal, genitourinary and CNS. CNS hemorrhages occurred in 6 patients and were fatal in 5. Three of the six patients had platelet counts > 10,000/mm^3.