CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-986 & 22-072

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	21-986; 22-072
Submission Date:	28 December 2005
Brand Name:	SPRYCEL ®
Generic Name:	dasatinib (BMS-354825)
Formulation:	20 mg, 50 mg and 70 mg film coated tablets
OCP Reviewers:	Julie M. Bullock, Pharm.D. Angela Men, M.D., Ph.D. Carol Noory, Ph.D.
Pharmacometrics Reviewers:	Angela Men, M.D., Ph.D. Roshni Ramchandani, Ph.D.
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OCP Team Leader:	Brian Booth, Ph.D.
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OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Bristol Meyers Squibb
Submission Type; Code:	Original NDA; 000
Dosing regimen:	70 mg Q12 hours
Indications	NDA 21-986: chronic myeloid leukemia (CML) NDA 22-072: Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)

OCP Briefing held on 25 May 2006 attended by: Julie Bullock, Angela Men, Carol Noory, Leslie Kenna, Brian Booth, Roshni Ramchandani, Gene Williams, Sohpia Abraham, Nam Atiqur Rahman, Shiew Mei Huang, Edward Kaminskas, Vikki Goodman, Michael Brave, Arzu Selen, Hank Malinowski, John Hunt, Christine Garnett, Donah Tran, Kofi Kumi, Mehul Mehta, Lei Zhang.

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1 EXECUTIVE SUMMARY

Dasatinib is an inhibitor of multiple oncogenic kinases that is being developed for oral use in the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). Studies in healthy volunteers and in patients support the development of dasatinib.

The applicant has conducted several phase 1 studies in healthy volunteers and patients with chronic, accelerated, and blast phase CML and Ph+ ALL to evaluate the safety and pharmacokinetics of dasatinib and its metabolites. Dasatinib is orally available with absorption peaking at approximately 1 hour. The pharmacokinetics of dasatinib are dose proportional and there are no significant differences between the pharmacokinetics in healthy volunteers and patients. After administration of radio-labeled dasatinib, 85% percent of the total radioactivity was eliminated in the feces, of which 19% was unchanged drug. The primary pathway of elimination of dasatinib is by oxidative metabolism via CYP3A4, and flavin containing monooxygenase 3 (FMO3). Only one active metabolite was identified (M4) and its contribution to the pharmacology of dasatinib is minimal. Drug-drug interaction studies indicate an 80% reduction in dasatinib exposure when co-administered with rifampin. Marked decreases in dasatinib exposure were also seen with co-administration with gastric pH modulators such as famotidine and OTC antacids. Dasatinib is considered to be a time-dependent inhibitor of CYP3A4 and increased the concentrations of simvastatin (a CYP3A4 substrate) when both drugs were administered concomitantly.

In addition, the applicant has also conducted five phase 2 studies in patients with CML and Ph+ ALL. Using logistic regression, pharmacokinetic and pharmacodynamic relationships for effectiveness (cytogenetic response, hematologic response) and toxicity in chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients were analyzed from the phase 2 data. A significant relationship between major cytogenetic response rate and average daily dose was identified in chronic CML studies. There was no significant correlation identified between the trough level of dasatinib and the probability of effectiveness and severe toxicity. A dose-response relationship was not discerned, this result may have occurred because about 50% of the patients were administrated with a combination of 70mg, 50 mg, 40 mg and/or 100 mg BID. In both chronic and advanced phase studies, about 50% and 30% of patients, respectively, needed a dose reduction or interruption because of severe toxicities.

1.1 RECOMMENDATIONS

Recommendations to the sponsor

A. Dosing adjustments for patients on CYP3A4 inducers
There was an approximate 80% decrease in the AUC of dasatinib when dasatinib was concomitantly given with rifampin. To adjust for this decrease, we recommended that the dasatinib dose be increased when taken with potent CYP3A4 inducers. (refer to Section 3 - Labeling).

B. Dosing adjustments for patients on CYP3A4 inhibitors
Based on preliminary data there is a 4 fold and 5 fold increase in the Cmax and AUC, respectively of dasatinib when given concomitantly with ketoconazole. To adjust for this increase, we recommend that the dasatinib dose be decreased to 20mg BID when co-administered with potent CYP3A4 inhibitors. (refer to Section 3 - Labeling)

C. Biowaiver request for 70mg tablet granted

Elimination characteristics, available safety and efficacy data for the relevant clinical dosing regimen, the *in vitro* dissolution data and formulation proportionality between the strengths, support approval of the sponsor's request for a waiver of the requirement to conduct a bioequivalence study for dasatinib 70 mg strength tablets.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

1.2 PHASE IV COMMITMENTS

A. Hepatic impairment study
Submit the study report for the hepatic impairment study when completed.

B. Ketoconazole study
Submit completed study report for the ongoing ketoconazole drug-drug interaction study.

Reviewer: Julie M. Bullock, Pharm.D.
Division of Clinical Pharmacology 5

Acting Team Leader: Brian Booth, Ph.D.
Division of Clinical Pharmacology 5

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Acting TL - **B Booth**, PM TL - **J Gobbaru;** Acting DDD - **A Rahman;**
Acting DD - **SM Huang**

1.3 CLINICAL PHARMACOLOGY SUMMARY

Dasatinib is available as 20 mg, 50 mg, and 70 mg immediate release film-coated tablets. All three strengths are manufactured from a common drug and are proportional in composition with different shapes, sizes and markings. To support the biopharmaceutics portion of the application, the sponsor conducted two bioavailability studies to evaluate the safety, tolerability, pharmacokinetics and the effect of food on dasatinib. These studies were also used to establish the bioequivalence of the 20 mg and 50 mg commercial products to the clinical trial formulations. In vitro bioequivalence was demonstrated for the 70-mg tablet based on linear pharmacokinetics, in vivo dose proportionality, formulation proportionality across strengths, and comparability of the dissolution profiles across the physiological pH range.

Following oral administration, dasatinib is rapidly absorbed with peak concentrations occurring between 0.2 to 6.0 hours after dosing. Dasatinib exhibits linear pharmacokinetics with dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg to 240 mg/day. The half-life of dasatinib is approximately 3-5 hours. There is no significant accumulation of dasatinib after multiple dosing for 8 days. Following a high-fat meal, the dasatinib Cmax decreased by 24% and AUC increased by 14%. These results are not clinically relevant, and therefore dasatinib may be taken without regard to meals.

Twenty-one metabolites are present in the systemic circulation, urine and/or feces following dasatinib administration. Metabolites M4, M20 and M24 were mainly formed by CYP3A4. Metabolite M5 is formed by flavin-containing monooxygenase (FMO3) and M6 is formed by unknown oxidoreductases. The N-dealkylated metabolite M4 (BMS-582691) is the only active metabolite for dasatinib. Metabolite M4's AUC was only 7% of the parent drug, and therefore the contribution of M4 to the overall pharmacology of dasatinib is minor. After a 100mg [^{14}C]-labeled dasatinib dose, parent drug was the major drug-related component in plasma (29%), BMS-606181 (M5) was the major drug-related component in urine (39.8%) and M20 in feces (36.6%). Over 85% of total radioactivity was eliminated in the feces, suggesting minimal renal excretion of dasatinib. The parent drug accounted for 19.1% in the feces. Of the radioactivity recovered in urine, parent drug accounted for 0.12%. Plasma protein binding of dasatinib is 96% and that of the active metabolite (M4) is 93%.

In vitro studies in human liver microsomes indicate that dasatinib was not an inducer but may be a weak inhibitor of CYP3A4. In vivo, concurrent administration of dasatinib with simvastatin (CYP3A4 substrate), caused an increase in the Cmax and AUC of simvastatin by approximately 37% and 20% respectively, indicating that dasatinib is a weak inhibitor of CYP3A4. In addition, administration of dasatinib with rifampin (CYP3A4 inducer) resulted in significant decreases in dasatinib Cmax and AUC by 81% and 82% respectively; therefore co-administration of dasatinib with CYP3A4 inducers should be avoided. A study looking at the effects of ketoconazole (CYP3A4 inhibitor) on dasatinib pharmacokinetics is ongoing.

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. The short term or long-term co-administration of dasatinib with H2 antagonists and potent proton-pump inhibitors is not recommended at this time due to significant decreases in dasatinib exposure (Cmax by 63%; AUC_{0-12} by 60%) when administered concomitantly with the H2 antagonist famotidine.

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 chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients using logistic regression. Data from five phase 2 studies in chronic phase (CA180013 CA180017) and accelerated 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. The relationships between average daily dose and effectiveness and severe toxicities were investigated also. A significant correlation was identified between the cytogenetic response rate vs. average daily dose in chronic CML patients. 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.

2 QUESTION BASED REVIEW

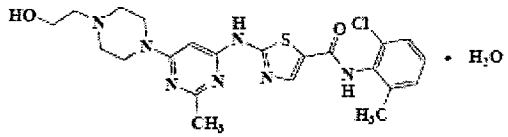
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dasatinib (BMS-354825) is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus.

Physico-chemical properties

- Structural formula:



- Established name: Dasatinib
- Molecular Weight: Monohydrate: 506.02
- Molecular Formula: $C_{22}H_{26}ClN_7O_2S \cdot H2O$
- Chemical Name: *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate

Dasatinib is insoluble in water at 24 ± 4°C. Dasatinib has three ionization constants (pKa) 6.8, 3.1 and 10.8. Dasatinib will be available as tablets for oral administration in strengths of 20, 50 and 70mg.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Dasatinib (BMS-354825) competes with adenosine triphosphate (ATP) for the ATP binding site in the kinase domain of selected protein tyrosine kinases. Dasatinib inhibits five kinases/kinase families including BCR-ABL and SRC family kinases along with other oncogenic kinases such as c-Kit, ephrin (EPH) receptor kinases and PDGFβ receptor.

Dasatinib is indicated for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy.

Dasatinib is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia and lymphoid blast chronic myeloid leukemia with resistance or intolerance to prior therapy.

2.1.3 What are the proposed dosage and route of administration?

The recommended dosage of dasatinib is 140mg/day administered orally in two divided doses (70mg BID) which would be taken in the morning and in the evening. The dose can be decreased to 50mg BID or 40mg BID.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Six studies were completed in healthy volunteers to support the clinical pharmacology and

biopharmaceutics portion of the NDA. The list of healthy volunteer studies can be found in Table 1.

TABLE 1. Studies supporting the clinical pharmacology and biopharmaceutics of dasatinib in healthy volunteers

Study	Question	Study Design	Intervention(s)	Total Treated
CA180009	food effect	3 period, 3 dose, crossover	dasatinib + fasting, dasatinib + high fat meal, dasatinib + low fat meal	54
CA180016	formulation comparability	4 arm, single dose, parallel	2 dasatinib formulations	75
CA180019	ADME	single dose	single dose of 120 μCi of C^{14}-labeled dasatinib	8
CA180020	pH effect	3 period, 6 dose, crossover	dasatinib alone, dasatinib + famotidine, dasatinib + antacid	24
CA180022	simvastatin	2 period, 2 dose, crossover	simvastatin alone, dasatinib + simvastatin	48
CA180032	rifampin	2 period, 2 dose, single-sequence	dasatinib alone, dasatinib + rifampin	20
Total				229

Source: Clinical Pharmacology Summary[19] and Summary of Biopharmaceutics Studies[20]

Five pivotal Phase 2 studies and one supportive Phase 1 study were conducted to support the efficacy claim in CML and Ph+ ALL patients. CA180013 and CA180017 are chronic phase studies. CA180005, CA180006 and CA180015 are accelerated phase studies. A summary of these studies is listed in Table 2.

Pivotal Phase 2 studies:

- **CA180017** was an open-label, randomized, single arm Phase 2 study of dasatinib and imatinib in patients with chronic phase CML who were resistant to imatinib 400 to 600 mg/day. Eligible subjects were randomized in a 2-to-1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID, with continuous daily treatment. The primary endpoint is major cytogenetic response (MCyR) at 12 weeks. The study is ongoing; 36 subjects (22 dasatinib; 14 imatinib) had been randomized as of 30-Jun-2005. Forty-five percent of subjects with chronic CML on therapy with dasatinib achieved a MCyR. Approximately 35% of patients had a dose reduction to 50 mg BID, or lower, due to toxicity. Only sparse PK sampling was obtained in this study.
- **CA180013** was an open-label Phase 2 study of dasatinib in subjects with chronic phase CML resistant to imatinib (> 600 mg/day) or ≤ 600 mg/day with mutations of the BCR-ABL gene, or who were intolerant of imatinib at any dose. Following screening, 186 patients were treated at 39 centers, in which 127 were imatinib-resistant and 59 were imatinib intolerant. Eligible subjects received dasatinib 70 mg continuously twice daily (BID). Dose escalation to 90 mg BID was allowed for subjects who showed evidence of progression or lack of response. Up to 2 dose reductions were allowed for toxicity. Thirty-two percent of imatinib-resistant subjects with chronic phase CML achieved a MCyR. Seventy-three percent of imatinib-intolerant subjects with chronic phase CML achieved a MCyR. Approximately 50% of patients had a dose reduction to 50 mg BID or lower due to toxicity. Sparse PK sampling was obtained in this study.

- **CA180005** was an open-label Phase 2 study in patients with accelerated phase CML with resistance to imatinib mesylate. Out of the total107 treated subjects; 99 were imatinib-resistant and eight were imatinib-intolerant. Dasatinib 70 mg BID was administrated and dose modifications were allowed for management of disease progression or toxicity. Eighty-one percent of imatinib-resistant patients with accelerated phase CML achieved overall hematological response (OHR). Fifty-nine percent of imatinib-resistant subjects with accelerated phase CML achieved a major hematological response (MaHR). Five out of eight imatinib-intolerant patients with accelerated phase CML achieved a MaHR. Approximately 47% of patients had a dose reduction or interruption due to toxicity. Both intensive and sparse PK sampling was collected on Days 1 and 8 in this study.
- **CA180006** was an open-label Phase 2 study in patients with myeloid blast phase CML resistant to or intolerant of imatinib mesylate. Seventy four patients were treated, including 68 who were imatinib-resistant and six who were imatinib-intolerant. Eligible subjects received oral dasatinib at a starting dose of 70 mg BID. Fifty-three percent of imatinib-resistant patients with myeloid blast phase CML achieved OHR. Thirty-four percent of imatinib-resistant patients with myeloid blast phase CML achieved a MaHR. One out of six imatinib-intolerant subjects with myeloid blast phase CML achieved a MaHR. Approximately 20% of patients had a dose reduction due to toxicity. Both intensive and sparse PK sampling was collected on Days 1 and 8 in this study.
- **CA180015** was an open-label Phase 2 study of dasatinib in patients with imatinib-resistant lymphoid blast CML or Ph+ ALL. Seventy eight eligible patients were treated (42 lymphoid blast CML subjects and 36 Ph+ ALL subjects). Eligible subjects received dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed for the management of disease progression or toxicity. Thirty-one percent of imatinib-resistant subjects with lymphoid blast CML achieved MaHR. Forty-two percent of imatinib-resistant subjects with Ph+ ALL subjects achieved MaHR. Thirty-six of imatinib-resistant subjects with lymphoid blast CML achieved OHR. Forty-seven of imatinib-resistant subjects with Ph+ ALL achieved OHR. Approximately 10% patients had a dose reduction due to toxicity. Sparse PK sampling was obtained in this study.

One supportive trial:

- **CA180002** was an open-label, Phase 1, dose-escalation study of dasatinib administered orally to patients with CML and Ph+ ALL who have primary or acquired hematologic resistance to or intolerance to imatinib mesylate. The primary objectives of this study are to determine the maximum tolerated dose (MTD), to define dosing limited toxicity (DLT), and to identify the dosing recommendations for Phase 2 studies. Patients received the following dosing regimens of dasatinib in the fasted state:
    - 15, 30, 50, 75, 105, 140, or 180 mg once daily (15-180 mg/day) for 5 consecutive days followed by 2 non-treatment days every week (Q5D Regimen)
    - 25, 35, 50, or 70 mg twice daily (50-140 mg/day) for 5 consecutive days followed by 2 non-treatment days every week (B5D Regimen)
    - 35, 50, 70, 90, or 120 mg twice daily (70-240 mg/day) continuous dosing

schedule (B7D Regimen)

Treatment with dasatinib resulted in hematologic and cytogenetic response rates in subjects across all phases of CML and in Ph+ ALL, which were similar to or higher than those achieved by the same subjects previously treated with imatinib. Intensive PK sampling of dasatinib and BMS-606181 were obtained in this study.

TABLE 2. Studies Supporting the Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Study (Phase)	Population	Study Design	N
CA180013 (2)	Chronic phase CML (imatinib resistant only)	Open-label, randomized	36 (22 Dasatinib: 14 Imatinib)
CA180017 (2)	Chronic phase CML	Open-label, Single-arm	186
CA180005 (2)	Accelerated phase CML	Open-label, Single-arm	107
CA180006 (2)	Myeloid blast phase CML	Open-label, Single-arm	74
CA180015 (2)	Ph+ALL or lymphoid blast CML	Open-label, Single-arm	78
CA180002 (1)	Chronic, accelerated, blast phase CML and Ph+ ALL	Open-Label, dose escalation	84

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Two phase 2 studies (CA180013 and CA180017) evaluated the activity and safety of dasatinib in subjects with chronic phase CML who were previously treated with imatinib. The primary endpoint in both studies was the rate of major cytogenetic response (MCyR).

Three single-arm, Phase 2 studies were performed to evaluate the activity and safety of dasatinib in advanced stage CML and Ph+ ALL (CA180005, CA180006, and CA180015). The primary endpoints in these studies were the rates of major hematologic response (MaHR) and overall hematologic response (OHR).

At the completion of these studies, the primary endpoint will be overall survival.

The primary response endpoints are listed in Table 3.

TABLE 3. Primary Endpoints in Phase 2 Clinical Trials

Study	Primary Endpoints	Definition
CA180013 **CA180017**	Major Cytogenetic Response (MCyR)	The complete absence of leukemic (Ph+) cells in the bone marrow of CML patients and Ph+ percentage drops to 35 percent or less
CA180005 **CA180006** **CA180015**	Overall Hematologic Response (OHR)	Complete hematologic response + No Evidence of Leukemia + Return to Chronic Phase
	Major Hematologic Response (MaHR)	Complete hematologic response + No Evidence of Leukemia

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The N-dealkylated metabolite M4 (BMS-582691) is the only active metabolite for dasatinib.

The plasma concentrations of BMS-582691 were measured by LC/MS/MS in CA180005 and CA180006. Please see section 2.2.5.1 (Table 10) for the PK parameters of BMS-582691. Metabolite M4's AUC was only 7% of the parent drug, and therefore the contribution of M4 to the overall pharmacology of dasatinib is minor.

2.2.4 Exposure-response

Because the five Phase 2 studies are ongoing and only partial PK information is available, the ability to correlate dose/exposure and response is limited.

Table 4 shows the number of subjects who have intensive and sparse PK sampling, only those subjects with PK data identified by the Agency were included in the exposure-PD analysis. Trough levels on Day 8 were not correlated with the efficacy and toxicity endpoints.

Dose-response relationships were also investigated. The average daily dose was calculated as: total administrated dose/days (including the days of interruption). All patients enrolled in these Phase 2 studies were included in the dose-response analysis.

TABLE 4. Number of Subjects with PK sampling (Agency)

Study	N with intensive PK		N with sparse PK
	Day 1	Day 8	
CA180005	29	25	10
CA180006	24	21	4
CA180013	0	0	133
CA180015	0	0	40
CA180017	0	0	21

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Chronic Phase Studies

C_{trough} vs. Response:

Sparse PK samples were obtained in CA180013 and CA180017. A logistic regression of C_{trough} level of dasatinib on Day 8 versus the probability of MCyR (primary endpoint) was performed (Figure 1). The results of the logistic regression model (Pred Prob-MCyR ~ C_{trough}) are listed in Table 5. The probability of MCyR is significantly different from zero ($p = 0.0342$). However, there is no significant relationship between C_{trough} of dasatinib and probability of MCyR identified in chronic phase studies.

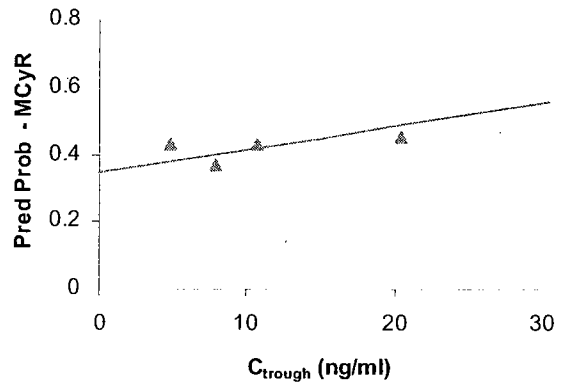


FIGURE 1: Probability of Major Cytogenetic Response (MCyR) vs. C_{trough} in Chronic Phase Studies

TABLE 5. Logistic regression of response (Probability of MCyR) as a function of C_{trough}.

Parameter	Estimate	Pr > ChiSq
Intercept	-0.6252	0.0342
C_{trough}	0.0283	0.2186

Dose vs. Response:

There is a significant relationship between probability of MCyR and average daily doses for patients with chronic CML (p = 0.01) (Figure 2). The median of average daily dose is 100 mg/day for patients. However, because the PD results come from the combination of 70, 50 and 40 mg dosing regimen, the final conclusion regarding this relationship could not be drawn.

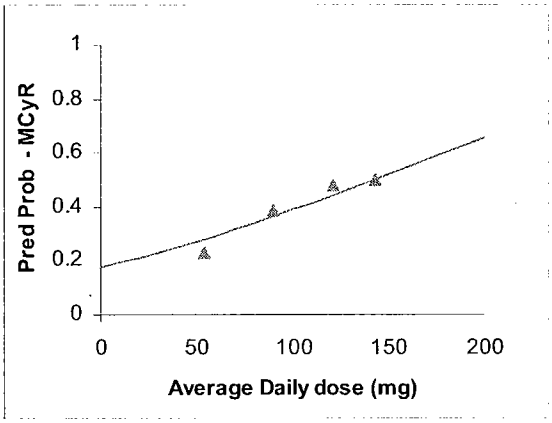


FIGURE 2: Probability of MCyR vs. Average Daily Dose in Chronic Phase Studies

Advanced Phase Studies:

C_{trough} vs. Response:

Both intensive and sparse PK samplings were obtained in CA180005 and CA180006. A linear correlation between exposure (AUC_{0-T}) and C_{trough} of dasatinib is demonstrated in Figure 3. In addition, sparse PK was collected in CA180015. Analysis was performed on the correlation between the C_{trough} level of dasatinib on Day 8 and the primary endpoints, OHR and MaHR (Figures 4 and 5). The results of the logistic regression model (Pred Prob-OHR/MaHR ~ C_{trough}) are listed in Table 6. There are no significant correlations between C_{trough} of dasatinib and OHR and MaHR identified in advanced phase studies.

TABLE 6. Logistic regression of response (Probability of OHR/MaHR) as a function of C_{trough}.

Primary Endpoints	Parameters	Estimate	Pr> ChiSq
OHR	Intercept	0.3585	0.2525
	C_{trough}	0.0127	0.5841
MaHR	Intercept	-0.1922	0.5268
	C_{trough}	-0.0018	0.9703

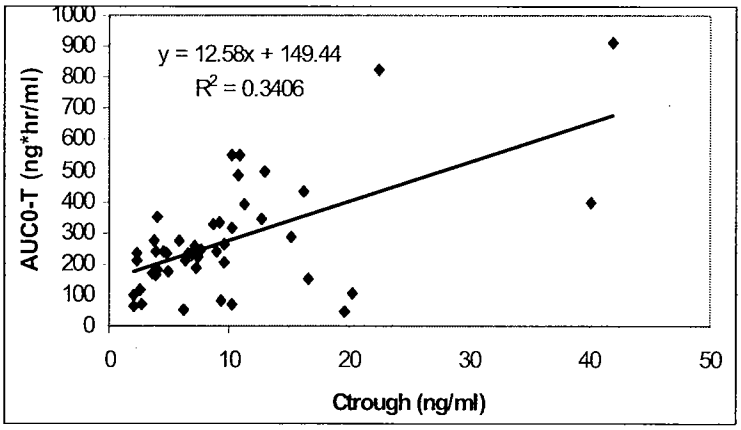


FIGURE 3: AUC_{0-T} vs. C_{trough} (Study CA180005 and CA180006)

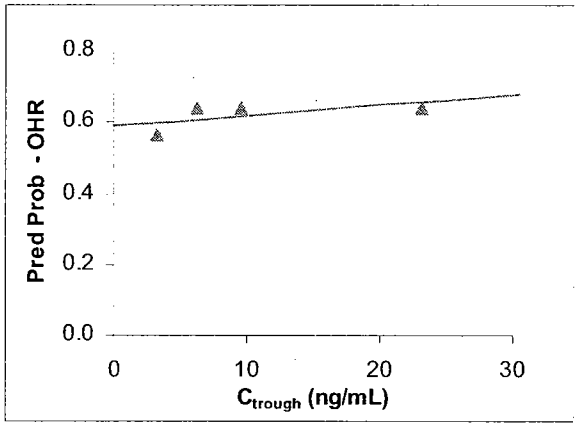


FIGURE 4: Probability of Overall Hematologic Response (OHR) vs. C_{trough} in Advanced Phase Studies

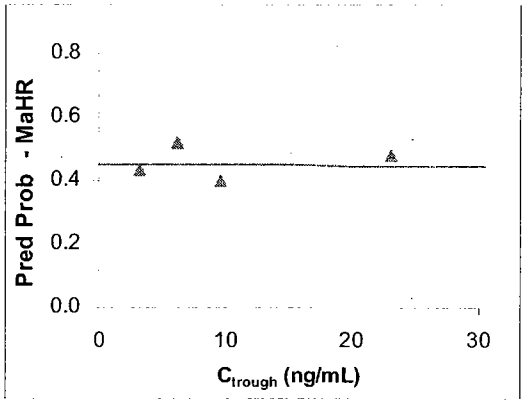


FIGURE 5: Probability of Major Hematologic Response (MaHR) vs. Ctrough in Advanced Phase Studies

Dose vs. Response:

There is no significant difference identified between probability of MaHR/OHR and average daily doses for patients with advanced disease (Figures 6 and 7). The median of average daily dose is 133 mg/day for patients.

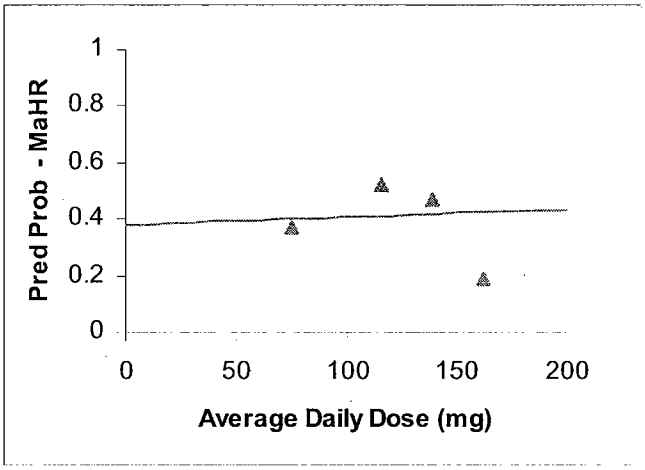


FIGURE 6: Probability of MaHR vs. Average Daily Dose in Advanced Phase Studies

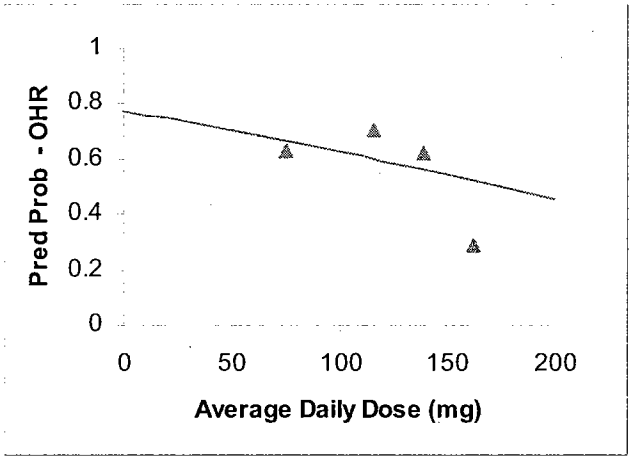


FIGURE 7: Probability of OHR vs. Average Daily Dose in Advanced Phase Studies

In summary, based on the limited data available, no significant correlation between C_{trough} of dasatinib and endpoints of effectiveness could be discerned. A significant relationship between the probability of MCyR and average daily dose was identified in patients with chronic CML. However, no relationship was found between the probability of MaHR/OHR and average daily dose in patients with advanced disease. Further data is being collected in five ongoing Phase 2 studies, and a population PK model is being developed which could help identify a better relationship between exposure and effectiveness.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

All drug-related adverse events (AEs) were pooled across all disease phases for the Phase 2 studies. The most frequently reported AEs (> 10%) included hematological toxicities (neutropenia, thrombocytopenia), gastrointestinal AEs (diarrhea, nausea, and vomiting), fluid

retention events, headache, fatigue, asthenia, rash, dyspnea, and pyrexia.

Based on the frequency of toxicities, the severe toxicities analyzed in the PK-PD analysis included the following:

- Neutropenia assessed by absolute neutrophil count (grade 3 and 4)
- Thrombocytopenia (grade 3 and 4)
- Anemia assessed by red blood cell count (grade 3 and 4)
- Pleural effusion (grade 2, 3 and 4)
- Nausea graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Vomiting graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Diarrhea graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Dyspnea (grade 3 and 4)
- Rash (grade 3 and 4)
- Pyrexia (grade 3 and 4)

Hematologic Toxicities:

There was no significant correlation identified between severe hematologic toxicities and C_{trough} of dasatinib. Probability of grade 3 and 4 hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, were not significantly correlated with C_{trough} of dasatinib, as indicated in Figure 8.

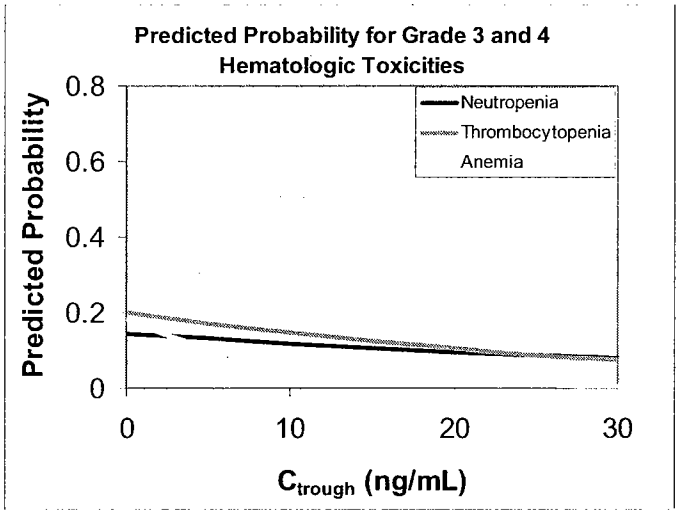


FIGURE 8: Predicted probability of Severe Grade 3/4 Hematologic Toxicities vs. C_{trough}

Gastrointestinal (GI) Toxicities:

Probability of grade 3 and 4 GI toxicities, including nausea, vomiting and diarrhea, did not significantly correlate with C_{trough} of dasatinib, as indicated in Figure 9. Compared with hematologic toxicity, the probability of GI severe toxicity is relatively low.

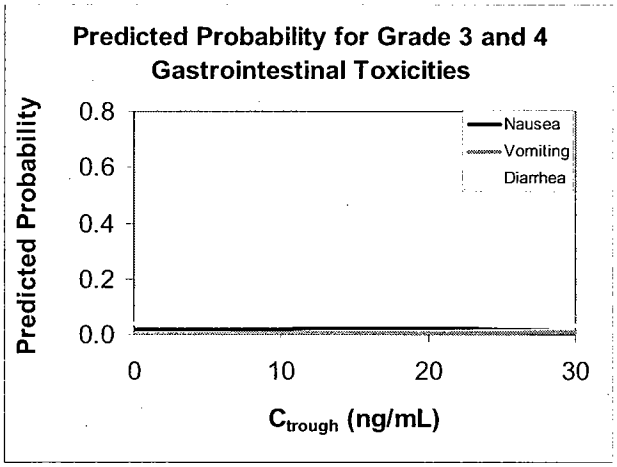


FIGURE 9: Predicted probability of Severe Grade 3/4 Gastrointestinal Toxicities vs. C_{trough}

Edema

Edema is a one of the most frequent toxicities for dasatinib. Grades 2, 3 and 4 are deemed severe clinical toxicities. A trend shows that the probability of pleural effusion increases with increasing C_{trough} of dasatinib. However, no significant correlation was identified from the logistic regression analysis (Figure 10).

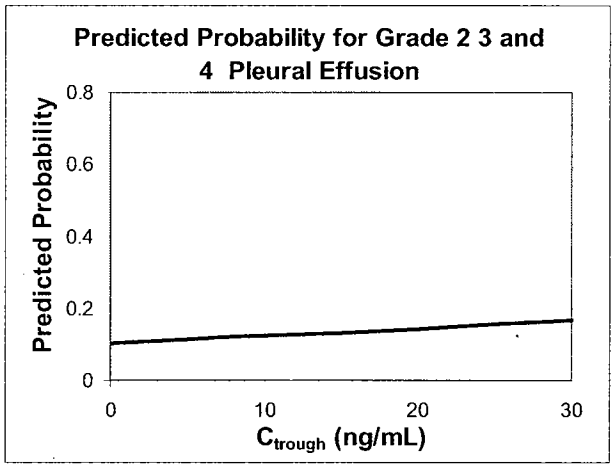


FIGURE 10: Predicted probability of Grade 2/3/4 Pleural effusion vs. C_{trough}

Other Severe Toxicities

Other grade 3 and 4 toxicities, including rash, pyrexia and dyspnea, did not show significant correlation with C_{trough} of dasatinib, as indicated in Figure 11.

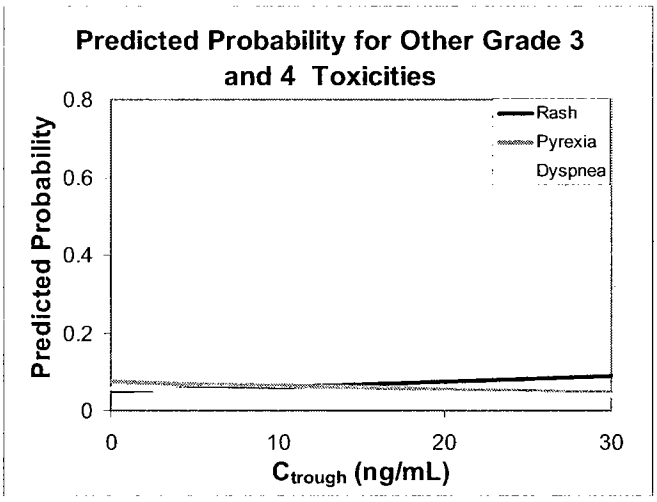


FIGURE 11: Predicted probability of Other Severe Grade 3/4 Toxicities vs. C_{trough}

2.2.4.3 Does this drug prolong the QT or QTc interval?

The Sponsor's and reviewer's analyses suggest that dasatinib does not prolong the QTc interval by more than 10 milliseconds.

Please refer to the Appendix 4.5 for further information.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant reported that the 70 mg BID dosing regimen employed in the Phase 2 trials proved to be acceptable based on both efficacy and safety. However, as listed in Table 7 and 8, approximately 50% of patients required dose adjustment. Fifty percent and 30% of patients in chronic and advanced phase studies, respectively, had dose reductions due to toxicities. No significant relationship was identified between the numbers of patients with and without dose reduction regarding the response (Figures 12, 13 and 14). The starting dose of 50 mg BID may deserve to be investigated in the future and ongoing clinical trials. Such information has been conveyed to the medical officer.

TABLE 7. Percent of Patients in Each Dosing Regimen for Subjects in Chronic Phase Studies (CA180013 and CA180017)

Dose (mg, BID)	Total	% of Patients
40	22	11
50	78	38
70	100	48
90	6	3
drop	2	1
Total	208	100

TABLE 8. Percent of Patients in Each Dosing Regimen for Subjects in Advance Phase Studies (CA18005, CA18006 and CA180015)

Dose (mg, BID)	Total	% of Patients
20	1	0

40	22	8
50	52	20
70	124	48
100	60	23
Drop	1	0
Total	259	100

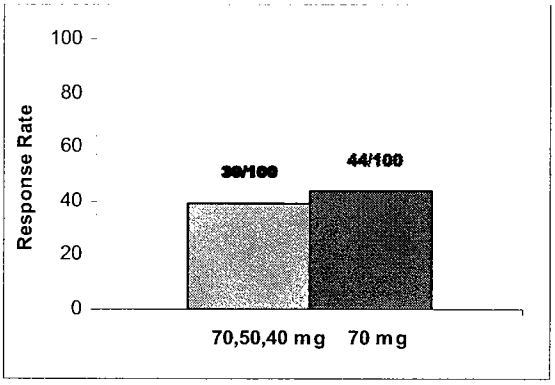


FIGURE 12: Response Rate of MCyR in Chronic Phase Studies

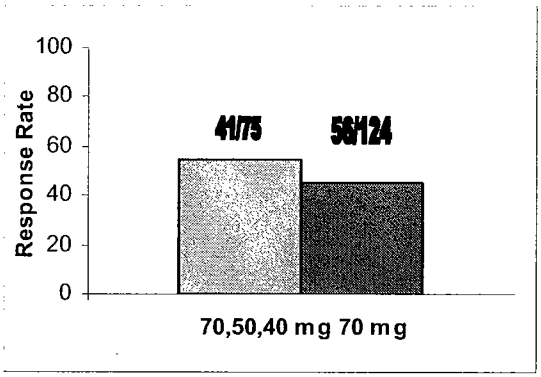


FIGURE 13: Response Rate of MaHR in Advanced Phase Studies

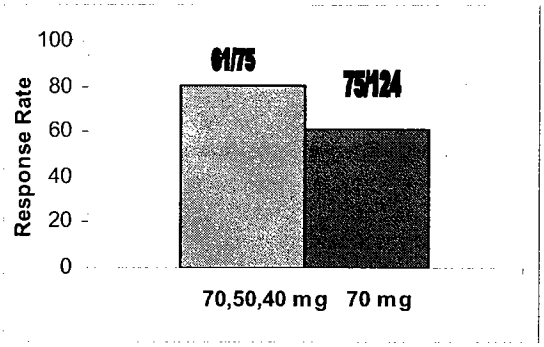


FIGURE 14: Response Rate of OHR in Advanced Phase Studies

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

2.2.5.1 What are the single dose and multiple dose PK parameters?

Figures 15 and 16 show the mean profiles obtained from PK sampling following the multiple doses (at steady-state) in CA180002. Dasatinib exhibits linear pharmacokinetics suggesting a dose proportional increase in AUC and linear elimination characteristics over the dose range of 25 mg BID to 120 mg BID.

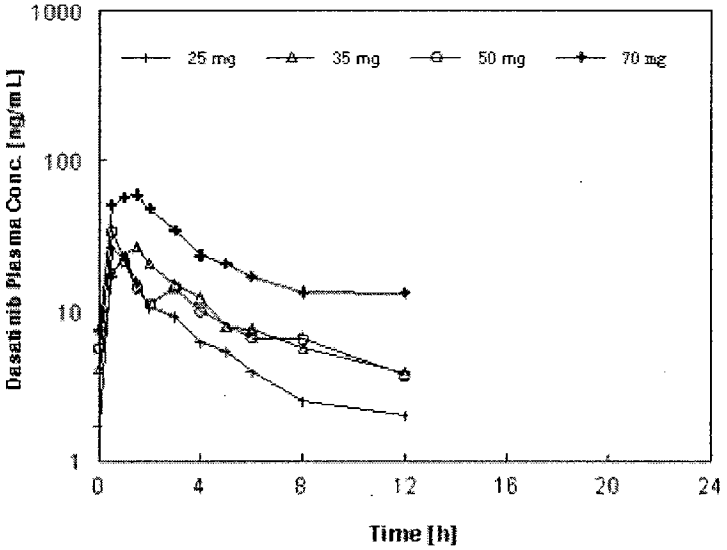


FIGURE 15: Dasatinib Concentration vs. Time Profiles (B5D) on Day 5 for 25-mg, 35-mg, 50-mg and 70-mg BID doses

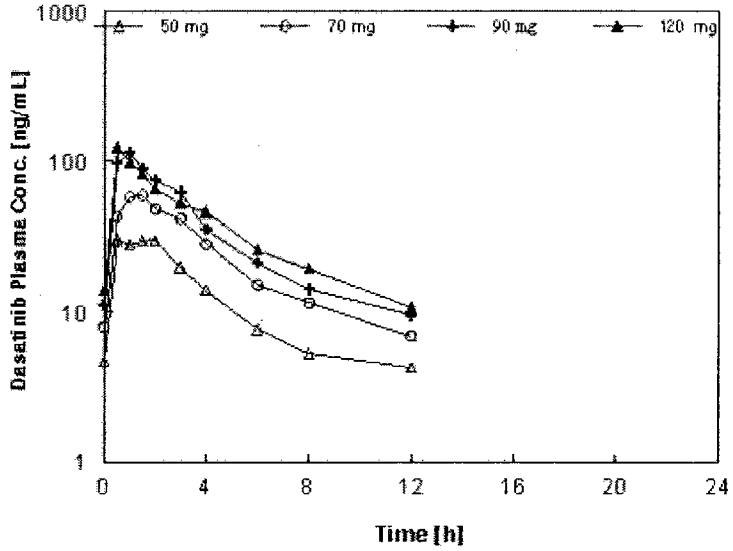


FIGURE 16: Dasatinib Concentration vs. Time Profiles (B7D) on Day 8 for 25-mg, 35-mg, 50-mg and 70-mg BID doses

Pharmacokinetic parameters on Day 1 and Day 8 obtained from studies CA180002 and

CA180005 & CA180006 are listed below in Table 9 for the 70mg BID dose. The values reported for CA180005 and CA180006 are similar to those reported for CA180002. There was no significant difference identified on the exposure of dasatinib between day 1 and day 8, as shown in Figure 17. Based on the half-life of dasatinib, 3-5 hours, the steady state should be reached in 1-2 days.

TABLE 9. PK parameters in subjects with intensive PK sampling

PK Parameters	Statistic	Day 1	Day 8
CA180002 (N=84) 70mg BID			
Cmax (ng/mL)	Geo.mean (CV%)	34.4 (82)	63.2 (75)
AUC0-T (ng*h/mL)	Geo.mean (CV%)	129.8 (74)	236.1 (52)
Tmax (hr)	Median (min, Max)	1.38 (0.5, 6.0)	1.42 (0.17, 3.0)
T1/2 (hr)	Mean (CV%)	3.77 (37)	4.76 (58)
CA180005 and CA180006 70mg BID			
Cmax (ng/mL)	N Geo.mean (CV%)	53 44.9 (75)	47 77.7 (61)
AUC0-T (ng*hr/mL)	N Geo.mean (CV%)	53 138.8 (74)	47 219.1 (65)
Tmax (hr)	N Median (Min,Max)	53 1.00 (0.42, 6.0)	45 1.00 (0.25, 4.75)
T1/2 (hr)	N Mean (CV%)	51 3.41 (40)	45 4.79 (45)

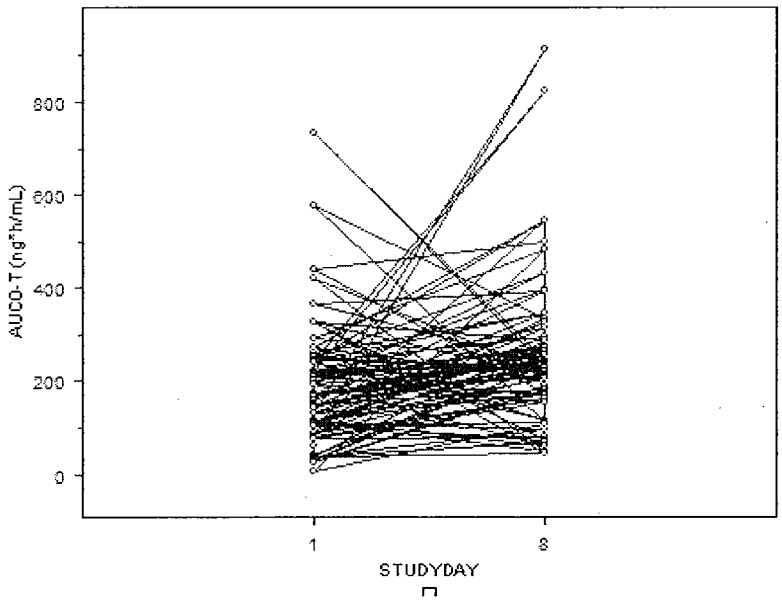


FIGURE 17: Exposure of Dasatinib on Study Day 1 and 8.

The pharmacokinetic parameters of BMS-582691 (M4), the active metabolite of dasatinib are listed in Table 10. The exposure of the N-dealkylated metabolite, BMS-582691 (M4), relative to dasatinib, as calculated by the ratio of geometric mean AUC(0-T), was approximately 4.0% and 5.0% on day 1 and day 8, respectively, in CA180005 and CA180006. The exposure of the metabolite relative to dasatinib in the phase 2 studies is similar to the value observed in the healthy subjects (7.1% on day 1). These data confirm the early indication that BMS-582691 is a minor metabolite of dasatinib. Based on this observation and the *in vitro* activity determined in cellular activity assays, the metabolite BMS-582691 is unlikely to play a major role in the observed pharmacology of dasatinib.

TABLE 10. Day 1 and Day 8 BMS-582691 (M4) PK Parameters in Subjects with Intensive PK Sampling (CA18005 and CA18006) after 70mg BID dosing.

Parameters	Statistic	Day 1	Day 8
Cmax (ng/mL)	N	39	46
	Geo.Mean	2.36	3.53
	CV%	54	61
Tmax (hr)	N	38	44
	Median	1.5	1.5
	Min, Max	0.5,4.3	0.25, 6.07
AUC 0-T (ng*hr/mL)	N	39	45
	Geo.Mean	5.28	10.86
	CV%	95	87
T1/2 (hr)	N	31	38
	Mean	3.78	5.27
	CV%	71	89

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Dasatinib

The majority of the studies with healthy volunteers used a 100mg dasatinib dose. Only one study (the gastric pH modulator study) used a 50mg dasatinib dose and none of the healthy volunteer studies used the proposed dose of 70mg. The PK of dasatinib from the healthy volunteer and patients summarized below in table 11.

In patients and in healthy volunteers dasatinib was absorbed following oral administration in approximately 1 hour. The mean terminal half-life ranged from 3.77 to 5.44 hours in patients and from 3.59 to 4.8 in healthy volunteers.

In general, the PK from patients was similar to that in healthy volunteers at the single dose of 50mg. The Cmax in patients for the B7D regimen was lower (17 ng/mL) than that seen in other patients, and in healthy volunteers (approx 35 ng/mL). The significance of this observation is debatable since the AUC_{0-t} in that regimen was comparable to that of other patients and healthy volunteers. The variability in subjects was greater compared to healthy volunteers but this is to be expected as patients have more potential sources of variability (poly-pharmacy, compliance, disease status, etc.) than healthy subjects.

TABLE 11: Summary pharmacokinetic parameters of dasatinib in studies with healthy volunteers and patients with leukemia

Study (Treatment) Dose (Formulation)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng•h/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
HEALTHY VOLUNTEERS					
CA180009 (N = 49) (Treatment A only) 100 mg (50 mg tablet)	92.09 (50)	304.24 (47)	290.57 (49)	1.00 (0.50, 3.00)	4.84 (2.10)
CA180016 (N = 19) (Treatment D only) 100 mg (50 mg tablet)	63.21 (63)	280.15 (49)	234.36 (56)	1.00 (0.50, 4.00)	4.45 (1.98)
CA180019 (N = 8) 100 mg (solution)	104.47 (29)	313.97 (42)	298.8 (44)	0.50 (0.25, 1.50)	3.59 (1.01)
CA180020 (N = 21) (Treatment A only) 50 mg PM (50 mg tablet)	36.57 (40)	152.13 (34)	137.50 (34)	1.00 (0.50, 4.00)	3.65 (0.60)
CA180020 (N = 22) (Treatment A only) 50 mg AM (50 mg tablet)	41.52 (54)	115.00 (44)	101.67 (45)	1.00 (0.50, 3.00)	4.01 (0.99)

Study (Treatment) Dose (Formulation)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng•h/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
CA180032 (N = 20) (Treatment A, Day 1, only) 100 mg (50 mg tablet)	85.56 (36)	294.05 (33)	280.27 (35)	1.00 (0.50, 3.00)	4.74 (1.58)
Combined[d] (N = 88) 100 mg (50 mg tablet)	83.49 (50)	296.76 (45)	275.13 (48)	1.00 (0.50, 4.00)	4.73 (1.99)
PATIENTS					
CA180002 (n=3) 50mg, Day 1 only Q5D regimen	34.6 (40)		111.4 (46)	1.00 (0.92, 1.08)	3.65 (1.11)
CA180002 (n=3) 50mg, Day 1 only B5D regimen	34.7 (80)		109.1 (68)	1.00 (0.50, 3.00)	5.20 (1.03)
CA180002 (n=8) 50mg, Day 1 only B7D regimen	17.2 (75)		101.2 (47)	2.33 (1.00, 5.07)	3.87 (1.01)
Combined[e] (n=58) 70mg BID, Day 1 only	44.9 [64.1] (75)		138.8 [198.25] (74)	1.00 (0.42, 6.0)	3.41[f] (40.17)

d - Data from CA18009, CA180016, and CA180032 combined.
e - 70mg BID data from CA180005 and CA180006 patients with intensive PK sampling only values in brackets are dose normalized to 100 mg.
f - n = 51

BMS-606181 the N-oxide metabolite (M5)

In general the formation of the in-active metabolite M5 in patients with leukemia was slower compared to healthy volunteers, with maximum concentrations occurring in healthy volunteers at 1.7 hours and in patients at 2-3 hours. The comparability of Cmax and AUC values is difficult because of the high variability in patients. In general, the trend was for patients to exhibit higher Cmax and AUC of M5 than healthy volunteers. In conclusion, there were no significant differences in the pharmacokinetics of metabolite M5 between patients and healthy volunteers.

BMS-582691 the N-dealkylated metabolite (M4)

The comparability of AUC from patients and healthy volunteers for the active metabolite M4 is difficult due to the high variability in patients (95% CV). The rate of absorption was similar in healthy volunteers and patients, with median Tmax occurring at 1.5 hours and mean Cmax of approximately 3-4 ng/mL for both populations. The half-life for both populations was around 3.6 hours.

2.2.5.3 What are the characteristics of drug absorption?

Absorption of dasatinib following oral administration occurred with a median Tmax of 0.5 to 1.5 hours post dose following single and multiple doses in patients and healthy volunteers. The median peak of M5 occurred at 1.75 hours in healthy subjects compared to 2.57 hours in subjects with leukemia.

The relative bioavailability of dasatinib was determined. A 100 mg solution of [^{14}C]-dasatinib was given in the human ADME study. The mean profile for the 100 mg solution is similar to the profiles for the 100 mg tablet. Using the ratio of geometric means, the AUCinf of the tablet (296 ng hr/mL) was compared to the solution (313 ng hr/mL). The relative bioavailability of dasatinib from the 100 mg dose was approximately 95% compared to the solution formulation.

2.2.5.4 What are the characteristics of drug distribution?

Protein Binding

The protein binding of dasatinib was determined in serum from humans at a concentration of 10μM (5060 ng/mL) (**Report 930003190**). The extent of serum protein binding of dasatinib was approximately 93.9% in the humans. A separate study (**Report 930011593**) looked at the protein binding of dasatinib and BMS-582691 (M4) at concentrations of 100 and 500 ng/mL. The protein binding of the parent compound was 96.3 and 96.4% at 100 and 500 ng/mL respectively, and 93.7 and 93.1% for M4 at 100 and 500 ng/mL respectively. This shows that the protein binding of dasatinib and M4 is not concentration dependent from 100 to 500 ng/mL.

Blood/Plasma Ratio (C_{rbc}/C_p)

The extent of blood partitioning of dasatinib was determined in fresh human blood (**Report 930003190**). The blood to plasma concentration ratio (C_{blood}/C_{plasma}) was 1.8 ± 0.1 after 30 min incubation suggesting a weak association with human red blood cells.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Eight healthy male subjects received a single oral dose of 100 mg of [^{14}C]-dasatinib solution containing 120 μCi of total radioactivity (**Study CA180019**). The majority of total radioactivity was recovered in the urine by 24 hours and in the feces by 72 hours. By Day 9 approximately 89% of total radioactivity had been recovered in the urine and feces combined.

Renal elimination of dasatinib is minimal (see Table 12) as the majority of the radioactivity was found in feces (85% of TRA) and the drug undergoes extensive metabolism. Dasatinib was the major drug-related component in human plasma representing 25% of the AUCinf of total radioactivity. BMS-606181 (M5) was a minor inactive metabolite representing only 1% of TRA in plasma.

TABLE 12: Mean cumulative percentages of Total Radioactivity (TRA), Dasatinib, and BMS-606181 (M5) in urine and/or feces.

Analyte	Percentage of Dose			
	Urine		Feces	
	Mean	SD	Mean	SD
TRA	3.58	1.17	85.32	17.28
Dasatinib	0.12	0.05	19.1	ND
BMS-606181 (M5)	1.20	0.49	ND	ND

TRA = total radioactivity; ND = Not determined

In pooled 2-hour plasma samples, **(Report 930011321)** metabolite M20 and its sulfate conjugate (M21) were detected in significant amounts as 12.5% and 9.5% of total radioactivity respectively (Table 13). Multiple metabolites were present at 3-5% of total radioactivity in plasma. In pooled urine samples metabolite M5 was detected in significant amounts as 39.8% of the total radioactivity. In feces, only Metabolite M20 and M23a,b were found in significant amounts as 36.6% and 12.7% of total radioactively respectively. M4 is the only active metabolite for dasatinib and represented only small percentages of total radioactivity in urine and feces.

TABLE 13: Relative percent distribution of radioactive metabolites in pooled plasma, urine and fecal extracts after oral administration of [^{14}C]-dasatinib solution to humans

	% Distribution of Total Radioactivity		
Metabolite ID	Plasma 2 h	Urine 0-168 hr	Feces 0-168 hr
M3a, b[b]	3.3	6.8	
M4 (active)		1.3	3.1
M5	4.5	39.8	
M6	3.6	1.3	10.4

Metabolite ID	% Distribution of Total Radioactivity		
	Plasma 2 h	Urine 0-168 hr	Feces 0-168 hr
M7	3.3	2.1	
M8a	3.4	5.5	
M8b, M23a,b [b,c]	1.4[c]		
M9			1.8
M20	12.5	4.1	36.6
M21	9.5	7.8	
M23a,b[b]			14.7
M24	3.1	6.0	4.7
M30	6.9		
M31	3.6		
M34	1.1	2.3	
M35a	3.6	4.2	
M36		4.4	
M37a,b[b]	4.1	2.5	
Parent	25.5	3.6	22.4
Total	89.4	91.7	93.7

b - In plasma, urine and feces metabolites 3a,b, M23a,b, and M37a,b were positional isomers and were not well resolved on HPLC

c - In plasma Metabolites 8b and M23a,b were not well resolved on HPLC. The % distribution is the total % of all three metabolites

2.2.5.6 What are the characteristics of drug metabolism?

Results from biotransformation investigations **(Report 930011321)** performed on human plasma, urine and fecal samples collected in the ADME study CA180019 indicate that dasatinib is metabolized to at least 21 metabolites that are present in systemic circulation, urine and/or feces. Parent drug was the major drug-related component in plasma, BMS-606181 (M5) was the major drug-related component in urine (39.8%) and M20 in feces (36.6%). The metabolites present in plasma were M20, M21, and M30 and they represented 12.5%, 9.5% and 6.9% of the total plasma radioactivity respectively at the 2 hour time point. The two metabolites BMS-582691 (N-dealkylated [M4]) and BMS-606181 (N-oxide [M5]) were less than 5% of plasma radioactivity. As a percentage of the administered radioactive dose, all of the metabolites identified in the urine were approximately <1%, except for M5 which was 1.4%. In the feces, parent drug and metabolites M6, M23a, b, and M20 were 19.1%, 8.9%, 12.5% and 31.2%, respectively, of the radioactive dose.

The *in vitro* metabolism of dasatinib was studied by incubating 20 μM [^{14}C]-dasatinib with human hepatocytes and liver microsomes. Dasatinib was extensively metabolized in hepatocytes (22%) after a 3-hour incubation period and in human liver microsomes (65%) after a 15-min incubation period.

The major in vitro metabolic pathways involved:

(1) hydroxylation on the chloromethylphenyl group to form metabolites M20 and M24;

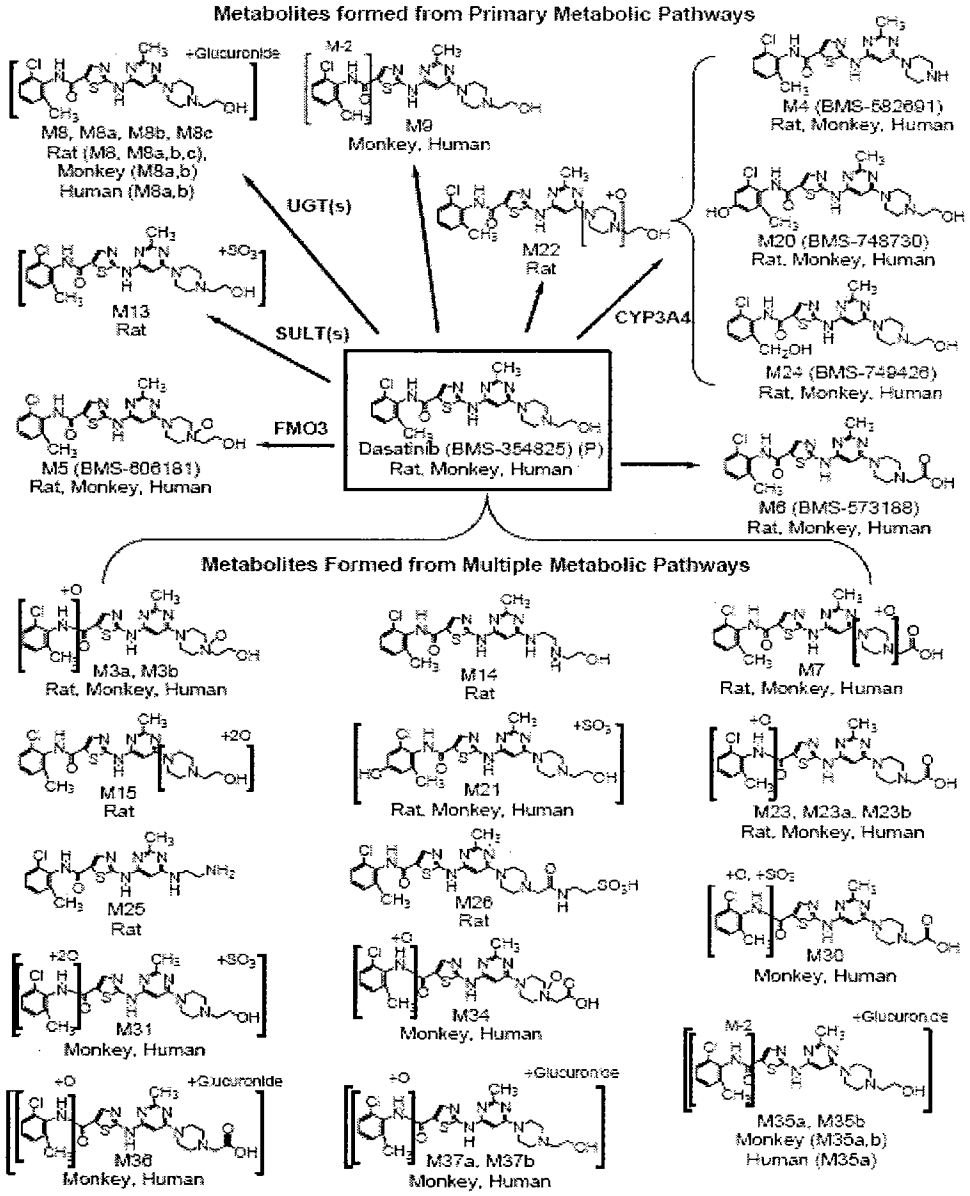
(2) oxidation on the hydroxyethyl piperazine group leading to N-dealkylation (M4), N-oxidation (M5), and oxidation of the terminal alcohol to carboxylic acid (M6);

(3) sulfation of the phenyl ring-hydroxylated metabolites.

The metabolic pathway of dasatinib can be found in Figure 18.

The major metabolites identified in human liver microsomes were the N-oxide (M5, BMS-606181) and the N-dealkylated metabolite (M4, BMS-528691), 4% each. Metabolites M20 (BMS-748730) and M24 (BMS-749426) were detected as the most abundant metabolites in human liver microsomes (39.2%). Only a small amount of the carboxylic acid derivative (M6, BMS-573188) were in human liver microsomes (1.6%), but large amounts were detected in human hepatocytes (9.2%). In human hepatocytes the major oxidative metabolites were M6, M5, and M4 which compromised 9.2, 2.3, and 1.0% of the total

radioactivity.



Metabolites M28a, M28b, M29a, M29b, and M29c were only detected in vitro and are not shown above.

FIGURE 18: Proposed Pathways for the Metabolism of Dasatinib in vivo

2.2.5.7 What are the characteristics of drug excretion?

Fecal excretion is the major route of elimination of dasatinib. Over 216 hours following an oral 100 mg dose of [^{14}C]-dasatinib in the human ADME study, the majority (85.3%) of the administered dose was recovered in the feces and only 3.6% of the dose was recovered in the urine.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

A linear relationship exists between AUClast and dose (Figure 19) on the first day of dosing

and at steady states on Day 5/8 and Day 26/29 (CA180002).

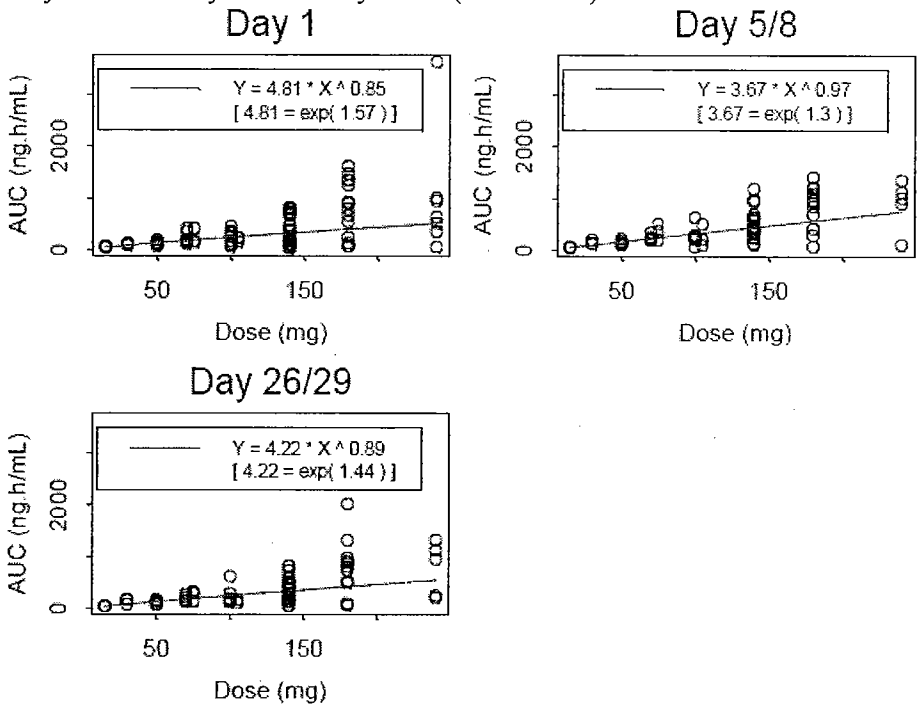


FIGURE 19: AUC vs. Dose (CA180002)

2.2.5.9 How do the PK parameters change with time following chronic dosing?

The mean profiles obtained from PK sampling following the first dose and steady-state in CA180002 show that the PK of dasatinib does not change with time (Figure 19 in Section 2.2.5.8).

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Possible sources of reduced reliability may include practice variability across the large number of clinical sites, including the use of a broader range of concomitant medications; increased variability in dosing and sampling times; and increased variability in subjects' underlying disease status, and in the status of metabolizing organs. Population PK is being developed which could help to identify the major causes of variability.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Age, gender, and body weight were investigated for their impact on the exposure of dasatinib. No significant contributions of age and gender are identified (Figures 20 & 21). However, exposure of dasatinib on Day 8 decreases with increasing of body weight (Figure 22). About 90% of enrolled patients where white. Based on the limited number of subjects enrolled in other race categories, no clinically meaningful comparisons can be made based on race.

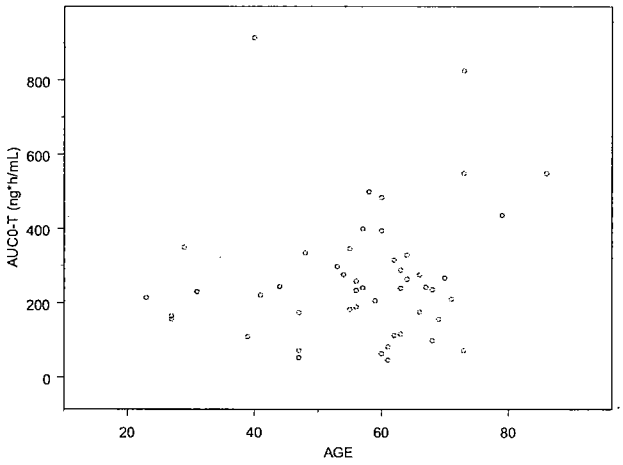


FIGURE 20: Exposure of Dasatinib on Day 8 vs. Age

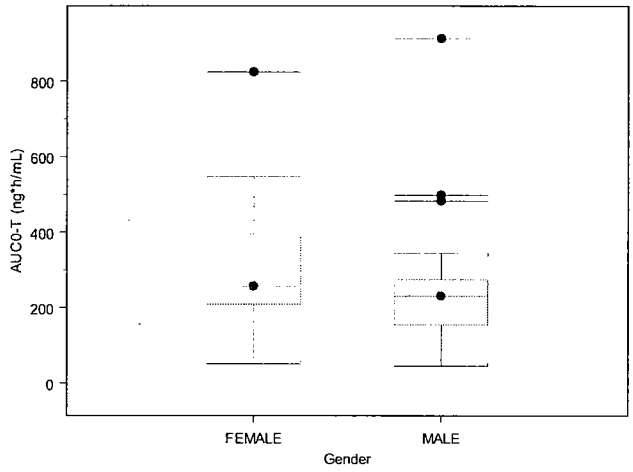


FIGURE 21: Exposure of Dasatinib on Day 8 vs. Gender

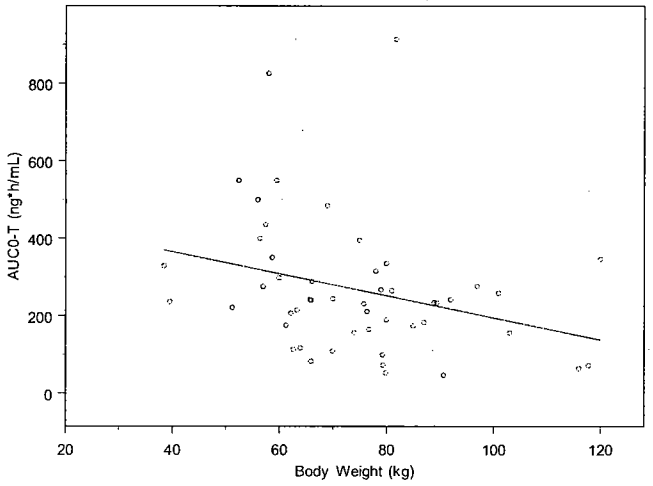


FIGURE 22: Exposure of Dasatinib on Day 8 vs. Body Weight

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

No pediatric studies were included in the current submission.

2.3.2.2 Renal impairment

Given that < 1% of a dose of dasatinib is eliminated renally (majority of parent drug and metabolites are eliminated in the feces), adjustments for renal impairment do not appear necessary.

2.3.2.3 Hepatic impairment

A study investigating the effect of hepatic impairment on dasatinib and its metabolites is planned.

2.3.2.4 What pregnancy and lactation use information is there in the application?

No data regarding the excretion of dasatinib and its metabolites in the milk of humans or animals was provided.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

No specific studies or analyses were designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of dasatinib

2.4.2 Drug-drug interactions

2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Since the major enzyme involved in dasatinib metabolism in vitro was CYP3A4, inhibitors and inducers of CYP3A4 could effect the pharmacokinetics of dasatinib.

In vitro studies also suggest that dasatinib is a time-dependent inhibitor of CYP3A4 and may therefore influence the pharmacokinetics of CYP3A4 substrates.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

In vitro studies (**Report 930011323**) with expressed enzymes, human liver microsomes (HLM) and human liver S9 indicate that the following enzymes are involved in forming the primary oxidative metabolites of dasatinib:

- N-dealkylated metabolite M4: CYP1A1, 1B1, 3A4, and HLM
- N-oxide metabolite M5: FMO3, CYP1A2, 1B1 and HLM
- Carboxylic acid metabolite M6: HLM and human liver S9
- Hydroxylated metabolites M20 and M24: CYP3A4 and HLM

When the results were normalized based on their abundance in the human liver, nearly all of the formation of M4, M2 and M24 is contributed by CYP3A4, while FMO3 is the primary

enzyme responsible for the formation of M5. Metabolite M6 was formed both in human liver S9 and in HLM by unknown oxidoreductases. The percent formation the primary oxidative metabolites can be found in Table 14 which was taken from the sponsors report.

TABLE 14. Percent formation of primary oxidative metabolites in incubations with human expressed enzymes, HLM, and S9.

Enzymes[a]	[^{14}C]Dasatinib Concentration	[^{14}C]Dasatinib Remaining (% total)	Formation of Metabolites (% total)				Total[b] (%)
			M4	M5	M6	M20+ M24	
HLM	2 µM	25	3.7	6.8	ND	39.5	75
	20 µM	62	2.3	5.5	1.1	14.5	84.5
HLM + Troleandomycin	20 µM	89	ND	6.8	ND	2.2	98
HLM – Heat[c]	20 µM	70.3	3.2	1.8	ND	20.3	95.6
CYP1A1	2 µM	23	10.5	3	ND	6.2	42.7
	20 µM	80	9.5	2.5	ND	1.3	93.3
CYP1A2	2 µM	96	ND	0.8	ND	ND	96.8
	20 µM	92	ND	5.4	ND	ND	97.4
CYP1B1	2 µM	26	7.8	25.9	ND	4.4	64.1
	20 µM	80	7.6	7.3	ND	1.0	95.9
CYP3A5	2 µM	87	2.3	0.9	ND	5.1	95.3
	20 µM	92	1.3	1.3	ND	2.5	97.1
CYP3A4	2 µM	2	ND	ND	ND	3.2	5.2
	20 µM	19	3.6	1.8	ND	48	72.4
CYP3A4 – Ketoconazole	2 µM	79	0.2	0.4	ND	7.8	87.4
	20 µM	91	0.8	1.1	ND	5.4	98.3
FMO3 pH7.5	2 µM	18	ND	76.3	ND	ND	94.3
	20 µM	51.5	ND	47.1	ND	ND	98.6
FMO3 – Heat[c]	20 µM	96	ND	2.4	ND	ND	98.4
FMO pH 9.5	20 µM	16	ND	82	ND	ND	98
S9 – NADPH	20 µM	46	2.6	5.1	2.6	32	85.7
S9 – NADH	20 µM	57	2.2	11.9	1.2	21.5	93.8

[a] CYP2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 4A11 were also incubated with 2 and 20 µM of [^{14}C]dasatinib. In these incubations, >93% of the parent drug remained and no metabolites were produced except M5, which represented ~0.4-1.3% of the radioactivity in each sample.

[b] Some of the totals are less than 100% because metabolites other than the five primary oxidative metabolites were formed: e.g. the 2 µM incubations with CYP1A1 and 1B1 contained 14 and 18% of total radioactivity as metabolites that eluted before M20; the 2 µM and 20 µM incubations with CYP3A4 contained early eluting metabolites representing 91 and 19% of the total radioactivity; the incubations with HLM and S9 also contained additional metabolites. Presumably, these early eluting metabolites are secondary metabolites produced from further metabolism of the primary metabolites.

[c] Samples were incubated at 45°C for 5 min in the absence of NADPH. Under these conditions, FMO activity is known to be inactivated.[5]

ND = not detected by radioactivity.

The effect of inhibitors on the formation of the oxidative metabolites were evaluated in HLM incubation (see table 14). The CYP3A4 inhibitors ketoconazole and troleandomycin did not inhibit the formation of M5, but did inhibit the overall metabolism of dasatinib in HLM by >70%. Ketoconazole inhibited the formation of M20 and M24.

HLM and expressed FMO3 were heat-treated for 5 mins prior to incubation with [^{14}C]dasatinib to investigate the contribution of FMO3 to the formation of M5. After heat-treatment, which would inactivate the heat-sensitive FMO3 enzyme, the formation activity of M5 was inactivated by 73 and 95% in HLM and expressed FMO3 respectively.

The kinetic constants for the primary oxidative metabolites in HLM and expressed CYP3A4 are below.

TABLE 15. Km and Vmax values for the formation of primary oxidative metabolites of dasatinib in HLM and expressed CYP3A4.

Enzyme	Metabolite	Km (μM)[a] (Mean ± SE)	Mean V_{max}[b] (Mean ± SD)	V_{max}/Km[c]
HLM	M4	88.6 ± 34.5	958 ± 285	10.8
	M5	79.9 ± 14.1	1133 ± 144	14.2
	M20	1.14 ± 0.38	319 ± 14.0	279
	M24	4.79 ± 1.34	48.0 ± 15.3	10.0
CYP3A4	M4	88.3 ± 58.4	15.3 ± 3.60	0.173
	M20	5.55 ± 0.70	11.0 ± 4.20	1.98
	M24	8.28 ± 1.46	1.37 ± 0.25	0.167

a Kinetic values were estimated from Michaelis-Menten analysis
b The unit for Vmax was pmole/mg protein /min for HLM and pmole/pmole CYP/min for CYP3A4.
c The unit for Vmax/Km for HLM - μL/mg protein/min; for CYP3A4 - μL/pmol CYP/min

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In-vitro induction

An *in-vitro* human pregnane-X receptor (hPXR) transactivation assay was used to assess the potential of dasatinib to induce CYP3A4 with rifampicin as a positive control (**Report 930003190**). Dasatinib did not promote hPXR-dependant transactivation of CYP3A4 at the concentrations of 0.1, 1, 10 and 25 μM concluding that dasatinib has little potential to induce CYP3A4 through the activation of hPXR. Additional studies were undertaken with known CYP inducers to further investigate the potential of dasatinib to induce hepatic CYP enzymes 1A2 (phenacetin), 2B6 (bupropion), 2C9 (diclofenac) and 3A4 (testosterone) (**Report 930011325**). The results are listed below (Table 16) and indicate that dasatinib is not an inducer of CYP enzymes.

TABLE 16. Evaluation of dasatinib as an inducer of CYP enzymes in Human hepatocytes

Test Article	Concentration	CYP Enzyme Activity Fold Change as Compared to 0.1% DMSO Control			
		1A2	2B6	2C9	3A4
DMSO control	0.1%	1	1	1	1
Dasatinib	0.2 μM	1-2	0.8-1	0.7-1	0.6-1
Dasatinib	1 μM	0.8-1	0.7-1	0.7-1	0.9-1
Dasatinib	5 μM	0.9-1	0.7-1	0.9-1	1
Dasatinib	25 μM	0.5-0.7	0.6-2	0.7-1	0.2-0.3b
3-methylcholanthrene[a]	2 μM	15-20	2	1	0.6-0.9
Phenobarbital[a]	1000 μM	2-3	8-13	1-3	3-5
Rifampicin[a]	10 μM	1-2	2-9	2	3-6

a positive control reference compounds

In-vitro inhibition

The potential for dasatinib to inhibit CYP enzymes was investigated in HLM (**Report 930011322**). Dasatinib did not inhibit CYP1A2, 2B6, 2C19, 2D6 or 2E1 at concentrations up to 50μM (Table 17). Dasatinib did inhibit CYP2A6, 2C8, 2C9 and 3A5. CYP2C8 followed a competitive inhibition model with a Ki of 3.6 μM. Based on the mean steady state total Cmax of approximately 0.12μM for 70mg BID continuous oral dosing in patients with CML, the Cmax/Ki ratio for 2C8 is 0.03 which is less than the 0.1 threshold, indicating a low probability of drug-drug interactions with dasatinib and CYP2C8 substrates. The inhibition of CYP3A4 by dasatinib is difficult to assess because of the time-dependant nature of the inhibition (Ki = 1.9; k_{inact} = 0.022 min^{-1}; I/Ki = 0.06) which is similar to the known time-

dependant inhibitors diltazaem (Ki 2.8 μM; k_{inact} = 0.13min^{-1}) and erythromycin (Ki = 5.1 μM; k_{inact} = 0.03 min^{-1}).

In conclusion, *in-vitro* studies indicate that dasatinib is a potential time-dependant inhibitor of CYP3A4, and has little potential to induce CYP3A4.

TABLE 17. Evaluation of dasatinib as an inhibitor of CYP enzymes in HLM

CYP Enzyme (probe substrate reaction monitored)	IC50 and Ki Values (μM)	
	IC50 (μM)	Ki (μM)
CYP1A2 (Phenacetin O-deethylation)	>50	ND
CYP2A6 (Coumarin 7-hydroxylation)	35	ND
CYP2B6 (Bupropion hydroxylation)	>50	ND
CYP2C8 (Paclitaxel 6-hydroxylation)	12	3.6
CYP2C9 (Tolbutamide hydroxylation)	50	ND
CYP2C19 ((S)-Mephenytoin 4'-hydroxylation)	>50	ND
CYP2D6 (Bufuralol 1'-hydroxylation)	>50	ND
CYP2E1 (Chlorzoxazone 6-hydroxylation)	>50	ND
CYP3A4 (Midazolam 1'-hydroxylation)	18c	ND
CYP3A4 (Testosterone 6β-hydroxylation)	10c	ND

In-vivo evaluation of inhibition

To investigate the inhibition potential of dasatinib, a drug-drug interaction study with Simvastatin (a CYP3A4 substrate) was completed (**study CA180022**). Forty-eight healthy adult subjects received the following 2 treatments under fasted conditions with a 7 day washout period between each treatment:

- Treatment A: Simvastatin 80 mg (single dose)
- Treatment B: Simvastatin 80 mg with dasatinib 100mg.

Since dasatinib is a time-dependant inhibitor of CYP3A4, the dose of dasatinib should have been dosed to steady-state. As a result, the findings in this study could be underestimating the CYP3A4 inhibition potential of dasatinib.

The point estimates and 90% CI's were calculated for Treatment B/Treatment A ratios of geometric means for simvastatin Cmax, AUCinf and AUC_{0-t}. The results are summarized below in Table 18.

TABLE 18. Statistical Analysis of simvastatin Cmax, AUCinf and AUC_{0-t} with or without dasatinib.

Pharmacokinetic Parameter	Adjusted Geometric Mean		Ratio	Ratios of Geometric Means Point Estimate (90% Confidence Interval)
	Treatment A	Treatment B		
Cmax (ng/mL)	26.68	36.53	B vs. A	1.369 (1.194, 1.569)
AUCinf (ng•h/mL)	117.95	141.29	B vs. A	1.198 (1.059, 1.355)
AUC_{0-t} (ng•h/mL)	108.05	132.97	B vs. A	1.231 (1.102, 1.374)

The 90% CI's for the ratios of geometric means for Cmax, and AUC suggest that co-administration of dasatinib increases the exposure of simvastatin. Simvastatin exposure was increased by 20 to 23% and Cmax increased by approximately 37% when co administered with a single dose of 100 mg dasatinib. This suggests that dasatinib has CYP3A4 inhibition potential, but not enough to be considered a weak inhibitor. Because the design of this study was not optimal the inhibition of potential of dasatinib may be more significant than what was concluded from this trial.

The sponsor proposed in the current label that caution should be used when dosing CYP3A4 substrates with narrow therapeutic indices concomitantly with dasatinib. Because the current study results are not significant enough to classify dasatinib as a weak inhibitor according to

the FDA guidance and considering the I/Ki of 0.06, an additional study would more than likely not provide additional information which would result in more restrictive labeling for CYP3A4 substrates. In conclusion, although the study design did not provide for the maximum inhibition potential of dasatinib, additional studies with CYP3A4 substrates is not warranted.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The membrane permeability of dasatinib was investigated in Caco-2 cell monolayers. A permeability coefficient (A→B) of 102 nm/sec was seen at 50 μM. The average B→A permeability was 222 nm/sec which is twice the A→B permeability. This experiment has two limitations. First, the sponsor should have used a range of concentrations to look at the efflux of dasatinib instead of only using 50μM. In addition, a known P-gp substrate should have been included in the experiment to serve as a positive control. However, since the net flux ratio is > 2, this suggests that dasatinib is an P-pg substrate and inhibition studies with P-pg inhibitors are needed.

To further investigate if dasatinib is a P-gp substrate, a P-gp inhibitor, GF-120918 (Ki not given) was added to the above experiment. In the presence of GF-120918, the A→B permeability was increased to 161 nm/sec, while the B→A permeability decreased to 126 nm/sec which suggests that dasatinib may be a p-glycoprotein substrate. This study also had its limitations including; (1) using an unknown P-gp inhibitor (GF-120918), (2) not using 2 or more potent P-gp inhibitors, and (3) no positive control. However, because the net flux ratio (BA/AB) was significantly decreased to 0.8 this indicates that dasatinib is a P-gp substrate and further in vivo data is needed to explore potential drug interactions with co-administered drugs that are P-gp inhibitors.

Additional Caco-2 cell monolayer experiments using digoxin (a Pg-p substrate; 5 μM) as the probe substrate and verapamil (a P-gp inhibitor; 10 μM) as the positive control were done to study dasatinib as an inhibitor of P-gp. The transport of digoxin across Caco-2 cells was not inhibited by dasatinib at concentrations of 1 and 10 μM (10% at 1 μM and 11% at 10 μM) while verapamil (the positive control) inhibited digoxin transport by 59%. This concludes that dasatinib is not an inhibitor of P-gp and is unlikely to cause drug-drug interactions with co-administered drugs that are substrates for P-gp.

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

The contribution of oxidoreductases, and UGT's towards the metabolism of dasatinib are unknown at present.

2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Dasatinib is to be administered as a single agent.

2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Co-administration of Dasatinib with CYP3A4 Inhibitors

A study with ketoconazole has been completed, but was not submitted with the NDA. CA180021-Segment 1 was an open, label, single-sequence, study to determine the effect of co-administration of ketoconazole 200 mg every 12 hours and dasatinib once daily on the steady state PK of dasatinib in subjects with advanced solid tumors. Briefly, subjects received dasatinib 20 mg QD on Days 1-8, and Ketoconazole 200 mg BID was dosed on Days 3-8.

Preliminary results indicate that ketoconazole increased the Cmax and AUC of dasatinib by 4-fold and 5-fold respectively. Currently the labeling recommendation will be to decrease the dasatinib dose to 20 mg BID in the presence of potent CYP3A4 inhibitors. Further changes to the label may be needed once the full study report is submitted and reviewed.

Co-administration of Dasatinib with CYP3A4 Inducers

The effect of rifampin, a potent inducer of CYP3A4 on the PK of dasatinib was investigated in CA180032. Twenty healthy adult subjects received the following treatments:

- single oral dose of 100 mg dasatinib on Day 1
- 600 mg rifampin every evening from Day 2 to 9 + 100mg dasatinib on Day 9

According to the FDA drug-drug interaction guidance, the study design and choice of CYP3A4 inducer are appropriate.

Point estimates and 90% CI's were calculated for Day 9 to Day 1 ratios of the geometric means of Cmax and AUC of dasatinib. The results of the statistical analysis is below in Table 19.

TABLE 19: Statistical analysis of 100mg dasatinib Cmax and AUC following administration with or without rifampin 600mg.

Pharmacokinetic Parameter	Geometric Mean		Ratio	Ratios of Geometric Means Point Estimate (90% Confidence Interval)
	Without rifampin	With rifampin		
Cmax (ng/mL)	85.56	16.16	with vs. without	0.189 (0.163, 0.219)
AUCinf (ng•h/mL)	294.05	53.21	with vs. without	0.181 (0.160, 0.204)
AUC_{0-t} (ng•h/mL)	280.27	44.20	with vs. without	0.158 (0.132, 0.189)

Co-administration of dasatinib with rifampin lowered the exposure of dasatinib by 81%, 82% and 84% for Cmax, AUCinf, and AUC_{0-t} respectively compared to when dasatinib was administered alone. The results of this study indicate that the dasatinib dose should be increased to compensate for the reduced dasatinib AUC. A possibility is to increase the dose 3-fold and then increase step-wise in 20-mg increments based on patient tolerability and response.

Co-administration of Dasatinib with drugs that lower the gastric pH.

Since the solubility of dasatinib is pH dependant and the bioavailability of dasatinib could be reduced in the presence of acid reducing agents, a study of the interactions between dasatinib, antacids and H2-receptor antagonists was completed. The following treatments were administered in a crossover fashion to 24 healthy subjects:

- Treatment A - Dasatinib 50 mg Q12 hours (control)
- Treatment B
  - PM dose: Dasatinib 50 mg 2 hours prior to 40mg oral famotidine
  - AM dose: Dasatinib 50 mg (10 hours after famotidine dose)
- Treatment C
  - PM dose: Maalox 30 mL 2 hours prior to dasatinib 50mg
  - AM dose: Dasatinib 50 mg with Maalox 30mL

Point estimates and 90% CI's for the B/A and C/A ratios for Cmax and corrected AUC_{0-12} population geometric means for each of the 2 dasatinib doses were calculated from the results of the ANOVA. The results of the sponsors analysis are below in Table 20.

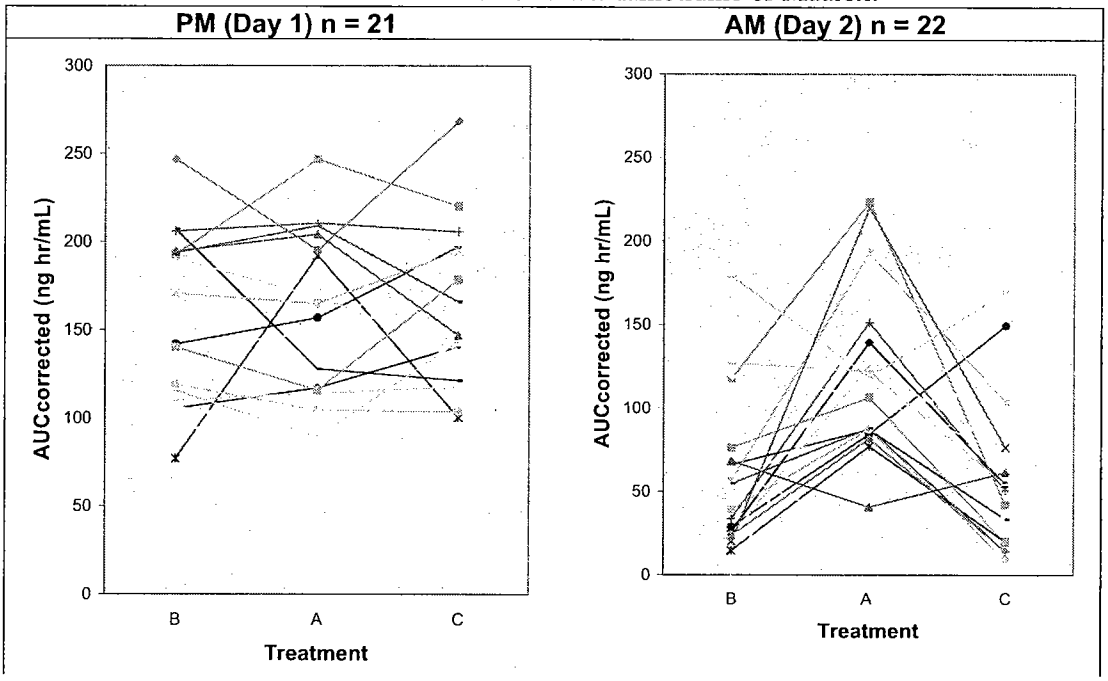
TABLE 20: Statistical analysis for 50 mg dasatinib Cmax and AUC following co-administration with pH gut modulators Maalox and famotidine.

Day	Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
		Formulation	Adjusted Geometric Means	Ratio	Point Estimate	90% Confidence Limits
Day 1 (PM)	Cmax (ng/mL)	A	37.57			
		B	40.43	B vs A	1.076	(0.872, 1.328)
		C	47.51	C vs A	1.264	(1.025, 1.560)
	AUC(0-12h) (ng•h/mL)	A	140.41			
		B	139.45	B vs A	0.993	(0.895, 1.103)
		C	147.33	C vs A	1.049	(0.945, 1.165)
Day 2 (AM)	Cmax (ng/mL)	A	40.86			
		B	15.16	B vs A	0.371	(0.239, 0.576)
		C	17.07	C vs A	0.418	(0.269, 0.649)
	Corrected AUC(0-12h) (ng•h/mL)	A	99.51			
		B	39.28	B vs A	0.395	(0.255, 0.612)
		C	45.20	C vs A	0.454	(0.293, 0.704)

Formulations:
A = dasatinib 50 mg q12h (control)
B = dasatinib 50 mg q12h – famotidine 40 mg single dose (dasatinib 2h before famotidine in the PM and 10h after famotidine in the AM)
C = dasatinib 50 mg q12h + Maalox 30 mL q12h (dasatinib 2h after Maalox in the PM and co-administered in the AM)

Famotidine did not cause any concern with regards to dasatinib's AUC when it was administered 2 hours after dasatinib. The Cmax of dasatinib however increased slightly (7%) after treatment on Day 1. However, significant decreases can be seen when dasatinib is administered 10 hours after famotidine (treatment B, day 2). A 63% reduction in Cmax, and a 60% reduction in AUC_{0-12} can be seen when dasatinib is administered 10 hours after a dose of famotidine.

For Treatment C, administration of dasatinib 2 hours after a dose of Maalox did not result in a significant change in AUC (increase of 4%), but Cmax did increase by approximately 26%, which is not considered clinically important. However, administration of dasatinib concomitantly with Maalox on Day 2 (AM dose) did cause significant decreases in dasatinib's Cmax (58%) and AUC_{0-12} (54%). Figure 23 displays the individual trends in AUC and Cmax seen after administration of either famotidine or Maalox.



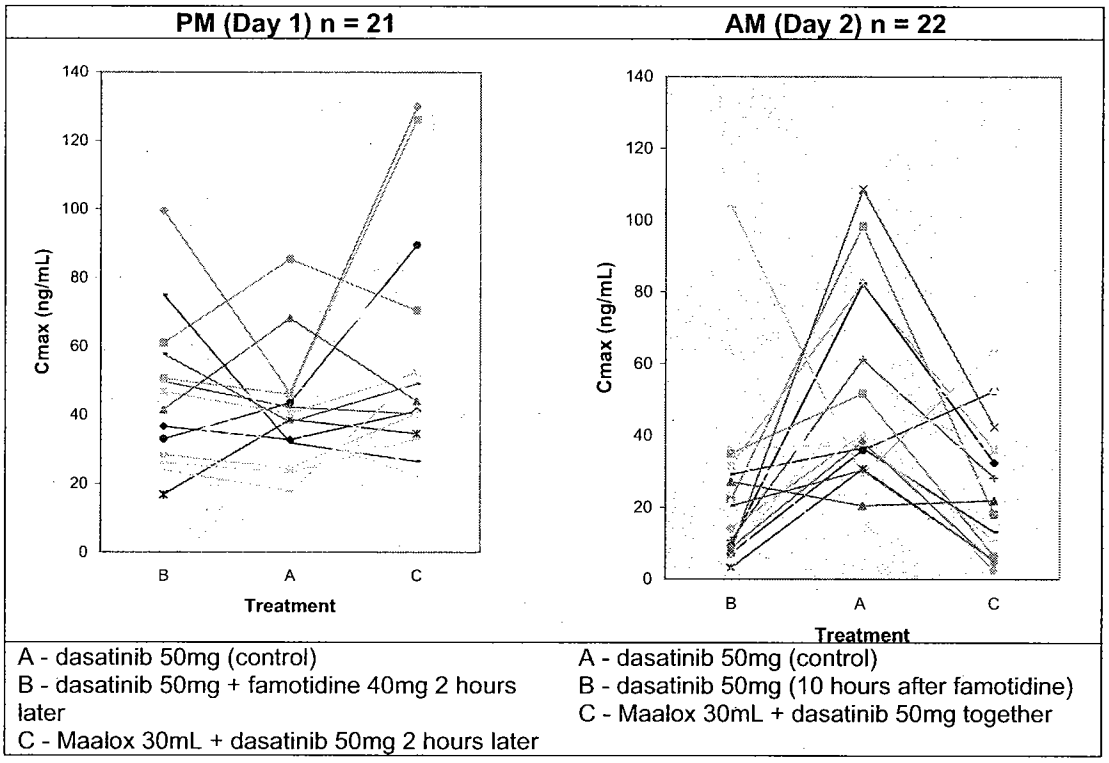


FIGURE 23: Individual AUC_{0-12} corrected and Cmax versus Treatment for Day 1 (PM) & Day 2 (AM)

The sponsor recommended that H2 antagonists and proton pump inhibitors should not be co-administered with dasatinib. Considering these agents (H2 antagonists, and proton pump inhibitors) are designed to cause a prolonged decreases in gastric-pH for the treatment of acid-reflux disease, a safe dosing recommendation for concomitant use of these mediations cannot be made without further study.

In addition, the sponsor recommended that dasatinib administration be separated by at least 2 hours from OTC antacids. An ideal circumstance for dosing antacids is difficult to conclude from this study. Dosing dasatinib 2 hours after Maalox resulted in a 26% increase in Cmax and a slight increase in AUC (4%, not statistically significant), probably as a result of acid rebound which is common after administration of antacids. In addition, the sponsor did not study the effect of OTC antacids if taken 2 hours AFTER dasatinib administration. However, given that gastric emptying occurs every 2 hours, the effect of the OTC antacid should be minimized if dasatinib is given 2 hours after an OTC antacid.

Until a dosing recommendation for the administration of H2 antagonists or proton pump inhibitors with dasatinib can be found, alternative treatments for acid reflux disease should be available for patients. Therefore, concomitant administration of OTC antacids is appropriate if administered at least 2 or more hours BEFORE or AFTER dasatinib. It cannot be concluded that administering OTC antacids 2 hours AFTER dasatinib will not result in changes to dasatinib concentrations. Based on the quick absorption of dasatinib, gastric emptying 2 hours, and that the effective length of most antacids is 2 hours, one can assume that changes to the dasatinib absorption would be minor if OTC antacids were taken 2 hours after dasatinib administration.

Further study of dasatinib with gastric pH modulators in patients, is warranted so more

informed dosing recommendations can be identified.

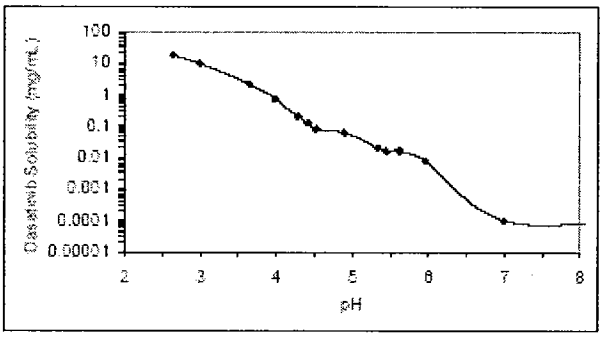
2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Dasatinib has low aqueous solubility and high permeability, and is classified as a BCS (Biopharmaceutical Classification System) Class II compound.

Solubility

Dasatinib is a free base with three pK_a values of 3.1, 6.8 and 10.9. Dasatinib exhibits pH dependent solubility: solubility decreases with increasing pH over the normal physiological pH range. The aqueous solubility of dasatinib ranged from ~ 18 mg/mL at pH 2.6 to < 1 µg/mL at pH 7.0 at 24°C. The highest proposed commercial strength (i.e., 70 mg) of dasatinib tablets is not soluble in 250 mL of water in a pH range of 4.3 to 7.0 at 24°C, and hence, dasatinib is considered a low solubility compound in the Biopharmaceutical Classification System (BCS). The solubility profile is shown in Figure 24.



[1] pH adjusted accordingly with HCl or NaOH

FIGURE 24: Equilibrium Aqueous Solubility[1] of Dasatinib at 24 ± 4°C

Permeability:

Refer to section 2.2.5.5 for in vivo permeability.

The in vitro permeability was evaluated using the Caco-2 monolayers system. The permeability of dasatinib is comparable to metoprolol and dexamethasone which are FDA recommended internal standards for high permeability. These agents are approximately 3–5 fold greater than nadolol and sulfasalazine, the FDA recommended internal standards for low permeability. These results indicate that dasatinib meets the requirements that define high permability. In addition, dasatinib appears to be a much weaker substrate for efflux pump(s) than digoxin in the Caco-2 cell monolayer system. Based on *in vitro* Caco-2 studies, the permeability of dasatinib was comparable to metoprolol and dexamethasone, indicating that dasatinib is a highly permeable compound.

2.5.2 What is the composition of the to-be-marketed formulation?

The sponsor proposes to market Dasatinib film-coated tablets in strengths of 20 mg, 50 mg, and 70 mg. All three strengths are manufactured from a common drug and are proportional in composition with different shapes, sizes and markings. The formulations are shown in the following table.

TABLE 21. Composition of Proposed Commercial Dasatinib Tablets

Composition of Proposed Commercial Dasatinib Tablets: 20 mg, 50 mg and 70 mg						
Component	Compendial Reference	Function	% w/w[a]	Amount (mg/tablet)		
				20 mg	50 mg	70 mg
Dasatinib[b]	—	Active		20	50	70
Lactose Monohydrate[c]	NF, Ph. Eur.					
Microcrystalline Cellulose	NF, Ph. Eur.					
Hydroxypropyl Cellulose	NF, Ph. Eur.					
Croscarmellose Sodium	NF, Ph. Eur.					
Magnesium Stearate	NF, Ph. Eur.					
White.	—	Film Coat				
	USP, Ph.Eur.		—	—	—	—
Tablet Weight	—		—	83.2	207.0	288.4

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

Film-coated 20 and 50 mg strengths were developed for Phase II clinical studies to cover a dose range of 20-100 mg (twice a day). The composition of the 20 mg and 50 mg proposed to-be-marketed formulations are comparable to that of the Phase II clinical film-coated tablets; however the difference is the debossing. These tablets were not bioequivalent to the Phase I 5-mg and 50 mg strengths. A 70 mg strength tablet was developed for the purpose of commercialization in addition to the 20 and 50 mg strengths. A biowaiver was requested for the 70 mg commercial tablet, which was not evaluated in the pivotal Phase II clinical studies. The request for a biowaiver for the 70-mg proposed commercial film-coated tablet is approved based on the criteria listed in the FDA 2003 BA/BE guidance document: linear elimination characteristics, the available safety and efficacy data for the relevant clinical dosing regimen, the in vivo dose response proportionality, the comparable *in vitro* dissolution data and the formulation proportionality of the 20, 50 and 70 mg tablet strengths which are all manufactured from a common . The three proposed commercial film-coated tablets, 20 mg, 50 mg and 70 mg, are only differentiated from each other by tablet size, shape, and debossing which should not impact the overall clinical pharmacology of the drug.

Phase 1 Formulations:

Film-coated clinical tablet formulations of 5 and 50 mg strengths were developed and utilized in the initial Phase 1 clinical studies. Qualitatively, both tablet formulations have identical compositions; however, the 5 and 50-mg tablets were manufactured from w/w drug , respectively, using a

Phase 2 Formulations:

The 20 and 50-mg tablets were developed for Phase II clinical studies using a w/w drug manufactured via a . The w/w drug the same qualitative composition and uses a similar manufacturing process as the % w/w drug load granulations used to manufacture tablets for Phase I clinical studies with the exception of the film coat. An in vivo study has shown that the Phase II formulation are not bioequivalent to the Phase I formulations. The proposed commercial

strength tablets, 20, 50, and 70 mg, will be manufactured from the same — w/w drug — and use similar processes that were used to manufacture tablets for Phase II clinical studies. The difference between the Phase II clinical formulations and the proposed commercial tablets is in their debossing. Dissolution testing comparing the 20 mg and 50 mg clinical batches and several commercial batches of equivalent strengths indicated that the dissolution profiles of the same strength are similar (f2 <50). The following table summarizes the dissolution and f2 analysis of several commercial lots. This difference in debossing is not expected to have any impact on the quality or performance of dasatinib tablets.

TABLE 22. Dissolution Profile comparison of Commercial vs. Clinical Batches

DISSOLUTION PROFILE COMPARISON OF COMMERCIAL VS. CLINICAL 20 MG AND 50 MG BATCHES							
Lot	T/R	10 min	15 min	30 min	45 min	60 min	f2
20 mg							
4L77202	R	76	89	98	99	99	
4M64169	T	81	90	96	97	97	76.6
5A04130	T	81	89	94	95	96	71.2
5A04132	T	77	88	95	98	98	86.1
5A04134	T	90	96	98	98	98	57.4
5C06213	T	75	90	97	98	99	93.6
5C06214	T	72	88	95	96	96	75.2
5C06215	T	78	94	102	102	101	72.4
5C06217	T	75	91	98	99	99	92.4
5C06219	T	74	89	97	97	98	88.1
5C06221	T	71	88	97	97	98	78.3
5C06222	T	82	95	100	100	101	69.6
5C06223	T	70	87	97	98	98	75.4
5C06224	T	71	87	96	97	98	76.6
5C06225	T	77	96	101	101	101	71.0
5C06226	T	72	87	95	95	96	73.2
5C06227	T	74	90	98	99	99	92.5
5C06219	T	75	91	97	97	97	85.5
5C06230	T	77	92	98	99	99	88.1
5C06232	T	74	92	101	102	101	77.4
5C06233	T	76	93	100	100	101	80.5
5C06236	T	71	86	94	95	95	69.0
5C06241	T	79	93	100	100	100	78.6
5C06243	T	66	83	91	92	93	56.4
5C06246	T	73	90	99	100	100	86.1
5C06247	T	79	93	100	100	101	78.6
5J02850	T	87	95	100	100	101	63.0
Lot		10 min	15 min	30 min	45 min	60 min	f2
50 mg							
4L77205	R	70	82	94	97	98	
4L85341	T	70	82	95	97	98	98.0
5A10548	T	70	81	91	94	95	79.5
5A10549	T	72	84	93	95	97	85.5
5A10557	T	70	80	89	92	94	70.6
5C05064	T	68	83	94	96	96	88.1
5C05065	T	69	87	97	98	98	77.2
5C08599	T	85	94	99	100	101	52.0
5C08601	T	69	85	94	96	96	84.9
5C08609	T	68	84	95	96	96	85.5
5H01126	T	79	91	95	97	97	61.8
5H01127	T	80	89	95	97	98	62.7
5H01128	T	79	92	99	99	99	59.1

Phase I and Phase II formulation comparability

In order to provide a link between the performances of the Phase II drug product (proposed

commercial formulation) to the performance of the Phase 1 drug product, the sponsor conducted a formulation comparability study in normal healthy volunteers (CA180016). The Cmax, AUC (0-T) and AUC (0-INF) did not meet the bioequivalence confidence interval. However, the data suggested that the distributions of the exposures was comparable, the median Tmax of dasatinib was identical, and the elimination half-life of dasatinib was unaffected across the formulations tested.

Biowaiver

A biowaiver was requested for the 70 mg tablet based on FDA's "Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations- 2003". The following information is provided to support the approval of the biowaiver:

1. Formulation: The composition of the 70 mg strength tablet (Test product), manufactured from the same common [redacted] as the Phase II clinical/commercial tablets (20 and 50 mg, Reference products), is proportionally similar to the lower strength tablets. All active and inactive ingredients are in exactly the same proportion with the exception of the film coat. The slightly higher percentage of the film coat for the lower strength tablets (i.e., 20 and 50 mg) is due to their greater specific surface area resulting from smaller tablet size.
2. Dosage Safety and Efficacy: A dose of 70 mg, administered as 20 + 50 mg tablets, has been tested in Phase II clinical trials and has been found to be well tolerated.
3. Dissolution: The similarity in the *in vitro* dissolution profiles and calculated similarity factors was shown between the Reference (20, 50 and 20 + 50 mg) and Test (70 mg) products in three different media: pH 1.2 (USP), pH 4.0 acetate buffer containing 1% Triton X-100 (proposed regulatory method), and pH 4.5 (USP).
4. Linear Pharmacokinetics: Dasatinib exhibits dose proportional increases in AUC, and linear elimination characteristics over the clinical dose range.

2.5.4 What moieties should be assessed in bioequivalence studies?

Dasatinib (BMS-354825) should be assessed in human plasma. For exploratory purposes, the N-oxide metabolite (BMS-606181) of dasatinib was also quantified in the urine samples. Since the total amount of the metabolite recovered in the urine was minimal (approximately 1% of the total dosed dasatinib), the concentration data were not included in the analysis.

2.5.5 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Data from Study CA180009 indicated that dasatinib bioavailability was increased by food when administered as the Phase II formulation. Given that the effect of food on the AUC(INF) (14% increase for a high fat meal and 21% increase for a light fat meal) was small relative to the variability in exposure in the fasted state, this result is not expected to be of clinical relevance and dasatinib may be taken without regard to meals.

The sponsor conducted Clinical Study CA180009 to determine the effect of a light-fat meal and a high-fat meal on the PK of dasatinib. Based on the bioequivalence confidence interval criteria, the results of this study indicated that a light-fat meal increased the rate as well as the extent of absorption of dasatinib. The Cmax and AUC(INF) values were increased by 22% and 21%, respectively, under fed conditions compared to the fasted treatment. Since preliminary patient data from Study CA180002 (the maximum administered dose study in

solid tumor patients), suggest that even with dose increases of 29%, and > 70% above the recommended 70 mg twice daily dose, there is no increase in severe hematologic or nonhematologic toxicity of dasatinib, this increase many be of limited clinical relevance. The high-fat meal decreased the Cmax by 24%, the Tmax was prolonged by 1 hour, and AUC(INF) was increased by 14% compared to fasting conditions. The change in dasatinib exposure when it is taken following a high-fat meal is less than 15%. The clinical relevance of both the increase in Cmax and AUC (INF) seen with the light-fat meal and the decrease in Cmax seen with the high-fat meal is minimal. Since the Phase 2 studies were dosed without regard to food no restrictions on dosing will be added to the label.

2.5.6 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

The dissolution method provided adequate information regarding the release rate of the drug product. The sponsor evaluated 20 dissolution media and various levels of both SLS and Triton X-100 surfactants. For more detailed information on the dissolution development see Appendix 3 - Dissolution Assessment. The following method was found to be sensitive and specific for dasatinib:

Apparatus:	USP Apparatus II (Paddle Method)
Rotation Speed:	60 rpm
Medium:	pH 4.0 acetate buffer with 1% Triton X-100
Volume:	1000 mL
Analytical:	—
Tolerance:	Q= ~ , at 30 minutes

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Dasatinib (BMS 354825) and its N-oxide metabolite (BMS-606181) were evaluated in human plasma. N-oxide metabolite (BMS-606181) was measured in urine.

2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Plasma and urine samples were assayed for dasatinib (BMS-354825) and the metabolite BMS-606181, by a validated reverse-phase liquid chromatography method with an isocratic mobile phase and tandem electrospray positive ion Q1 mass spectrometry detection (LC/MS/MS). The assay was sensitive and specific, using solid-phase extraction prior to chromatographic separation. BMS 583475 was used as an internal standard. The concentration range of the LC/MS/MS plasma and urine assay methods used was 1 to 1000 ng/mL and 10 to 500 ng/mL, respectively. Spiked analytical quality control (QC) samples were analyzed along with the study samples to assess the accuracy and precision of each analytical run. The analytical parameters are given in the following table.

TABLE 23. Summary of Bioanalytical methods for analytes in clinical pharmacology studies

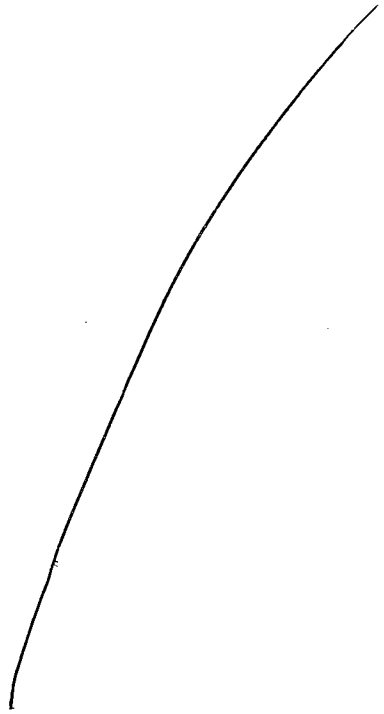
Studies	**CA180002 CA180019**	**CA180019**	**CA180032**	**CA180020 CA180022**	**CA180032**
Matrix	Plasma	Urine	Plasma	Plasma	Plasma
Analyte	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181 BMS-582691
Method	LS/MS/MS				
Volume/Amount	0.1 mL				

Studies	**CA180002 CA180019**	**CA180019**	**CA180032**	**CA180020 CA180022**	**CA180032**
Matrix	Plasma	Urine	Plasma	Plasma	Plasma
Analyte	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181	Dasatinib BMS-606181 BMS-582691
Standard Curve Range	1 to 1000 ng/mL	10 to 500 ng/mL	1 to 1000 ng/mL	1 to 1000 ng/mL	1 to 1000 ng/mL
Regression Model	1/x weighted quadratic				
Precision (%CV)					
Intra-Assay	≤4.2%	≤2.5%	≤6.2%	≤6.1%	≤5.3%
Inter-Assay	≤3.0%	≤1.6%	≤5.9%	≤4.7%	≤5.3%
Accuracy (% deviation					
Accuracy	within ≤4.5%	within ≤6.0%	within ≤9.2%	within ≤9.1%	within ≤9.0%
Stability:					
Short term	24 h @ RT	24 h @ RT	ND	ND	22 h @ RT
Long Term (-20°C)	≤54 weeks	≤19 weeks			≤14 weeks
Freeze/Thaw	3 cycles	3 cycles	8 cycles	8 cycles	6 cycles

3 DETAILED LABELING RECOMMENDATIONS

Changes which were sent to the sponsor are below. Only relevant clinical pharmacology sections are included.

Double underlines indicate content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.



5 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

__✓ § 552(b)(4) Draft Labeling

4 APPENDICES

4.1 APPENDIX 1 - INDIVIDUAL STUDY REVIEWS

4.1.1 Study CA180002 - Phase 1 Dose Escalation Study

STUDY REVIEWER: Angela Men, Ph.D., M.D.

TITLE: A Phase I Dose-Escalation Study to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of BMS-354825 in the Treatment of Patients with Chronic, Accelerated, or Blast Phase Chronic Myelogenous Leukemia, or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Who Have Hematologic Resistance to Imatinib Mesylate (Gleevec).

PK data are from first cycle (4 weeks) of treatment for the first 84 subjects enrolled and treated.

OBJECTIVES:

To characterize the plasma pharmacokinetics of BMS-354825 (dasatinib) and BMS-606181, the N-oxide metabolite (M5).

To obtain DLT, and the dose for phase 2 studies.

METHODOLOGY:

This was an open-label, Phase 1, dose-escalation study of dasatinib administered orally to patients with chronic, accelerated, or blast phase chronic myelogenous leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who have primary or acquired hematologic resistance to or intolerance of imatinib mesylate. Patients received the following dosing regimens of dasatinib in the fasted state:

- 15, 30, 50, 75, 105, 140, or 180 mg once daily (15-180 mg/day) for 5 consecutive days followed by 2 non-treatment days every week (Q5D Regimen)
- 25, 35, 50, or 70 mg twice daily (50-140 mg/day) for 5 consecutive days followed by 2 non treatment days every week (B5D Regimen)
- 35, 50, 70, 90, or 120 mg twice daily (70-240 mg/day) continuous dosing schedule (B7D Regimen)

Of note, in the interim clinical study report the Q5D regimen is referred to as the "QD regimen, in chronic phase subjects," the B5D regimen is referred to as the "BID regimen, in chronic phase subjects," and the B7D regimen is referred to as the "BID regimen, in advanced disease subjects." A treatment cycle was defined as a 4-week period. The starting dose for the first cohort of patients was 15 mg. A minimum of 3 patients with chronic phase CML were treated at each dose level for the Q5D and BID dosing schedules. Generally, a cohort of 3 patients each with accelerated phase CML and with either blast phase CML or Ph+ ALL were treated at each dose level. However, if patients with chronic phase CML on the BID schedule completed 1 cycle (i.e., 4 weeks) and a new higher dose level of twice daily dosing for chronic phase CML patients was to open, patients with more advanced disease (i.e., accelerated or blast phase CML, or Ph+ ALL) also accrued to this higher dose level once at least one patient at the current dose level was followed for a minimum of 1 cycle and did not have dose-limiting toxicity (DLT). Dose escalation was to continue until the maximally tolerated dose (MTD) was reached. (Note: a MTD was not reached in this study.)

Pharmacokinetic assessments of dasatinib and BMS-606181 were performed on Days 1, 5, and 26 (nominal days) for the 5-days-on and 2-days-off BID or QD Regimen (B5D or Q5D) and on Days 1, 8, and 29 for the BID Regimen (B7D).

NUMBER OF SUBJECTS: A total of 84 subjects were included in PK analyses.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:
In this study, 5 and 50 mg Phase I clinical film-coated tablets were used. Dasatinib was administered under fasted conditions.
5 mg tablet: 3C72889, 4C88975, 4G78659, 5A01426, 5C02739
50 mg tablet: 3C72907, 4C91969, 4G78663

DURATION OF TREATMENT: This is an ongoing study; subjects received at least 1 dose of dasatinib in the first cycle (4 weeks) of treatment for the PK assessments.

CRITERIA FOR PK EVALUATION:
The pharmacokinetics of orally administered dasatinib and BMS-606181 were derived from plasma concentration versus time data. The pharmacokinetic (PK) parameters assessed for dasatinib included: Cmax, Tmax, AUC(TAU), CL (apparent oral clearance), T-HALF, Vz/F (apparent volume of distribution in the terminal phase) and AI (accumulation index). The PK parameters assessed for BMS-606181 included: Cmax, Tmax, and AUC(0-T).

Analysis:
The PK parameters considered in the statistical analysis of dasatinib were Cmax, Tmax, AUC(TAU), T-HALF, and, although not specified in the protocol, accumulation index (ratio of AUC(TAU) on Days 5/8 or Days 26/29 over AUC(TAU) on Day 1), apparent oral clearance (CLo), and apparent volume of distribution in the terminal phase (Vz/F). The PK parameters Cmax, AUC(0-T) and Tmax for BMS-606181 were also calculated post-hoc.

Summary statistics were tabulated for the PK parameters of dasatinib and BMS-606181 both by disease status, dosing regimen (Q5D, B5D, B7D), dose and study day and by dosing regimen, dose and study day (grouping across disease status). Summary statistics were also provided for Tmax, T-HALF, CLo, and Vz/F of dasatinib by study day (grouping across disease status and dosing regimen and dose). Geometric means and coefficients of variation were presented for Cmax, AUC(TAU), AUC(0-T), and accumulation index. Medians, minima, and maxima were reported for Tmax. Means and standard deviations were provided for CLo, Vz/F and T-HALF.

In addition, the following statistical analyses were conducted post-hoc for dasatinib:

- To assess dose-proportionality, statistical linear regression analyses of log(AUC(TAU)) on log(dose), one for each study day, were conducted separately by regimen (QD and BID) and for all regimens combined.
- For the BID and combined analyses, AUC(TAU) and dose from the BID regimens were multiplied by 2 to make them comparable to the QD regimens. Point estimates and 90% confidence intervals were provided for the model parameters.
- To explore the effect of disease status on the pharmacokinetics of dasatinib, summary statistics were tabulated by disease status and study day for the parameters Tmax, T-HALF, CLo and Vz/F. Box plots of T-HALF, CLo and Vz/F, respectively, by disease status were presented for each study day.
- To explore the effect of age, gender, and race on the pharmacokinetics of dasatinib, summary statistics and box plots of CLo by age (< 65 and ≥ 65 years [65+]), gender and race (white and other), respectively, were provided by study day. Summary statistics and plots were provided for Vz/F and T-HALF.
- Scatter plots of CLo versus body surface area (BSA) and body weight by study day were also provided.

Statistical regression analyses between CLo and BSA or body weight for each study day were

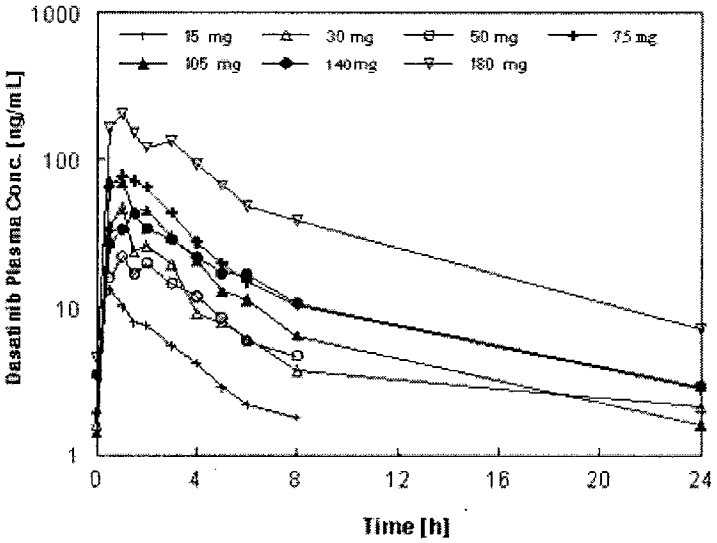
conducted to more formally assess these relationships.

RESULTS:

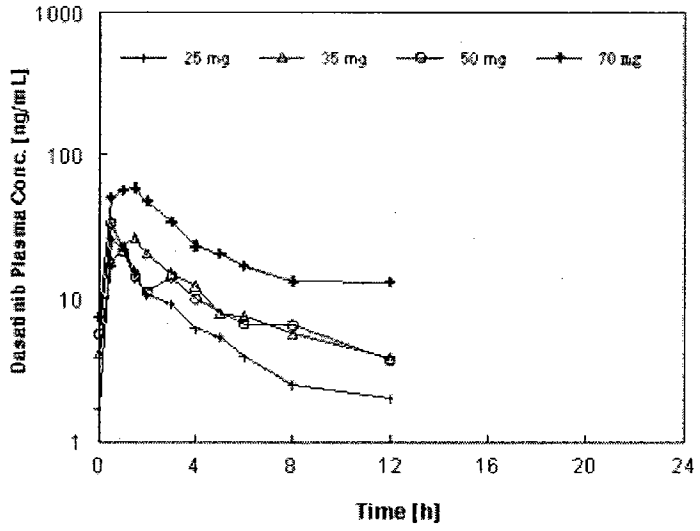
Pharmacokinetics of Dasatinib

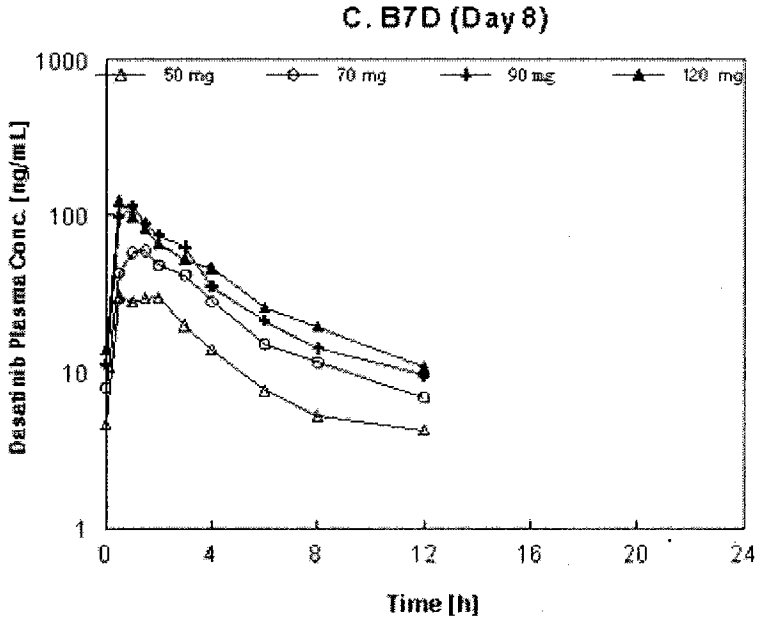
Mean dasatinib concentration-time profiles on Day 5 following Q5D and B5D dosing regimens and on Day 8 following B7D dosing regimen are presented in the figures below.

A. Q5D (Day 5)



B. B5D (Day 5)





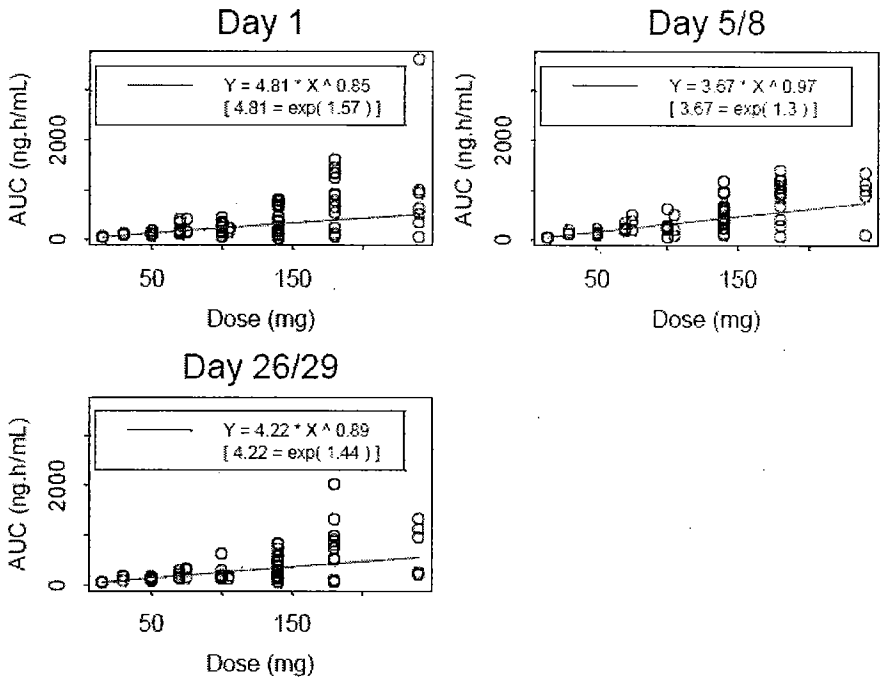
Dasatinib was rapidly absorbed after oral administration with the maximum concentration reached at a median Tmax of 1.17 h on Day 1 (for all dosing regimens and doses combined). The maximum concentration and the area under the concentration time curve values increased in a dose related manner for all the dosing regimens. However, high intersubject variability was observed. Combining all the dose groups and dosing regimens, the mean (SD) apparent T-HALF was 4.77 (2.94) h on Day 5/8 and 6.35 (6.80) h on Day 26/29, with the median value at 4.00 and 4.33 h on Day 5/8 and 26/29, respectively.

Both apparent oral clearance (CLo) and apparent volume of distribution in the terminal phase (Vz/F) showed high variability. Combining across the dose groups and dosing regimens, the mean CLo was 403.93 (412.18) L/h on Day 5/8 and 532.44 (508.56) h on Day 26/29, with the median value at 302.95 and 350.20 L/h on Day 5/8 and 26/29, respectively; the mean Vz/F was 2723.96 (3020.35) L on Day 5/8 and 6208.26 (14234.26) L on Day 26/29, with the median value at 1736.51 and 2279.31 L on Day 5/8 and 26/29, respectively.

At the proposed therapeutic dose of 70 mg BID (B5D and B7D regimens combined) and across study days, median Tmax and mean T-HALF ranged from 1.00 to 1.42 h and 3.77 to 5.44 h across study days, respectively; the mean (SD) CLo was 363.79 (295.68) and 557.93 (529.49) L/h on Days 5/8 and 26/29, respectively; the mean (SD) Vz/F was 2504.72 (2329.65) and 5018.45 (6531.67) L on Days 5/8 and 26/29, respectively; the geometric mean accumulation index (AI) were 1.61 and 1.01 on Day 5/8 and Day 26/29, respectively.

Dose Proportionality

To investigate dose proportionality, statistical linear regression analyses were performed on log(AUC(TAU)) versus log(dose) separately for each regimen (QD and BID) by study day. In addition, the analyses were also conducted for all regimens combined by study day. Scatter plots of AUC(TAU) versus dose with the estimated regression curves from the combined analyses for Days 1, 5/8 and 26/29, respectively, are presented in the figures below.



Note: For B5D/B7D, Dose = Total Daily Dose and AUC = 2*AUC(TAU).

The results of statistical regression analyses for dasatinib log(AUC(TAU)) vs log(Dose) suggest that AUC(TAU) increases approximately proportionally to the dose. Similar results were obtained when AUC(TAU) was analyzed separately for the BID and QD regimens.

Effect of Disease Status, Age, Gender, and Race

The assessment of the effect of disease status, age, gender, and race on the PK of dasatinib was based on the comparison of the key PK parameters (CLo, Vz/F, and T-HALF), which was possible since dose proportionality was observed in AUC(TAU) combined across regimens. No clinically relevant differences in the PK parameters were observed among the respective groups.

Effect of Body Weight and Body Surface Area

No clinically relevant relationship was detected between CLo and body weight or body surface area on any study day.

Pharmacokinetics of BMS-606181

The maximum concentration and the area under the concentration time curve (AUC(0-T)) of BMS-606181 increased in a dose-related manner for all the dosing regimens and dose levels. The median time to reach the maximum concentration ranged between 1.08 and 4.08 h across all dosing regimens and doses, indicating rapid conversion of dasatinib to BMS-606181. The ratio of the geometric mean of the area under the concentration time curve of BMS-606181 over that of dasatinib, unadjusted for the molecular weight, ranged from less than 1% to 16% across doses and study days; at the proposed therapeutic dose of 70 mg BID, the metabolite to dasatinib geometric mean AUC ratio ranged from 6 to 8% across study days.

PK CONCLUSIONS:

- Following oral administration, dasatinib was rapidly absorbed with peak plasma concentrations reached at median Tmax value of 1.17 h on Day 1 (all dosing regimens and doses combined). At the proposed therapeutic dose of 70 mg BID (dosing regimens B5D+B7D), median Tmax values ranged from 1.00 to 1.42 h (across study days).

- Maximum concentration and the area under the concentration versus time curve values for dasatinib increased in a dose related manner.
- Linear regression analyses suggested that the area under the concentration versus time curve (AUC) increases approximately proportionally to dose over the dose range of 25 to 120 mg BID.
- Dose proportionality in AUC was also noted for the QD regimen (dose range 15 to 180 mg QD) for AUC combined across regimens (dose range 15 to 240 mg/day). However, the variability for these data was high.
- Combining across dose groups and dosing regimens, the mean apparent half-life was 3.99 h on Day 1, 4.77 h on Day 5/8 and 6.35 h on Day 26/29. At the proposed therapeutic dose of 70 mg BID (dosing regimens B5D+B7D), mean half-life of dasatinib was 3.77, 4.76, and 5.44 h on Days 1, 5/8 and 26/29, respectively.
- Following multiple-dose administration, dasatinib did not show a consistent trend in accumulation on Day 5/8 or Day 26/29. At the proposed therapeutic dose of 70 mg BID geometric mean accumulation index of dasatinib was 1.61 and 1.01 on Days 5/8 and 26/29, respectively.
- Combining across dose groups and dosing regimens, the mean (SD) CLo was 403.93 (412.18) L/h on Day 5/8 and 532.44 (508.56) h on Day 26/29. At the proposed therapeutic dose of 70 mg BID mean (SD) CLo of dasatinib was 363.79 (295.68) and 557.93 (529.49) L/h on Days 5/8 and 26/29, respectively.
- Combining across dose groups and dosing regimens, the mean (SD) Vz/F was 2723.96 (3020.35) L on Day 5/8 and 6208.26 (14234.26) L on Day 26/29. At the proposed therapeutic dose of 70 mg BID, the mean (SD) Vz/F of dasatinib was 2504.72 (2329.65) and 5018.45 (6531.67) L on Days 5/8 and 26/29, respectively.
- CLo was not significantly related to body weight or body surface area. These data support the use of fixed dose (mg) of dasatinib for the treatment of cancer patients.
- Disease status, age, gender, and race had no clinically relevant effects on the PK of dasatinib.
- Cmax and AUC(0-T) of BMS-606181 (N-oxide metabolite) increase in a dose-related manner.
- The ratio of the geometric mean AUC values of BMS-606181 and dasatinib, unadjusted for the molecular weight, ranged from less than 1% to 16% across doses and study days. At the proposed therapeutic dose of 70 mg BID these ratios ranged from 6 to 8%, suggesting that BMS-606181 is a minor metabolite of dasatinib.

PD Results:

Efficacy: The main efficacy endpoints were hematologic response, cytogenetic response and molecular response.

Safety: The main safety endpoint was to establish the maximum tolerated dose (MTD), maximum administered dose (MAD), dose limiting toxicities (DLTs), and a recommended Phase 2 dose of dasatinib in subjects with CML and Ph+ ALL who had hematologic resistance to or intolerance of imatinib mesylate. Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs).

Pharmacokinetic/Pharmacodynamic: Plasma pharmacokinetics of dasatinib were evaluated on (i) Days 1, 5, and 26 of Cycle 1 for subjects on the 5-day-on and 2-day-off schedule and (ii) Day 1 and 8 of Cycle 1 and Day 1 of Cycle 2 for subjects on continuous dosing.

STATISTICAL METHODS:
Descriptive statistics were used to summarize demographic characteristics, safety and laboratory observations. Categorical variables were summarized in frequency tables. Continuous and other numeric variables were summarized by presenting the number of observations, mean, standard deviation, median, minimum and maximum.

Response rates (hematologic and cytogenetic) along with their 95% exact confidence intervals were estimated by subject status (resistant vs. intolerant) as reported in the case report forms and total for each disease group. Kaplan-Meier estimates of the median "time to variables" (ie, durations of hematologic and cytogenetic response, time to hematologic and cytogenetic response) were provided along with their 95% confidence intervals. The Kaplan-Meier estimate of the probability curve was also provided for each disease group.

The categories and definitions of severity used for AEs are defined in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. For each AE, the causal relationship to dasatinib was determined by the investigator (certain, probable, possible, not likely, or unrelated). The investigator adverse event terms were coded and grouped by system organ class using the MedDRA dictionary Version 8.0.

SUMMARY OF RESULTS:

Number of Subjects Accrued: The study was closed to accrual on 11-May-2005. This report summarizes a full set of data for each cycle of treatment up to 31-May-2005 on the first 84 subjects enrolled and treated by 15-Feb-2005, thus providing a minimum of 3 months follow-up for each subject.

Number of Subjects Accrued at Each QD Dose Level: CML (Only)
Dose Level N = 21

Dose Level	N = 21
15/ 30/ 50/ 75/ 105/ 140/ 180 QD	3/ 3/ 3/ 3/ 3/ 3/ 3

Number of Subjects Accrued at Each BID Dose Level: By Disease Group

Dose Level	Chronic	Accelerated	Myeloid Blast	Lymphoid Blast/ Ph+ ALL
	N = 19	N = 11	N = 23	N = 10
25 mg BID	3	-	-	-
35 mg BID	7	-	-	1
50 mg BID	3	3	3	2
70 mg BID	6	3	11	3
90 mg BID	-	2	5	4
120 mg BID	-	3	4	-

Demographics and Other Pertinent Baseline Characteristics: The median age of all 84 subjects was 56 years (range: 15 - 79 years); a third of them were ≥65 years of age. The subjects treated in this study were predominantly Caucasian (76%). The majority of subjects had a baseline performance score of either 0 (62%) or 1 (35%) as defined by the Eastern Cooperative Oncology Group (ECOG); only 3 subjects (4%) had the performance score of 2:1 with accelerated phase CML and 2 with lymphoid blast CML/Ph+ ALL.

Efficacy Results: Complete/major hematologic and major cytogenetic responses to dasatinib were reported in all phases of disease. Such responses were reported in imatinib-resistant as well as imatinib-intolerant subjects.

Response rate: Chronic Phase CML

Efficacy Endpoint	Chronic Phase CML	
	QD	BID
Imatinib-Resistant Subjects	N = 17	N = 15
Confirmed Complete Hematologic Response (CHR, %; 95% CI)	**94.1** (71.3 - 99.9)	**86.7** (59.5 - 98.3)
Major Cytogenetic Response (MCyR, %; 95% CI)	**41.2** (18.4 - 67.1)	**33.3** (11.8 - 61.6)
All Subjects: Resistant + Intolerant	N = 21	N = 19
Confirmed CHR (%; 95% CI)	**95.2** (76.2 - 99.9)	**89.5** (66.9 - 98.7)
MCyR (%; 95% CI)	**47.6** (25.7 - 70.2)	**42.1** (20.3 - 66.5)

Response rate: Advanced Phase CML / Ph+ ALL

Efficacy Endpoint	Accelerated	Myeloid Blast	Lymphoid Blast/Ph+ ALL
	BID	BID	BID
Imatinib-Resistant Subjects	N = 7	N = 22	N = 9
Best Hematologic Response:			
- Confirmed Major (%; 95% CI)	**57.1**	**31.8**	**44.4**
	(18.4 - 90.1)	(13.9 - 54.9)	(13.7 - 78.8)
- Confirmed Minor (%; 95% CI)	**0**	**36.4**	**11.1**
	(0.0 - 41.0)	(17.2 - 59.3)	(0.3 - 48.2)
- Confirmed Overall (%; 95% CI)	**57.1**	**68.2**	**55.6**
	(18.4 - 90.1)	(45.1 - 86.1)	(21.2 - 86.3)
MCyR (%; 95% CI)	**28.6**	**36.4**	**77.8**
	(3.7 - 71.0)	(17.2 - 59.3)	(40.0 - 97.2)
All Subjects: Resistant + Intolerant	N = 11	N = 23	N = 10
Best Hematologic Response:			
- Confirmed Major (%; 95% CI)	**54.5**	**30.4**	**50.0**
	(23.4 - 83.3)	(13.2 - 52.9)	(18.7 - 81.3)
- Confirmed Minor (%; 95% CI)	**0**	**34.8**	**10.0**
	(0.0 - 28.5)	(16.4 - 57.3)	(0.3 - 44.5)
- Confirmed Overall (%; 95% CI)	**54.5**	**65.2**	**60.0**
	(23.4 - 83.3)	(42.7 - 83.6)	(26.2 - 87.8)
MCyR (%; 95% CI)	**27.3**	**34.8**	**80.0**
	(6.0 - 61.0)	(16.4 - 57.3)	(44.4 - 97.5)

Many subjects in all phases of CML and Ph+ ALL who achieved only a partial, minor or no cytogenetic response on imatinib achieved higher cytogenetic response to dasatinib, including complete cytogenetic responses.

Mutations in the BCR-ABL gene have been reported in the literature to confer resistance to imatinib. In this study, BCR-ABL mutations were noted in 83%, 73%, 57% and 60% of chronic, accelerated, and myeloid blast phase CML and lymphoid blast phase CML/Ph+ ALL subjects, respectively. The majority of these subjects had hematologic and/or cytogenetic responses.

Safety Results:

Maximum Tolerated Dose: The criteria for MAD and MTD were not met in any of the treatment groups; and no MTD was reached in this study. The following events met the criteria of DLTs: (i) grade 4 thrombocytopenia at 35 mg BID on the 5 days on/2 days off schedule in a subject in chronic phase CML; none of the other 6 subjects enrolled in this cohort had grade 4 thrombocytopenia in the first 4 weeks of treatment, (ii) grade 3 pleural effusion and grade 4 pericardial effusion at 120 mg BID continuous daily dosing in a subject in myeloid blast phase CML; none of the remaining 3 subjects enrolled in this cohort had these DLTs in the first 4 weeks of treatment.

No patient was removed from the study either due to grade 4 thrombocytopenia or due to pericardial

or pleural effusion.

Overall Safety: The most frequent adverse events (reported in ≥ 50% of subjects in 2 or more disease groups) were fatigue, diarrhea, peripheral edema and headache. Twelve subjects died and 51 subjects reported at least one SAE during the study or up to 30 days after their last dose of dasatinib. The SAEs were considered by the investigator as related to dasatinib in 20 of 51 subjects. None of the subjects discontinued treatment due to adverse events. Most subjects had some degree of myelosuppression (grade 3 or 4 thrombocytopenia, neutropenia and/or leukopenia), which was more prominent among subjects with advanced disease than in those with chronic disease. Subjects with intolerance to imatinib were able to tolerate dasatinib and no imatinib-intolerant patient d **Deaths:** Twelve (12) subjects died on-study or within 30 days of their last dose of dasatinib (1 chronic QD, 1 chronic BID, 0 accelerated, 7 myeloid, 3 lymphoid blast/Ph+ ALL). Most deaths (9 of 12; 75%) were attributed to disease progression. Reasons for the other 3 deaths were: second metastatic solid tumor, sepsis, and concurrent disease progression and sepsis.

Serious Adverse Events: Fifty-one (51) subjects reported SAEs during the study or up to 30 days after their last dose of dasatinib. Twenty of these 51 subjects reported at least one SAE that was considered by the investigator as related to dasatinib; 3 of them later died due to disease progression (1 with pericardial effusion, 1 with tumor lysis syndrome and 1 with GI bleed).

Discontinuations Due to Adverse Event: Ten subjects (6 myeloid blast, 4 lymphoid blast/Ph+ ALL) discontinued treatment due to AEs; however, none of these events were drug-related and the reasons for discontinuation were considered to be events related to disease progression. The reported AEs that led to discontinuation in these 10 subjects were: disease progression (8 subjects), rapid progression of solid cancer (1 subject) or resistant mutation (1 subject). In all cases, these AEs were considered by theinvestigator as unrelated to dasatinib.

PD CONCLUSIONS:

- Dasatinib results in substantial hematologic and cytogenetic response rates across all phases of CML and in Ph+ ALL.
- Responses were durable across all phases of CML (up to 19 months in chronic phase, 11 months in accelerated phase, 10 months in myeloid blast phase and 5.1 months in lymphoid blast/Ph+ ALL).
- The majority of responses on dasatinib after imatinib resistance or intolerance were similar to or exceeded responses achieved by the same subjects when previously receiving imatinib treatment.
- Dasatinib can induce hematologic and cytogenetic responses in subjects harboring a broad range of BCR-ABL mutations, many of which confer resistance to imatinib.
- The most frequent adverse events were tolerable and severe adverse events could be managed by interruption or reduction in the dose.
- No subject was removed from the study for a drug-related adverse event.
- Subjects who discontinued imatinib due to intolerance before being enrolled in the present study were able to tolerate dasatinib and remain on treatment.
- Dasatinib demonstrates a favorable benefit/risk ratio for imatinib resistant or intolerant CML and Ph+ ALL.

4.1.2 Study CA180017 - Phase 2 Chronic CML

Study Reviewer: Angela Men, Ph.D., M.D.
Title: A Randomized Multicenter Open Label Study of BMS-354825 vs Imatinib Mesylate 800 mg/day in Subjects with Chronic Phase Philadelphia Chromosome-positive Chronic Myeloid Leukemia Who Have Disease That Is Resistant to Imatinib at a Dose of 400 - 600 mg/day

Study Initiation Date: 10-Feb-2005
Study Completion Date: The study is ongoing; 36 subjects had been randomized by 30-Jun-2005 (cutoff date for this interim report), enrolled at 18 sites worldwide

Introduction: This is an interim report of 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.

Objectives: The primary objective was to estimate the major cytogenetic response (MCyR) rates of dasatinib 70 mg BID and imatinib 800 mg/day (400 mg BID) at 12 weeks in subjects with chronic phase chronic myeloid leukemia (CML) resistant to imatinib 400 to 600 mg/day.

Methodology: This was 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. Eligible subjects were randomized in a 2-to-1 ratio to either dasatinib 70 mg BID or imatinib 400 mg BID, with continuous daily treatment. Randomization was stratified by site and cytogenetic response on prior imatinib therapy (any response, ie, complete, partial, minor, 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. Dose reduction of imatinib to 600 mg/day was allowed, provided the subject had not previously been treated at that dose level. Subjects with lack of response, confirmed disease progression or persistent intolerance despite dose reduction could be crossed over to the alternative treatment after an adequate washout period (2 days for dasatinib, 1 week for imatinib). After the crossover, treatment continued until further disease progression or development of intolerable toxicity. 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. On Day 8, subjects returned to the clinic where the morning dose was administered and blood samples were collected.

Efficacy: The primary efficacy endpoint was the major cytogenetic response (MCyR) at 12 weeks. MCyR rate was defined as the rate of complete cytogenetic response (CCyR) plus the rate of partial cytogenetic response (PCyR). Hematologic response was a secondary endpoint.

Response Rates at 12 weeks - All Randomized Subjects

	Number of Subjects (%)	
Efficacy Endpoints	Dasatinib N = 22	Imatinib N = 14
Cytogenetic Response		
MCyR	10 (45)	3 (21)
[95%CI]	[24.4, 67.8]	[4.7, 50.8]
CCyR	7 (32)	1 (7)
PCyR	3 (14)	2 (14)
MCyR by cytogenetic response on prior imatinib		
Any CyR	6/14	3/6
No CyR	4/8	0/8
Hematologic Response		
CHR	21 (95)	13 (93)

Safety: Safety was assessed continuously and was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs).

Summary of Safety - All Treated Subjects

	Number of Subjects (%)	
	Dasatinib N = 22	Imatinib N = 14
Death within 30 days of the last dose	0	0
Related SAEs	2 (9)	1 (7)
Relevant drug-related non-hematologic AEs		
Diarrhea	7 (32)	1 (7)
Nausea	7 (32)	7 (50)
Headache	6 (27)	1 (7)
Peripheral edema	2 (9)	3 (21)
Face or eyelid edema	2 (9)	3 (21)
Increased weight	2 (9)	4 (29)
Grade 3 hematologic toxicity		
Thrombocytopenia	3 (14)	2 (14)
Neutropenia	5 (23)	8 (57)
Leukopenia	1 (5)	4 (29)
Grade 4 hematologic toxicity		
Thrombocytopenia	6 (27)	0
Neutropenia	3 (14)	0
Leukopenia	2 (9)	0

CONCLUSIONS:
Dasatinib was effective in inducing CHR and MCyR after 12 weeks of treatment in subjects with chronic phase CML resistant to imatinib 400 to 600 mg/day, including in subjects who had not achieved cytogenetic response on prior imatinib therapy.

The principal safety findings were a higher incidence of nausea, neutropenia, and fluid retention in the imatinib group and of diarrhea, headache and severe thrombocytopenia in the dasatinib group. Overall, dasatinib had a manageable toxicity profile.

4.1.3 Study CA180013 - Phase 2 Chronic CML

Study Reviewer: Angela Men, Ph.D., M.D.
Title: A Phase 2 Study to Determine the Activity of BMS-354825 in Subjects with 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

Subjects: Two hundred one (201) subjects were enrolled at 41 centers worldwide and 186 subjects were treated at 39 centers

Study Initiation Date: 04-Feb-2005
Study Completion Date: The study is ongoing; accrual was closed on 15-Jul-2005 with a total of 424 subjects enrolled.

Introduction: This report is based on an interim analysis performed on 186 subjects who were enrolled by 12-May-2005, received their first dose of study drug by 31-May-2005, and had a minimum of 3 months of follow-up. Among the treated subjects, 127 were imatinib-resistant and 59 were imatinib intolerant. The data cutoff is 25-Oct-2005.

Objectives: The primary objective of this study was 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.

Methodology: This was an open-label Phase 2 study of dasatinib in subjects with chronic phase CML resistant to imatinib (> 600 mg/day) or ≤600 mg/day with mutations of the BCR-ABL gene, or who were intolerant of imatinib at any dose. Following screening, eligible subjects received dasatinib 70 mg continuously twice daily (BID). Dose escalation to 90 mg BID was allowed for subjects who showed evidence of progression or lack of response. Up to 2 dose reductions were allowed for toxicity. Treatment continued until progression of disease or development of intolerable toxicity or subject's decision to withdraw. All subjects were followed for a minimum of 30 days after the last

dose of study therapy or until recovery from all toxic effects, whichever was longer. Subsequent follow-up visits were to occur at least every 4 weeks until all study-related toxicities returned to baseline levels, resolved to ≤ CTC Grade 1, stabilized, or were deemed irreversible.
On Day 8, subjects returned to the clinic where the morning dose was administered and blood samples were collected.

Efficacy: The primary endpoint was MCyR to dasatinib in treated subjects with chronic phase CML who had resistance to imatinib. The hematologic responses were monitored and evaluated with regular blood drawings. The cytogenetic responses were monitored and evaluated with regular bone marrow biopsies. Hematologic and cytogenetic responses were evaluated for all treated subjects.

Response Rates - All Treated Subjects

	Number of subjects (%)		
	Intolerant N=59	Resistant N=127	Total N=186
Complete Hematologic Response	57 (96.6%)	109 (85.8%)	166 (89.2%)
95% exact CI	88.3% - 99.6%	78.5% - 91.4%	83.9% - 93.3%
Major Cytogenetic Response	38 (64.4%)	35 (27.6%)	73 (39.2%)
95% exact CI	50.9% - 76.4%	20.0% - 36.2%	32.2% - 46.7%

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs). On-study AEs were graded in severity by the investigators according to the NCI CTCAE, version 3.0 grading system. The investigator adverse event terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary, version 8.0 and were summarized by any grade, Grade 3 to 4 and Grade 5.

Overall Summary of Safety

	Imatinib-intolerant N = 59		Imatinib-resistant N = 127		Total N = 186	
Any AE	57	(97)	126	(99)	183	(98)
Grade 3 to 4 AEs	25	(42)	70	(55)	95	(51)
Drug-related AEs	56	(95)	121	(95)	177	(95)
Grade 3 to 4 drug related AEs	23	(39)	59	(46)	82	(44)
Death within 30 days of the last dose	0	(0)	3	(3)	3	(2)
Serious AEs	15	(25)	44	(35)	59	(32)
AEs that led to discontinuation	3	(5)	10	(8)	13	(7)
Drug-related AEs that led to discontinuation	2	(3)	8	(6)	10	(5)
Grade 3 to 4 hematologic laboratory abnormalities [a]						
Thrombocytopenia	21	(36)	64	(51)	85	(46)
Neutropenia	21	(36)	62	(50)	83	(45)
Leukopenia	11	(19)	32	(25)	43	(23)
Anemia	6	(10)	28	(22)	34	(18)

[a] Percent calculated based on number of subjects with laboratory measurements

CONCLUSIONS:

Efficacy

- Therapy with dasatinib (70 mg BID) results in a clinically relevant MCyR rate of 28% in pretreated subjects with chronic phase CML whose disease is resistant to imatinib
- A clinically relevant CHR rate of 86% is also achieved in this population.
- Subjects with chronic phase CML who are intolerant of imatinib are able to tolerate dasatinib resulting in a 97% CHR rate and a 64% MCyR rate.
- The responses are durable; as of the data cutoff of this interim report, none of the subjects who achieved CHR or MCyR have progressed or died.

Safety

• Dasatinib is safe and tolerable in subjects with heavily pretreated chronic phase CML. Thrombocytopenia, fluid retention, and pleural effusion were among the most relevant AEs.
• Subjects with chronic phase CML who are intolerant of imatinib are able to receive dasatinib without experiencing the same adverse events that caused them to discontinue imatinib therapy.

4.1.4 Study CA180005 - Phase 2 Accelerated Phase CML

STUDY REVIEWER: Angela Men, Ph.D., M.D.
TITLE: A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
INVESTIGATORS/STUDY CENTERS: 40 investigators enrolled and treated 107 subjects at 40 centers

INTRODUCTION: This report is based on an interim analysis performed for all subjects consecutively enrolled through 12-May-2005 (enrollment cutoff date) who received the first dose of study drug on or before 22-May-2005. This includes the first 120 enrolled and 107 treated subjects. The treated subjects included 99 that were imatinib-resistant and 8 that were imatinib-intolerant. The data cutoff date was 19- Oct-2005.

OBJECTIVES: The primary objective was 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.

METHODOLOGY: This was an open-label Phase 2 study in subjects with accelerated phase CML with primary and acquired resistance to imatinib mesylate. A separate group of subjects intolerant to imatinib was also enrolled. Subjects were followed for a minimum of 30 days after the last dasatinib dose or until recovery from all toxic effects, whichever was longer. Follow-up visits occurred at least every 4 weeks until all study-related toxicities returned to baseline levels or ≤ CTCAE Grade 1, stabilized, or were deemed irreversible.

PK Results:

Table 2.2A: Summary Statistics of Dasatinib Pharmacokinetic Parameters for Subjects with Intensive PK Sampling (Study CA180005)

PK Parameter	Statistic	Study Day 1	Study Day 8
Cmax (ng/mL)	N Geometric Mean CV (%)	29 54.33 62	27 67.39 77
AUC(0-T) (ng•h/mL)	N Geometric Mean CV (%)	29 170.59 61	27 295.97 70
Tmax (h)	N Median (min, max)	29 1.00 (0.42, 5.00)	27 1.00 (0.50, 4.75)
T-half (h)	N Mean SD	28 3.15 0.86	26 5.18 2.12

Table 2.3A: Summary Statistics of BMS-582691 Pharmacokinetic Parameters for Subjects with Intensive PK Sampling (Study CA180005)

PK Parameter	Statistic	Study Day 1	Study Day 8
Cmax (ng/mL)	N Geometric Mean CV (%)	24 2.54 54	24 3.77 67
AUC(0-T) (ng•h/mL)	N Geometric Mean CV (%)	24 6.90 85	24 11.80 85
Tmax (h)	N Median (min, max)	24 1.50 (0.50, 4.32)	24 1.50 (0.25, 5.57)
T-half (h)	N Mean SD	22 3.30 1.94	20 5.70 4.89

Efficacy: Co-primary endpoints were the rates of major hematologic response (MaHR) and overall hematologic response (OHR). The hematologic responses were monitored and evaluated with regular blood drawings. The cytogenetic responses were monitored and evaluated with regular bone marrow biopsies.

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs).

STATISTICAL METHODS:
Efficacy responses were programmatically determined from hematologic laboratory values, bone marrow biopsy values, and the presence or absence of extramedullary disease. Response rates and 95% confidence intervals (CIs) were estimated. Kaplan-Meier estimates and 95% CIs were provided for the time to and duration of response (MaHR and OHR).

SUMMARY OF RESULTS:
Disposition, Demographics, and Other Pertinent Baseline Characteristics:
A total of 120 subjects were enrolled and 107 received at least 1 dose of dasatinib. Of the 107 subjects, 99 treated subjects were classified as imatinib-resistant, while 8 were imatinib-intolerant. The age of the study population ranged from 23 to 86 years with approximately equal numbers of male (51%) and female (49%) subjects who were predominantly Caucasian (86%). ECOG performance status scores of 0 and 1 were reported in 47% and 39% of the subjects, respectively.

All subjects had a long history of CML and were extensively pretreated. The median time from initial CML diagnosis to the start of dosing was 91 months for all treated subjects. The majority (68%) of subjects received more than 3 years of imatinib therapy. Sixty-three (59%) subjects were treated with doses of imatinib > 600 mg/day. Overall, 83% of the subjects demonstrated a complete hematologic response (CHR) to imatinib, and 32% of the subjects demonstrated a major cytogenetic response (MCyR) to imatinib. Grade 3 to 4 hematologic abnormalities were: thrombocytopenia (23%), neutropenia (7%), WBC (5%), and anemia (5%). For all treated subjects, the median duration on study therapy was 4.2 months. For subjects still remaining on study (N=87), the median time on study therapy is 4.6 months.

A total of 20 (19%) subjects discontinued study treatment. All discontinuations of study therapy were in the imatinib-resistant subgroup. Of these discontinuations, there were 9 (9%) due to disease progression, 2 (2%) due to study drug toxicity, 1 (1%) due to an AE unrelated to study drug, 3 (3%) due to subject request, 4 (4%) due to death, and 1 (1%) due to 'other', which was reported as a total lack of cytogenetic response.

Efficacy Results:
The efficacy of dasatinib was demonstrated consistently across efficacy endpoints in the primary target population of imatinib-resistant subjects. None of the 58 responders with a major hematologic response progressed or died. The longest duration of response to date has been 7.9+ months and the shortest duration of response has been 1.1+ months.

Overall Summary of Efficacy - All Treated Subjects

Efficacy Endpoint	Resistant N = 99	Intolerant N = 8	Total N = 107
Major Hematologic Response	54 (55%)	4 (50%)	58 (54%)
95% CI	44% - 65%	16% - 84%	44% - 64%
Overall Hematologic Response	78 (79%)	7 (88%)	85 (79%)
95% CI	69% - 86%	47% - 100%	71% - 87%
Major Cytogenetic Response	28 (28%)	0 (0%)	28 (26%)
95% CI	20% - 38%	0% - 37%	18% - 36%

Safety Results:
Dasatinib demonstrated an acceptable safety profile in subjects with accelerated phase CML. The most common Grade 3 to 4 AEs reported in ≥ 10% of subjects were thrombocytopenia, febrile neutropenia, and diarrhea. Additionally, the safety profile of dasatinib in imatinib-intolerant subjects was consistent with that in imatinib-resistant subjects. Subjects who were intolerant to imatinib were able to receive dasatinib and none of these subjects discontinued from the current trial, suggesting a partial lack of cross intolerance between the 2 agents.

Overall Summary of Safety - All Treated Subjects

	Imatinib-Resistant N=99		Imatinib-Intolerant N=8		Total N=107	
	N	(%)	N	(%)	N	(%)
Any AE	99	(100)	8	(100)	107	(100)
Grade 3 to 4 AE	63	(64)	7	(88)	70	(65)
Drug-related AE	92	(93)	8	(100)	100	(94)
Grade 3 to 4 Drug-related AE	49	(50)	6	(75)	55	(51)
Deaths	4	(4)	0		4	(4)
SAEs	51	(52)	7	(88)	58	(54)
AEs that led to discontinuation	5	(5)	0		5	(5)
Drug-related AEs that led to discontinuation	1	(1)	0		1	(1)
Grade 3 to 4 Hematologic Abnormalities:						
Thrombocytopenia	78	(79)	7	(88)	85	(79)
Neutropenia	69	(70)	7	(88)	76	(71)
Leukopenia	56	(57)	6	(75)	62	(58)
Anemia	65	(66)	6	(75)	71	(66)

CONCLUSIONS:
Efficacy:

- Therapy with dasatinib (70 mg BID) resulted in a clinically important MaHR of 55% and an OHR of 79% in subjects with heavily-pretreated accelerated phase CML whose disease is resistant to imatinib.
- Therapy with dasatinib resulted in a clinically important MCyR of 28% and CCyR of 19% in subjects with heavily-pretreated accelerated CML whose disease is resistant to imatinib.
- Responses were durable; 58 subjects who achieved MaHR did not progress or die.
- Subjects with accelerated phase CML who are intolerant of imatinib tolerated dasatinib and hematologic responses were observed in 4 of 8 subjects.

Safety:

- Dasatinib demonstrated an acceptable safety profile in subjects with heavily-pretreated accelerated phase CML, even those with compromised bone marrow functions.
- Subjects with accelerated phase CML who were intolerant to imatinib tolerated dasatinib and none of these subjects discontinued from the current trial, suggesting a partial lack of cross intolerance between the 2 agents.

Overall:

- Based on the response rates in this study, dasatinib is an important therapeutic option for subjects with accelerated phase CML that is resistant to imatinib and for subjects with accelerated phase CML who are intolerant of imatinib.

4.1.5 Study CA180006 - Phase 2 Myeloid Blast Phase Chronic CML

STUDY REVIEWER: Angela Men, Ph.D., M.D.
TITLE: A Phase 2 Study of Dasatinib (BMS-354825) in Subjects with Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate
INVESTIGATORS/ STUDY CENTERS: 35 investigators enrolled and treated 74 subjects at 35 sites worldwide

INTRODUCTION: This is an interim report with data collected on the first 80 subjects enrolled on or before 17-May-2005, treated on or before 18-May-2005, and with a minimum of 3 months (12 weeks) follow-up for subjects who are still on study. Of the first 80 enrolled, 74 were treated, including 68 who were imatinib-resistant and 6 who were imatinib-intolerant. The data cutoff is 17-

Oct-2005.

OBJECTIVES: The primary objective was to estimate the major and overall hematologic response rates to dasatinib in myeloid blast phase CML subjects with primary or acquired resistance to imatinib.

METHODOLOGY: Eligible subjects received oral dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed for the management of disease progression or toxicity. All subjects were followed for a minimum of 30 days after the last dose of study therapy or until recovery from all toxic effects, whichever was longer. Follow-up visits occurred at least every 4 weeks until all study related toxicities returned to baseline levels or ≤Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]), stabilized, or were deemed irreversible.

PK Results:

Table 2.2B: Summary Statistics of Dasatinib Pharmacokinetic Parameters for Subjects with Intensive PK Sampling (Study CA180006)

PK Parameter	Statistic	Study Day 1	Study Day 8
Cmax (ng/mL)	N Geometric Mean CV (%)	24 35.60 93	19 101.26 40
AUC(0-T) (ng•h/mL)	N Geometric Mean CV (%)	24 108.16 93	19 268.85 57
Tmax (h)	N Median (min, max)	24 1.38 (0.47, 6.00)	19 0.67 (0.25, 3.00)
T-half (h)	N Mean SD	23 3.71 1.78	19 4.26 2.15

Table 2.3B: Summary Statistics of BMS-582691 Pharmacokinetic Parameters for Subjects with Intensive PK Sampling (Study CA180006)

PK Parameter	Statistic	Study Day 1	Study Day 8
Cmax (ng/mL)	N Geometric Mean CV (%)	14 2.13 54	18 3.58 43
AUC(0-T) (ng•h/mL)	N Geometric Mean CV (%)	14 3.84 110	18 10.48 87
Tmax (h)	N Median (min, max)	14 1.50 (0.55, 4.00)	18 1.50 (0.50, 6.07)
T-half (h)	N Mean SD	9 4.95 3.93	16 4.38 3.97

Efficacy: The hematologic responses were monitored and evaluated with regular blood drawings. The cytogenetic responses were monitored and evaluated with regular bone marrow biopsies.

Safety: Safety assessment was based on medical review of adverse events (AEs), clinical laboratory values, and electrocardiograms (ECGs) results. On-study AEs were graded in severity by the investigators according to the NCI CTCAE, version 3.0 grading system. The investigator adverse event terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary, version 8.0 and were summarized by any grade, Grade 3 to 4 and Grade 5.

STATISTICAL METHODS: Summary statistics (mean, median, range for continuous variables and frequency for categorical variables) were provided for all pre-treatment characteristics including disease history and prior therapy. Efficacy responses were programmatically determined from hematologic laboratory values, bone marrow cytology and cytogenetics, and extramedullary disease. Response rates and
95% confidence intervals (CIs) were estimated. Kaplan-Meier estimates and 95% CIs were provided for the time to response (major and overall) and the duration of response. Safety analyses included the frequency of assessment of adverse events, serious adverse events, deaths, discontinuations, and laboratory abnormalities. All analyses were presented for all treated subjects, imatinib-resistant and imatinib-intolerant subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics:

As of the data cutoff date for this interim analysis, the first 80 subjects had been enrolled and 74 had received at least 1 dose of dasatinib (68 imatinib-resistant and 6 imatinib-intolerant). Three subjects were enrolled on 17-May-05: only 1 of the 3 subjects was included in the primary efficacy and safety analysis; the other 2 subjects were excluded because of delayed first dosing. Six enrolled subjects did not receive dasatinib on this trial; the reasons included subjects not meeting the criteria for myeloid blast CML, screen failure (prolonged QT interval), or death prior to entering treatment. Among the 74 subjects treated, 39 (53%) subjects have discontinued dasatinib at the time of this report.

Disease progression was reported as the most common reason for discontinuing the trial, occurring in 22 of 39 off treatment subjects. Seven subjects had death listed as the reason for discontinuation, 4 discontinued because of study drug toxicity, the remaining 6 discontinued of other reasons, eg, AEs unrelated to study drug or non-compliance.

The median age of all subjects was 55 years (range 21 to 71 years); approximately half were 46 to 65 years of age. The subjects were predominantly male (55%) and Caucasian (76%). Most subjects (58%) had a baseline performance score of 0 or 1 as defined by the Eastern Cooperative Oncology Group (ECOG). All subjects had a long history of CML and were extensively pretreated. All subjects had received prior imatinib, consistent with entry criteria. Thirty-six (49%) subjects had received > 600 mg imatinib while the remaining 38 (51%) subjects had received 400-600 mg imatinib.

Nearly half of the subjects, 35 (47%) had received imatinib for > 3 years, 28 (38%) had received imatinib for 1-3 years, and only 11 (15%) had received imatinib for < 1 year.

The median time from initial CML diagnosis to first dasatinib dosing was 48.9 months. The median time on study therapy (ie, duration of treatment) was 3.29 months. For 35 subjects still on therapy, the median time on therapy was 4.6 months. Among treated subjects, 60 (81%) received > 90% of the planned dasatinib dose.

Efficacy Results: Dasatinib activity was demonstrated across all efficacy endpoints in the primary target population of imatinib-resistant subjects. As of data cutoff, none of the 22 responders with the major hematologic response progressed or died, with the shortest duration of response being 1.2+ months and the longest being 6.3+ months. One of these subjects (CA180006-95-6008) discontinued due to allogeneic bone marrow transplant.

Response Rates - All Treated Subjects

	Number of Subjects (%)		
	Imatinib- intolerant N=6	Imatinib-resistant N=68	Total N=74
Major Hematologic Response	1 (16.7%)	21 (30.9%)	22 (29.7%)
95% CI	0.4% - 64%	20.2% - 43.3%	19.7% - 41.5%
Overall Hematologic Response	3 (50.0%)	35 (51.5%)	38 (51.4%)
95% CI	11.8% - 88.2%	39.0% - 63.8%	39.4% - 63.1%
Major Cytogenetic Response	2 (33.3%)	19 (27.9%)	21 (28.4%)
95% CI	4.3% - 77.7%	17.7% - 40.1%	18.5% - 40.1%

Safety Results: Dasatinib demonstrated an acceptable safety profile in subjects with myeloid blast CML.

The most common Grade 3 to 4 AEs reported in ≥10% subjects were thrombocytopenia, neutropenia, anemia, pyrexia, and febrile neutropenia. Subjects who were intolerant of imatinib were able to tolerate dasatinib and none of these subjects were discontinued from the current trial for study drug toxicity, suggesting a lack of cross intolerance between the two agents.

Overall Summary of Safety - All Treated Subjects

	N (%)		
	Imatinib- intolerant N=6	Imatinib-resistant N=68	Total N=74
Any AE	6 (100)	68 (100)	74 (100)
Grade 3 to 4 AEs	4 (67)	44 (65)	48 (65)
Drug-related AEs	6 (100)	63 (93)	69 (93)
Drug-related Grade 3 to 4 AEs	3 (50)	39 (57)	42 (57)
Deaths	2 (33)	23 (34)	25 (34)
Serious AEs	3 (50)	50 (74)	53 (72)
AEs that led to discontinuation	0 (0)	20 (29)	20 (27)
Drug-related AEs that led to discontinuation	0 (0)	4 (6)	4 (5)

Overall Summary of Safety - All Treated Subjects

Grade 3 to 4 Hematologic Laboratory Abnormalities:

	N (%)		
	Imatinib- intolerant N=6	Imatinib-resistant N=68	Total N=74
Thrombocytopenia	3 (50)	58 (85)	61 (82)
Neutropenia	5 (83)	54 (79)	59 (80)
Leukopenia	4 (67)	42 (62)	46 (62)
Anemia	3 (50)	46 (68)	49 (66)

CONCLUSIONS:

Efficacy

- Therapy with dasatinib (70 mg BID) resulted in a clinically important MaHR rate of 31% and an OHR rate of 52% in subjects with heavily-pretreated myeloid-blast CML whose disease was resistant to imatinib.
- Therapy with dasatinib resulted in a clinically important cytogenetic response rate of 28% in subjects with heavily-pretreated myeloid-blast CML whose disease was resistant to imatinib.
- The responses were durable; all 22 subjects who achieved MaHR did not progress or die.
- Subjects with myeloid blast phase CML who were intolerant of imatinib were able to tolerate dasatinib and despite limited numbers of subjects, hematologic and cytogenetic responses were reported.

Safety

- Dasatinib was safe and tolerable in subjects with heavily-pretreated myeloid-blast CML, even those with compromised bone marrow functions.
- Subjects with myeloid-blast CML who were intolerant of imatinib were able to tolerate dasatinib, and none of these subjects were discontinued from the current trial for study drug toxicity, suggesting a lack of cross intolerance between the two agents.

4.1.6 Study CA180015 - Phase 2 Lymphoid Blast Phase CML or Ph+ALL

STUDY REVIEWER: Angela Men, Ph.D., M.D.

TITLE: A Phase 2 Study of BMS-354825 in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

INVESTIGATORS/ STUDY CENTERS: Subjects were enrolled and treated by 34 investigators at 34 Sites

INTRODUCTION: This is an interim report with data collected on the first 81 subjects enrolled on or before 23-May-2005 and treated on or before 01-Jun-2005, with a minimum of 3 months (12 weeks) follow-up for subjects who remained on study as of the data cutoff (20-Oct-2005). Of the first 81 subjects enrolled, 78 were treated (42 lymphoid blast chronic myeloid leukemia [CML] subjects and 36 Philadelphia chromosome positive acute lymphoblastic leukemia [Ph+ ALL] subjects).

OBJECTIVES: The primary objective of this study was 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.

METHODOLOGY: This was an open-label Phase 2 study of dasatinib in subjects with imatinib-resistant lymphoid blast CML or Ph+ ALL. A separate group of subjects with lymphoid blast phase CML or Ph+ ALL intolerant to imatinib was also enrolled. Eligible subjects received dasatinib at a starting dose of 70 mg twice daily (BID). Dose modifications were allowed for the management of disease progression or toxicity. Treatment continued until progression of disease or development of intolerable toxicity. All subjects were followed for a minimum of 30 days after the last dose of study therapy or until recovery from all toxic effects, whichever was longer. Follow-up visits occurred at least every 4 weeks until all study related toxicities returned to baseline levels or ≤National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, stabilized, or were deemed irreversible.

Efficacy: Co-primary endpoints were the rates of major hematologic response (MaHR) and overall hematologic response (OHR). The hematologic responses were evaluated with regular blood draws and the cytogenetic responses were evaluated with regular bone marrow biopsies.

Safety: Assessment of safety was based on medical review of adverse events (AEs), clinical laboratory tests, and electrocardiograms (ECGs).

STATISTICAL METHODS: Summary statistics (mean, median, range for continuous variables, and frequency for categorical variables) were provided for all pretreatment characteristics, including disease history and prior therapy. Efficacy responses were programmatically determined from hematologic laboratory values, bone marrow cytology and cytogenetics, and extramedullary disease. Response rates and 95% confidence intervals (CIs) were estimated. Kaplan-Meier estimates and 95% CIs were provided for the time to response (major and overall) and the duration of response. Safety analyses included the frequency of assessment of AEs, serious adverse events (SAEs), deaths, discontinuations, and laboratory abnormalities. All analyses were presented for all treated subjects, lymphoid blast CML subjects, Ph+ ALL subjects, and imatinib resistant subjects.

SUMMARY OF RESULTS:

Disposition, Demographics, and Other Pertinent Baseline Characteristics: As of the data cutoff for this interim analysis, the first 81 subjects had been enrolled and 78 had received at least 1 dose of dasatinib (42 lymphoid blast CML subjects; 36 Ph+ ALL subjects). Seventy-one treated subjects were imatinib-resistant (37 lymphoid blast CML and 34 Ph+ ALL); 7 treated subjects were imatinib-intolerant (5 lymphoid blast CML and 2 Ph+ ALL). Three enrolled subjects never received dasatinib; 1 died prior to entering treatment, 1 was a screen failure (prolonged QT interval), and 1 was enrolled but not treated (no further information available). As of the data cutoff, 11 (26%) lymphoid blast CML subjects and 13 (36%) Ph+ ALL subjects were still on treatment and 31 (74%) lymphoid blast CML subjects and 23 (64%) Ph+ ALL subjects had discontinued treatment. Approximately 40% of the subjects discontinued due to disease progression (17 [41%] lymphoid blast CML subjects and 15 [42%] Ph+ ALL subjects); only 3 subjects, 1 lymphoid blast CML and 2 Ph+ ALL, discontinued due to drug toxicity. Nine subjects were noted as discontinuations at the time of death (6 [14%] lymphoid blast CML subjects and 3 [8%] Ph+ ALL subjects). Two subjects in the lymphoid blast CML population and one subject in the Ph+ ALL population discontinued due to deterioration without progression. Seven subjects (5 [12%] lymphoid blast CML and 2 [6%] Ph+ ALL) discontinued due to "other" reasons, including stem cell transplant (3 subjects), bone marrow transplant (1 subject), transplantation (1 subject), started conditioning before transplantation (1 subject), and withdrawal of consent (1 subject).

The demographics of the lymphoid blast CML and Ph+ ALL populations were generally similar: median age, 47 and 46 years; race, 95% and 97% Caucasian; male gender, 52% and 64%; and ECOG scores of 0 to 1, 74% and 67%, respectively. All subjects had received prior imatinib therapy, consistent with entry criteria: 29% of lymphoid blast CML subjects and 53% of Ph+ ALL subjects had received imatinib for 1 to 3 years. Fifty-two percent of the lymphoid blast CML subjects and 47% of the Ph+ ALL subjects had received an imatinib dosage > 600 mg/day.

Subjects in this study had a long history of CML and Ph+ ALL and were extensively pretreated. The median time from initial diagnosis to the start of dosing was 28 months for the lymphoid blast CML subjects and 20 months for the Ph+ ALL subjects. In this study, the median duration of therapy was 2.8 months in lymphoid blast CML subjects and 2.7 months in Ph+ ALL subjects. For the subjects who were still on study as of the data cutoff, the median duration of therapy was 3.8 months for the lymphoid blast subjects (N = 11) and 4.6 months for the Ph+ ALL subjects (N = 13).

Efficacy Results: Treatment with dasatinib 70 mg BID resulted in clinically important hematologic and cytogenetic response rates in both lymphoid blast CML and Ph+ ALL subjects (See efficacy tables below).
As of the data cutoff, only 3 of the 12 lymphoid blast CML subjects with MaHR had progressed or died, with the shortest duration of response being 1.6+ months and the longest being 4.0+ months. Similarly, as of the data cutoff only 3 of the 15 PH+ ALL subjects with MaHR had progressed or died, with the shortest duration of response being 1.2+ months and the longest being 4.7+ months.

Overall Summary of Efficacy - All Treated Subjects with Lymphoid Blast CML

	Number of Subjects (%)		
	Intolerant* N = 5	Resistant N = 37	Total N = 42
Efficacy Endpoint			
Major Hematologic Response	1 (20.0)	11 (29.7)	12 (28.6)
95% CI	NA	15.9% - 47.0%	15.7% - 44.6%
Overall Hematologic Response	1 (20.0)	13 (35.1)	14 (33.3)
95% CI	NA	20.2% - 52.5%	19.6% - 49.5%
Major Cytogenetic Response	3 (60.0)	18 (48.6)	21 (50.0)
95% CI	NA	31.9% - 65.6%	34.2% - 65.8%

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

Overall Summary of Efficacy - All Treated Subjects with Ph+ ALL

	Number of Subjects (%)		
	Intolerant* N = 2	Resistant N = 34	Total N = 36
Efficacy Endpoint			
Major Hematologic Response	2 (100.0)	13 (38.2)	15 (41.7)
95% CI	NA	22.2% - 56.4%	25.5% - 59.2%
Overall Hematologic Response	2 (100.0)	14 (41.2)	16 (44.4)
95% CI	NA	24.6% - 59.3%	27.9% - 61.9%
Major Cytogenetic Response	2 (100.0)	19 (55.9)	21 (58.3)
95% CI	NA	37.9% - 72.8%	40.8% - 74.5%

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

Safety Results:
Dasatinib demonstrated an acceptable safety profile in subjects with lymphoid blast CML or Ph+ ALL. The most common Grade 3 to 4 AEs seen in ≥10% of lymphoid blast CML subjects were febrile neutropenia, pyrexia, fatigue, pneumonia, and anemia. The most common Grade 3 to 4 AEs in Ph+ ALL subjects were febrile neutropenia, pyrexia, and dyspnea.

Overall, some degree of myelosuppression was common, both at baseline and on treatment, occurring in most lymphoid blast CML and Ph+ ALL subjects. On-study Grade 3 to 4 myelosuppression occurred with similar frequency in both populations. Only 2 of the 7 imatinib-intolerant subjects were discontinued from the current trial for AEs or study drug toxicities, suggesting a partial lack of cross - intolerance between the 2 agents in this population.

Overall Summary of Safety - All Treated Subjects

	Number of Subjects (%)		
	Lymphoid Blast CML N = 42	Ph+ ALL N = 36	Total N=78
Any AE	42 (100)	35 (97)	77 (99)
Grade 3 - 4 AE	26 (62)	25 (69)	51 (65)
Drug-related AE	36 (86)	31 (86)	67 (86)
Grade 3 -4 drug-related AE	18 (43)	20 (56)	38 (49)
Deaths	15 (36)	15 (42)	30 (38)
Serious AE	32 (76)	28 (78)	60 (77)
AEs that led to discontinuation	15 (36)	13 (36)	28 (36)
Drug-related AEs that led to discontinuation	0	3 (8)	3 (4)
Grade 3 to 4 hematologic abnormalities			
Leukopenia	29 (69)	23 (64)	52 (67)
Neutropenia	33 (83)	26 (74)	59 (76)
Thrombocytopenia	37 (88)	27 (75)	64 (82)
Anemia	22 (52)	16 (44)	38 (49)

CONCLUSIONS:

Efficacy

- Therapy with dasatinib 70 mg BID resulted in clinically important MaHR rates of 30% in lymphoid blast CML subjects and 38% in Ph+ ALL subjects whose disease was resistant to imatinib.
- Therapy with dasatinib 70 mg BID resulted in clinically important OHR rates of 35% in lymphoid blast CML subjects and 41% in Ph+ ALL subjects whose disease was resistant to imatinib.
- Therapy with dasatinib 70 mg BID resulted in clinically important MCyR rates of 49% in lymphoid blast CML subjects and 56% in Ph+ ALL subjects whose disease was resistant to imatinib.
- The responses to dasatinib were durable: As of the data cutoff, 3 of the 12 lymphoid blast CML subjects with MaHR had progressed or died, and 3 of the 15 PH+ ALL subjects with MaHR hadprogressed or died.
- Most of the subjects with heavily-pretreated lymphoid blast CML or Ph+ ALL who are intolerant of imatinib are able to tolerate dasatinib and achieve hematologic and cytogenetic responses.

Safety

- Dasatinib 70 mg BID demonstrated an acceptable safety profile in subjects with heavily-pretreated lymphoid blast CML or Ph+ ALL, even those with compromised bone marrow functions.
- Most subjects with heavily pretreated lymphoid blast CML or Ph+ ALL who are intolerant of imatinib are able to tolerate dasatinib without discontinuing from the study for AEs or study drug toxicities, suggesting a partial lack of cross-intolerance between the 2 agents in this population.

4.1.7 Major AEs in Phase 2 studies

Major AE	N
DIARRHEA	551
FATIGUE	507
FEVER	476
NAUSEA	364
THROMBOCYTOPENIA	357
HEADACHE	355
ASTHENIA	222
VOMITING	221
COUGH	210
NEUTROPENIA	206
ANOREXIA	176
ANEMIA	158
DYSPNEA	157
WEIGHT LOSS	126

CONSTIPATION	117
PLEURAL EFFUSION	105
BONE PAIN	99
WEIGHT GAIN	99
SHORTNESS OF BREATH	94
RASH	88
ABDOMINAL PAIN	85
DIZZINESS	79
NIGHT SWEATS	77
CHILLS	73
INSOMNIA	67
PERIORBITAL EDEMA	65
BACK PAIN	64
HYPERTENSION	57
ANXIETY	53

4.1.8 PK collection on the Phase 2 studies:

Table 2.1: Phase 2 Studies in Subjects with Leukemia

Study	Population	Subjects with dense PK samples	Subjects with sparse PK samples	PK[a,b] Assessment Hours
CA180005	Accelerated CML	29,27[c]	10	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10
CA180006	Blast Phase CML	24,22[d]	4	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10
CA180013	Chronic CML	0	133	0, 3, 8, 12
CA180015	Ph+ ALL	0	41	0, 3
CA180017	Chronic CML	0	21	0, 3, 8, 12

Source: Individual Study Protocols

[a] Fourteen subjects in studies CA180005 (N=10) and CA180006 (N=4) had sparse samples collected on day 8 at 0 and 3 h.

[b] For studies CA180013, CA180015 and CA180017, there were a total of 195 subjects with sparse samples.

[c] N=29 on day 1 and N=27 on day 8. PK parameters for Subject CA180005-1-5065 and Subject CA180005-1-5071, both on Day 8, were excluded from the summary statistics because these subjects reported 0 and 0.5 h nominal times as 0 h actual times; the data were judged to be unreliable. PK parameters for Subject CA180005-33-5010, Day 8, were excluded from the summary statistics because the subject received 50 mg twice daily.

[d] N=24 on day 1 and N=22 on day 8. PK parameters for Subjects CA180006-1-6063, CA180006-69-6036, CA180006-44-6004, Day 8 were excluded from the summary statistics due to an inadequate number of plasma concentration-time data compared to the other subjects.

4.1.9 Study CA180032 - Rifampin drug-drug interaction

STUDY REVIEWER: Julie M. Bullock, Pharm.D.

TITLE OF STUDY: The effects of rifampin on the oral pharmacokinetics of BMS-354825 in healthy subjects

INVESTIGATORS AND CENTERS:

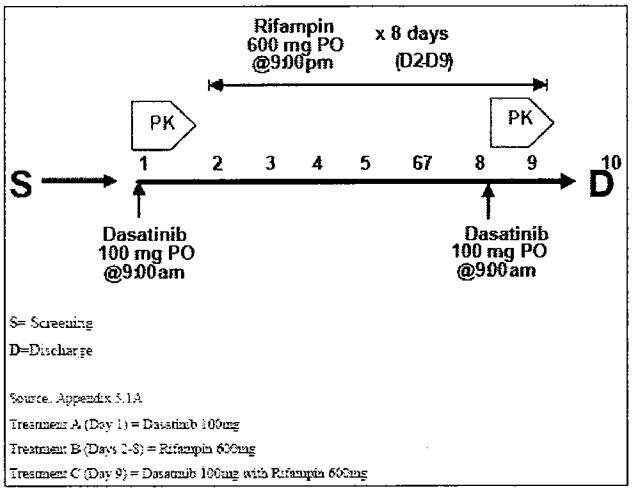
Tong Li, MD
Bristol-Meyers Squibb Clinical Research Center.
Hamilton, NJ

STUDY PERIOD: 12-Mar-2005 to 3-Apr-2005

CLINICAL PHASE: 1

OBJECTIVES: The primary objective was to assess the effects of rifampin on the PK of dasatinib in healthy subjects. Secondary objectives included assessing safety and tolerability of a single dose of dasatinib before and after 8 days of dosing with rifampin in healthy subjects.

STUDY DESIGN: This was a single-sequence study design to evaluate the effects of eight daily doses of 600mg rifampin on the single dose PK of dasatinib. The study schematic is below:



TREATMENTS:

Each subject received the following treatments no randomization occurred:

- Treatment A = Dasatinib 100mg (2 x 50mg tablets) fasted
- Treatment B = Rifampin 600mg QD on Days 2-8 at 9PM
- Treatment C = Rifampin 600mg at 9PM with Dasatinib 100mg (2 x 50mg tablets) fasted at 9AM.

Rifampin was supplied by the study site as a commercial formulation capsule. The following batch numbers of dasatinib and lots numbers of rifampin were used in this trial:

Treatment	Formulation	Strength (Unit)	Label Batch Number	Product Batch Number	Lot Number
Dasatinib	film-coated clinical formulation tablets	50 mg	5A09452.5C	5A10557	---
Rifampin	commercial formulation capsule	300 mg	---	---	3035104

SAMPLE COLLECTION: Blood samples for the measurement of dasatinib, BMS-582691 (M4) and BMS-606181 (M5) were obtained at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 hours post dose for all subjects who completed treatment in the study.

SUBJECTS: Healthy subjects ages 18 to 50 years of age were enrolled into the study. Twenty subjects were enrolled and treated and completed the study.

SAFETY ASSESSMENTS & RESULTS: All subjects who received any drug were evaluable for safety. Physical examination, weight, vital signs, 12-lead ECGs were obtained throughout the study. Reports of AE's were infrequent, with headache being the most frequent. One subject had a QTcF of 451 on Day 9 before dasatinib was administered with rifampin. Six subjects had a total of 7 QTcF changes from baseline between 30 and 60 msec, 2 of which occurred with dasatinib was administered alone and 5 when dasatinib was administered with rifampin. The clinical relevance of these findings is debatable since there was no placebo control.

ANALYTICAL METHODOLOGY & RESULTS: Human EDTA plasma samples were frozen and shipped to Samples were stored at approximately -20°C prior to analysis. Samples were assayed initially for dasatinib and BMS-606181 (M5) by a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method. The plasma samples were analyzed again for BMS-528691 (M4) using a validated LC/MS/MS method. Plasma samples were analyzed for dasatinib and M4 in a total of 9 analytical runs. Samples for BMS-606181 were analyzed in a total of 8 analytical runs. The performance parameters of the standard curves and QC samples are summarized in the following table.

BMS-354825 Standard Curve	
Correlation Coefficient	0.9968
S.D.	0.0022
%CV	0.2
LLQ ng/mL	1.00

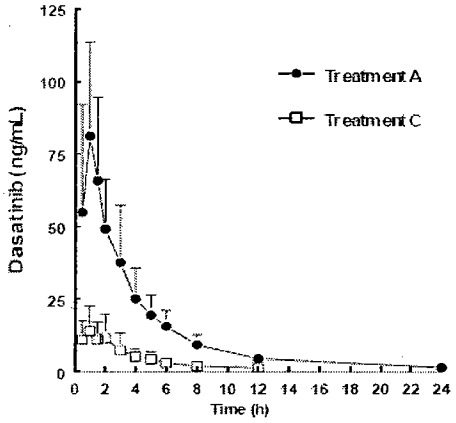
ULQ ng/mL	1000.00			
N	9			
BMS-354825 QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
%Deviation	-4.7	-0.8	-4.2	-3.1
Between Run Precision (%CV)	4.5	3.4	4.3	8.0
Within Run Precision (%CV)	3.2	4.3	3.4	3.4
Total Variation (%CV)	5.5	5.4	5.5	8.7
n	27	27	27	27
Number of Runs	9	9	9	9
BMS-582691 (M4) Standard Curve				
Correlation Coefficient	0.9976			
S.D.	0.0014			
%CV	0.1			
LLQ ng/mL	1.00			
ULQ ng/mL	1000.00			
N	9			
BMS-582691 (M4) QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
%Deviation	-12.7	-1.1	-2.3	-1.0
Between Run Precision (%CV)	2.5	2.2	1.9	2.6
Within Run Precision (%CV)	3.9	2.0	1.8	1.7
Total Variation (%CV)	4.7	3.0	2.6	3.1
n	35	36	36	36
Number of Runs	9	9	9	9
BMS-606181 (M5) QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
Correlation Coefficient	0.9943			
S.D.	0.0059			
%CV	0.6			
LLQ ng/mL	1.00			
ULQ ng/mL	1000.00			
N	8			
BMS-606181 (M5) QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
%Deviation	-3.7	0.6	-4.1	-6.6
Between Run Precision (%CV)	6.5	0.0	7.0	5.1
Within Run Precision (%CV)	4.9	12.0	3.3	3.7
Total Variation (%CV)	8.2	10.8	7.7	6.3
n	24	24	24	24
Number of Runs	8	8	8	8

PHARMACOKINETIC EVALUATION & RESULTS: PK parameters for dasatinib, M4 and M5 were calculated by a non-compartmental method using Kinetica. The Cmax and Tmax were obtained from experimental observations. Using no weighting factor, the terminal log-linear phase of the concentration-time curve was identified by least-square linear regression of at least 3 data points that yielded a maximum G-criteria, which is also referred to as adjusted R-squared. The T-HALF was calculated as Ln2/Lz, where Lz was the absolute value of the slope of the terminal log-linear phase. The AUC(0-T) was calculated using the mixed log-linear trapezoidal algorithm in Kinetica™. The AUC(INF) was estimated by summing AUC(0-T) and the extrapolated area, computed by the quotient of the last observable concentration and Lz. The sponsors mean concentration time profiles and summary statistics for dasatinib after Treatment A and C are below (sponsors figure 11.2.1). The mean concentration time profile for BMS-582691 (M4 formed mainly by CYP3A4) is also provided below.

	Dasatinib Pharmacokinetic Parameters				
Treatment	Cmax (ng/mL) Geom. Mean (CV%)	AUC(INF) (ng·h/mL) Geom. Mean (CV%)	AUC(0-T) (ng·h/mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
A (n = 20)	85.56 (36)	294.05 (33)	280.27 (35)	1.00 (0.50, 3.00)	4.74 (1.58)
C (n = 20)	16.16 (49)	53.21 (41)	44.20 (46)	1.00 (0.50, 3.00)	3.42 (1.17)

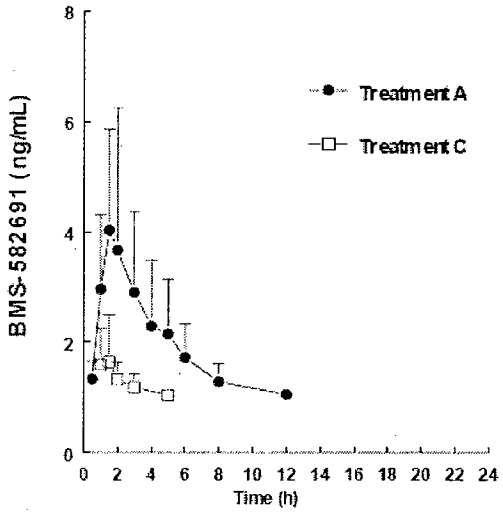
Treatment A (Day 1) = Dasatinib 100 mg
Treatment C (Day 9) = Dasatinib 100 mg with rifampin 600 mg

Figure 11.2.1: Mean (SD) Plasma Concentration versus Time Profiles for Dasatinib



Source: Supplemental Table 11.2.1A
Treatment A (Day 1) = Dasatinib 100 mg
Treatment C (Day 9) = Dasatinib 100 mg with rifampin 600 mg

Figure 11.2.2: Mean (SD) Plasma Concentration versus Time Profiles for BMS-582691



Source: Supplemental Table 11.2.2A
Treatment A (Day 1) = Dasatinib 100 mg
Treatment C (Day 9) = Dasatinib 100 mg with rifampin 600 mg

STATISTICAL ANALYSIS & RESULTS: All subjects who received dasatinib were included in the PK data set but only subjects with values from both Day 1 and Day 9 were included in the summary statistics of dasatinib PK parameters. To assess the effect of rifampin on the PK of dasatinib, ANOVA were performed on log (Cmax), Log (AUC0-t) and log (AUCinf) of dasatinib. The factors in each analysis were subject and study day. Point estimates and 90% confidence intervals were calculated for the Day 9 to Day 1 ratios of geometric means of dasatinib AUC and Cmax. The results of the sponsors statistical analysis is below.

Table 11.2.1B: Results of Statistical Analyses for Dasatinib Cmax, AUC(INF) and AUC(0-T)

Pharmacokinetic Variable	Geometric Means		Ratio of Geometric Means		
	Treatment A (Day 1)	Treatment C (Day 9)	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	85.56	16.16	C vs A	0.189	(0.163, 0.219)
AUC(INF) (ng·h/mL)	294.05	53.21	C vs A	0.181	(0.160, 0.204)
AUC(0-T) (ng·h/mL)	280.27	44.20	C vs A	0.158	(0.132, 0.189)

Source: Supplemental Tables S.11.2.1C, S.11.2.1D and S.11.2.1E
Treatment A (Day 1) = Dasatinib 100 mg
Treatment C (Day 9) = Dasatinib 100 mg with rifampin 600 mg

DISCUSSION & CONCLUSION:

- In the presence of rifampin at steady state the Cmax, AUC0-t and AUCinf of dasatinib were reduced by 81%, 84% and 82% respectively.
- The Cmax and AUC for M4, the metabolite formed mainly by CYP3A4 were also significantly reduced in the presence of rifampin.
- Only 3 subjects had quantifiable concentrations of M5 on Day 9, but those who did have data from Day 1 and Day 9 showed marked reductions in M5 concentrations by Day 9.
- Metabolic ratios (metabolite: parent) were less than 10% indicating that both metabolites are minor metabolites of dasatinib.
- Dasatinib dose should be increased in the presence of potent CYP3A4 inducers.

4.1.10 Study CA180020 - Gastric acid pH modulators interaction

STUDY REVIEWER: Julie M. Bullock, Pharm.D.

TITLE OF STUDY: A Phase 1 Study of the Effect of Gastric Acid pH Modulators on the Oral Bioavailability of BMS-354825 in Healthy subjects

INVESTIGATORS AND CENTERS:

Tong Li, MD
Bristol-Meyers Squibb Clinical Research Center.
Hamilton, NJ

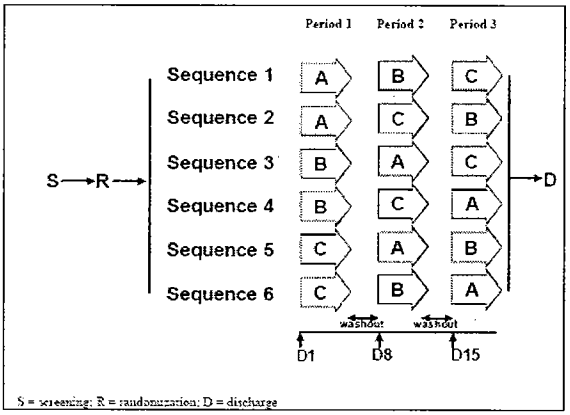
STUDY PERIOD: 03-Apr-2005 to 30-Apr-2005

CLINICAL PHASE: 1

OBJECTIVES:

- Primary Objective: To assess the effects of a 40mg oral dose of famotidine, given either 2 hours after or 10 hours before administration of 50mg BMS-354825 and the effects of a 30mL dose of aluminum hydroxide/magnesium hydroxide-containing antacid, given 2 hours before or concomitantly administered with 50mg dasatinib on the PK of a 50mg oral dose of dasatinib in healthy subjects.
- Secondary Objective: To assess the safety and tolerability of two 50mg oral doses of dasatinib in healthy subjects given 13 hours apart.

STUDY DESIGN: This was an open-label, randomized, 3-period, 3-treatment, crossover study in 24 healthy subjects. Subjects were randomized to receive 1 of 6 treatment sequences (see figure below). There was a 7 day washout period between each treatment period.



TREATMENTS:

Each subject received each of the following 3 treatments:

- A: Dasatinib 50mg q12 hours (control)
- B: Dasatinib 50mg q12 hours + famotidine 40mg single dose (dasatinib 2 hours before famotidine in the PM and 10h after famotidine in the AM)
- C: Dasatinib 50mg q12h + Maalox 30mL q12h (dasatinib 2 hours after Maalox in the PM and co-administered together in the AM)

Famotidine and Maalox were provided by the study site. Dasatinib was provided by the sponsor as 50mg tablets. Below is the information from the treatments used in this study.

Treatment	Formulation	Strength (Unit)	Label Batch Number	Product Batch Number	Lot Number
Dasatinib	Tablet	50 mg	5A09452 5C	5A10557	--
Famotidine (Pepcid)	Tablet	40 mg	--	--	P5010
Maalox	Liquid	30 mL	--	--	327177

Meals were administered according to the schema below. Dasatinib was administered in all treatments 4 hours after dinner or 2 hours before breakfast.

Table 5.5.1: Meal and Treatment Schema

Time (hr:)	-4.5	-4	-3	-2	-1	0	1	2	3	4	5	6	7
Treatment A													
PM	Dinner					Dasatinib 50 mg			Snack				
AM						Dasatinib 50 mg		Breakfast					
Treatment B													
PM	Dinner					Dasatinib 50 mg		Famotidine 40 mg	Snack				
AM						Dasatinib 50 mg		Breakfast					
Treatment C													
PM	Dinner			Maalox 30 mL		Dasatinib 50 mg			Snack				
AM						Dasatinib 50 mg		Breakfast					

SAMPLE COLLECTION: Blood samples were obtained after each dasatinib dose at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours (PM dose only) post dose for all subjects who completed treatment in the study.

SUBJECTS: 24 subjects were enrolled and 2 discontinued early.

SAFETY ASSESSMENTS & RESULTS: Physical examinations, physical measurements with vital signs, 12-lead ECG, and clinical laboratory evaluations were performed at selected times throughout the study. There were no deaths or SAE's during the trial and no trend was seen among the treatment groups in the reporting of AEs. Seventeen of the 24 subjects had 1 or more treatment-emergent AEs

with headache being the most frequently reported. One subject discontinued the trial due to AEs of headache, nausea, and vomiting (all events occurred during treatment C). No ECG abnormalities were identified.

ANALYTICAL METHODOLOGY & RESULTS: Human EDTA plasma samples were frozen and shipped to —→ Samples were stored at approximately -20°C prior to analysis for dasatinib. A validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method was used. Plasma samples were analyzed for dasatinib in a total of 18 analytical runs. The performance parameters of the standard curves and QC samples are summarized in the following table.

BMS-354825 Standard Curve				
Correlation Coefficient	0.9983			
S.D.	0.0014			
%CV	0.1			
LLQ ng/mL	1.00			
ULQ ng/mL	1000.00			
N	18			
BMS-354825 QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
%Deviation	-1.7	4.4	1.5	-2.2
Between Run Precision (%CV)	3.0	3.3	2.2	2.7
Within Run Precision (%CV)	3.2	2.6	2.3	1.8
Total Variation (%CV)	4.4	4.2	3.2	3.2
n	71	72	72	72
Number of Runs	18	18	18	18

PHARMACOKINETIC EVALUATION & RESULTS: Pharmacokinetic parameters of dasatinib were determined using non-compartmental method and Cmax and Tmax were obtained from experimental observations. The half-life (thalf) was calculated as Ln2/Lz, where Lz was the absolute value of the slope of the terminal log-linear phase. The AUC_{0-12} was calculated using the mixed log-linear trapezoidal algorithm in Kinetica. The AUCinf was estimated by summing AUC_{0-12} and the extrapolated area computed by the quotient of the concentration 12 hours post-dose and Lz. AUC_{0-12} and AUCinf values in the morning were corrected by subtracting the residual area from the prior evening's dose.

Below are the summary statistics for Dasatinib PK parameters calculated by the sponsor, followed by the mean concentration time curves for the AM and PM doses of each treatment.

Table 11.2.1A: Summary Statistics for Dasatinib Pharmacokinetic Parameters

Day	Treatment	Dasatinib Pharmacokinetic Parameters				
		Cmax (ng/mL) Geometric Mean (CV%)	AUC(0-12h) (ng·h/mL) Geometric Mean (CV%)		AUC(INF) Geometric Mean (CV%)	Tmax (h) Median (Min, Max)
			Corrected[a]	Uncorrected		
Day 1 (PM)	A (n = 21)[b]	36.57 (40)	137.50 (34)	--	152.13 (34)	1.00 (0.50, 4.00)
	B (n = 21)[b]	39.00 (48)	135.55 (35)	--	150.82 (36)	1.00 (0.50, 3.00)
	C (n = 21)[b]	46.08 (59)	143.89 (33)	--	158.57 (33)	1.00 (0.50, 2.00)
Day 2 (AM)	A (n = 22)	41.52 (54)	101.67 (45)	117.48 (41)	115.00[c] (44)	1.00 (0.50, 3.00)
	B (n = 22)	15.40 (97)	40.24 (75)	60.45 (66)	54.27[c] (68)	0.75 (0.00, 3.00)
	C (n = 22)	17.27 (74)	46.33 (72)	62.84 (62)	60.09[c] (65)	1.00 (0.50, 6.00)

[a] AUC(0-12h) and AUC(INF) were corrected by subtracting the residual area from the previous dose.

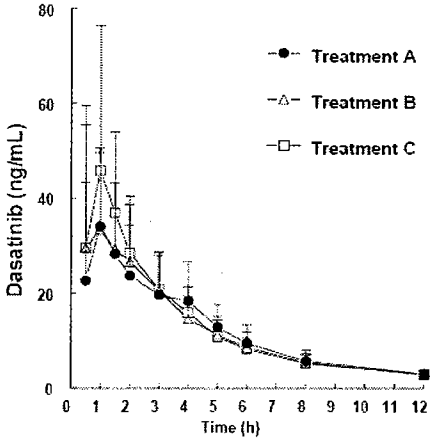
[b] Subject CA180030-1-18 had no measurable plasma concentration data following the PM dose of dasatinib in the control treatment (A), thus PK parameters from this subject were excluded from the summary statistics and statistical analyses for the PM dosing.

[c] Corrected AUC(INF).

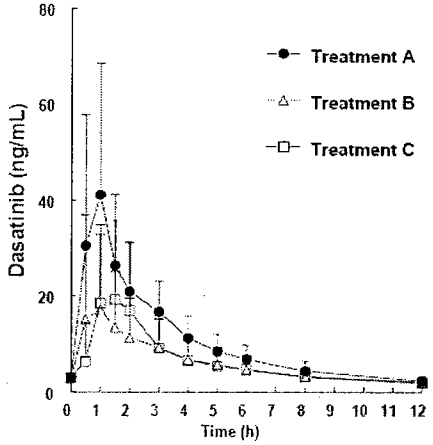
Treatments:
A = dasatinib 50 mg q12h (control)
B = dasatinib 50 mg q12h + famotidine 40 mg single dose (dasatinib 2h before famotidine in the PM and 10h after famotidine in the AM)
C = dasatinib 50 mg q12h + Maalox 30 mL q12h (dasatinib 2h after Maalox in the PM and co-administered in the AM)

Source: Supplemental Tables S.11.2.1B and S.11.2.1C

2.1A: Mean (SD) Plasma Concentration Versus Time Profiles for Dasatinib (BMS-354825) Following the Day 1 (PM) Dose



1B: Mean (SD) Plasma Concentration Versus Time Profiles for Dasatinib (BMS-354825) Following the Day 2 (AM) Dose



- The Cmax of Dasatinib was slightly lower for the PM administration than the AM administration while the AUC0-12 for the PM administration was higher than the AM AUC0-12 The difference in AUC could be a function of the AUC correction employed by the sponsor.
- Administration of dasatinib 2 hours prior to administration of famotidine did not cause any significant increases or decreases in AUC or Cmax. The Cmax was slightly higher than dasatinib alone.
- Administration of Maalox 2 hours prior to administration of dasatinib did not cause any

significant increases or decreases in AUC or Cmax.

- Co-administration of dasatinib 10 hours after famotidine causes a 63% reduction in Cmax and a 60% reduction in AUC_{0-12}.
- Co-administration of dasatinib with Maalox causes a 58% decrease in Cmax and a 54% decrease in AUC_{0-12}.
- Only the administration of dasatinib 10 hours after famotidine caused any changes in Tmax (0.75 hr vs. 1.00 hr for control).

STATISTICAL ANALYSIS & RESULTS: To assess the effect of famotidine or Maalox on the PK of dasatinib, analyses of variance (ANOVA) were performed on log(Cmax), and log[corrected AUC_{0-12}] separately for each dasatinib dose. The factors in each analysis were treatment sequence, subject within sequence, treatment period, and treatment. Additional ANOVA evaluated the significance of first-order carry over effects.

Point estimates and 90% CI's for the B/A and C/A ratios for Cmax and corrected AUC_{0-12} population geometric means for each of the 2 dasatinib doses were calculated from the results of the ANOVA. The results of the sponsors analysis are below:

Table 11.2.1B: Results of Statistical Analyses for Dasatinib Cmax and AUC(0-12h)

Day	Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
		Formulation	Adjusted Geometric Means	Ratio	Point Estimate	90% Confidence Limits
Day 1 (PM)	Cmax (ng/mL)	A	37.57			
		B	40.43	B vs A	1.076	(0.872, 1.328)
		C	47.51	C vs A	1.264	(1.025, 1.560)
	AUC(0-12h) (ng•h/mL)	A	140.41			
		B	139.45	B vs A	0.993	(0.895, 1.103)
		C	147.33	C vs A	1.049	(0.945, 1.165)
Day 2 (AM)	Cmax (ng/mL)	A	40.86			
		B	15.16	B vs A	0.371	(0.239, 0.576)
		C	17.07	C vs A	0.418	(0.269, 0.649)
	Corrected AUC(0-12h) (ng•h/mL)	A	99.51			
		B	39.28	B vs A	0.395	(0.255, 0.612)
		C	45.20	C vs A	0.454	(0.293, 0.704)

Formulations:
A = dasatinib 50 mg q12h (control)
B = dasatinib 50 mg q12h + famotidine 40 mg single dose (dasatinib 2h before famotidine in the PM and 10h after famotidine in the AM)
C = dasatinib 50 mg q12h + Maalox 30 mL q12h (dasatinib 2h after Maalox in the PM and co-administered in the AM)

DISCUSSION & CONCLUSION

- Since dasatinib solubility is pH dependant the bioavailability of dasatinib may be reduced in the presence of acid-reducing agent such as aluminum hydroxide and/or magnesium hydroxide containing agent, H2-receptor antagonists, and proton-pump inhibitors.
- Although not set a-priori the AUC_{0-12} for PM treatments B vs. A and C vs. A met the 90% CI equivalence criteria of 0.8-1.25. The Cmax for the PM treatments met the lower bound of 0.8 but failed slightly for the upper bound of the 90% confidence interval.
- Co-administration of dasatinib 10 hours after administration of famotidine caused a significant decrease in both Cmax and AUC. The extent of this decrease could be amplified with other gut pH modulators such as the proton pump inhibitors (omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprazole) as well as other H2 antagonists (ranitidine and cimetidine).
- Administration of Maalox 2 hours prior to dasatinib caused an increase in Cmax of approximately 26% but had no effect on AUC_{0-12} (AUC was within the 90% CI equivalence range). A significant reduction was observed with Maalox was co- administered with dasatinib for the AM dose.

- Administration of dasatinib with OTC antacids should be separated by at least 2 hours.
- Long-term or short-term contaminant dosing with H2 antagonists and proton pump inhibitors may not be warranted with the use of dasatinib considering that these agents (if taken as directed either QD or BID) are mechanistically meant to maintain a decrease in gastric-pH for acid reflux disease .

4.1.11 Study CA180022 - Simvastatin Drug-drug interaction

STUDY REVIEWER: Julie M. Bullock, Pharm.D.

TITLE OF STUDY: The effects of BMS-354825 on the Pharmacokinetics of Simvastatin in Healthy Subjects

INVESTIGATORS AND CENTERS:

STUDY PERIOD: 13-Apr-2005 to 27-Apr-2005

CLINICAL PHASE: 1

OBJECTIVES

Primary:

- To assess the effect of 100mg of dasatinib on the single-dose PK of 80mg simvastatin in healthy volunteers.

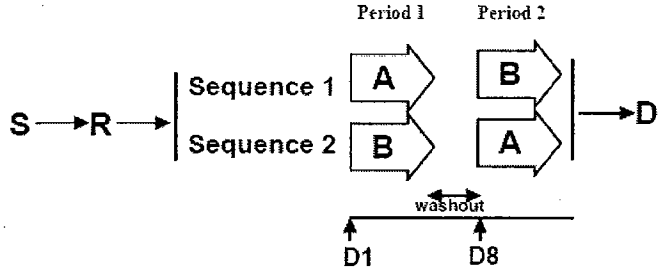
Secondary:

- To assess the effect of 100mg dasatinib on the single-dose PK of simvastatin in health subjects
- To assess the safety and tolerability of 100mg dasatinib co-administered with 80mg simvastatin

STUDY DESIGN

This was an open-label, randomized, 2-period, 2-treatment, crossover study in healthy subjects. All subjects were randomized into one of two treatment sequences (see figure 5.1) where they received both treatments.

Figure 5.1: Treatment Assignments / Sequences



S = screening, R = randomization, D = discharge
Treatments:
A = simvastatin 80 mg
B = simvastatin 80 mg + dasatinib 100 mg

There was at least a 7 day washout period between each period. For each treatment period, subjects were confined to the clinical research unit until 24 hours post dose

TREATMENTS

Subjects received 1 of the following 2 treatments in each period:

- Treatment A: Oral simvastatin 80mg in fasted condition
- Treatment B: Oral simvastatin 80mg + dasatinib 100mg in fasted condition

Subjects were required to fast for 10 hours before until 4 hours after study drug administration. Study drug was administered with 240 mL of water. The following formulations of study medication were used (see table 5.5.2). Simvastatin was purchased commercially by the study site's pharmacy

Table 5.5.2: Drug Information

Treatment	Formulation	Strength (Unit)	Label Batch Number	Product Batch Number	Lot Number
Dasatinib	Tablet	50 mg	5A09452.5D	5A10549	--
Simvastatin (ZOCOR)	Tablet	80 mg	--	--	R4465

SAMPLE COLLECTION

Blood samples (3mL) for the measurement of simvastatin, simvastatin acid and dasatinib (treatment B only) were obtained at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dosing for all subjects.

SUBJECTS

A total of 48 subjects were enrolled, treated and completed the study. Subject demographics are below in Sponsors table 8.3.

Table 8.3: Demographic and Subject Characteristics

Characteristic	All Subjects N = 48
Age, years	
Mean	40
Range	18 - 50
Gender, n (%)	
Male	20 (42)
Female	28 (58)
Race, n (%)	
White	43 (90)
Black/African American	4 (8)
American Indian/Alaskan Native	1 (2)
Body Mass Index (kg/m^2)	
Mean	25.8
Range	20.9 - 31.7

SAFETY ASSESSMENTS

Physical examinations, vital sign measurements, 12-lead ECGs and clinical laboratory evaluations were performed at selected times throughout the study.

ANALYTICAL METHODOLOGY

Assay Method for Dasatinib and Simvastatin in Human Plasma

Human EDTA plasma samples were frozen and shipped on dry ice to the — — for analysis. Samples were stored frozen at -70°C for simvastatin and -20°C for dasatinib. The dasatinib samples were inadvertently stored at -70°C for 5 days upon receipt and were then transferred to -20°C storage until analyzed. This had no impact on the results as dasatinib samples can be stored at -20°C or below. A validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method was used for the simvastatin, simvastatin acid and dasatinib assay. Plasma samples were analyzed for dasatinib in a total of 5 analytical runs. Samples were analyzed for simvastatin and simvastatin acid in a total of 15 and 13 analytical runs, respectively. The performance parameters of the standard curves and QC samples are summarized in the following table.

BMS-354825 Standard Curve				
Correlation Coefficient	0.9983			
S.D.	0.0006			
%CV	0.1			
LLQ	1.00			
ULQ	1000.00			
N	5			
BMS-354825 QC Samples	**QC3 3.0ng/mL**	**QC35 35.0ng/mL**	**QC400 400.0ng/mL**	**QC800 800.0ng/mL**
%Deviation	4.7	7.2	5.0	2.3
Between Run Precision (%CV)	1.7	0.0	1.3	2.2
Within Run Precision (%CV)	2.3	15.3	9.2	2.5
Total Variation (%CV)	2.9	14.2	9.3	3.3
n	20	20	20	20
Number of Runs	5	5	5	5
Simvastatin Standard Curve				
Correlation Coefficient	0.9975			

S.D.	0.0008				
%CV	0.1				
LLQ (ng/mL)	0.15				
ULQ (ng/mL)	60.00				
N	15				
Simvastatin QC Samples	**QC0.45 0.45ng/mL**	**QC2 2.0ng/mL**	**QC9 9.0 ng/mL**	**QC45 45.0ng/mL**	**QC300 300.0ng/mL**
%Deviation	6.7	3.0	3.7	5.0	5.2
Between Run Precision (%CV)	2.4	2.0	3.4	3.4	15.3
Within Run Precision (%CV)	5.8	6.3	2.4	2.7	13.4
Total Variation (%CV)	6.3	6.6	4.2	4.4	20.4
n	60	60	60	58	8
Number of Runs	15	15	15	15	2
Simvastatin Acid Standard Curve					
Correlation Coefficient	0.9968				
S.D.	0.018				
%CV	0.2				
LLQ (ng/mL)	0.05				
ULQ (ng/mL)	20.00				
N	13				
Simvastatin Acid QC Samples	**QC0.45 0.45ng/mL**	**QC2 2.0ng/mL**	**QC9 9.0 ng/mL**	**QC45 45.0ng/mL**	**QC300 300.0ng/mL**
%Deviation	6.7	-1.5	2.7	4.2	-10.2
Between Run Precision (%CV)	4.6	2.6	3.6	3.7	N/A
Within Run Precision (%CV)	5.5	5.9	2.0	2.6	N/A
Total Variation (%CV)	7.2	6.5	4.1	4.5	N/A
n	52	52	52	51	4
Number of Runs	13	13	13	13	1

PHARMACOKINETIC EVALUATION:

The study was designed to have a power of approximately 90% to conclude that dasatinib + simvastatin would result in no increase with respect to Cmax and a 94% power to conclude no increase with respect to AUCinf. Forty-eight subjects were enrolled to allow for dropouts. Pharmacokinetic parameters of dasatinib, simvastatin, and simvastatin acid were determined using a non-compartmental method and Cmax and AUC were obtained from experimental observations. The half-life (thalf) was calculated as Ln2/Lz, where Lz was the absolute value of the slope of the terminal log-linear phase. The AUC_{0-t} was calculated using the mixed log-linear trapezoidal algorithm in Kenetica. The AUCinf was estimated by summing AUC_{0-t} and the extrapolated area, computed by the quotient of the last observable concentration and Lz. All subjects who received any study drug (simvastatin or dasatinib) were included in the PK data set, but only subjects with values for simvastatin Cmax and AUCinf from both treatment periods were included in the summary statistics and analysis. Below are the summary statistic tables for simvastatin, simvastatin acid, and dasatinib.

Table 11.2.1A: Summary Statistics for Simvastatin Pharmacokinetic Parameters

Treatment	Simvastatin Pharmacokinetic Parameters				
	Cmax (ng/mL) Geometric Mean (CV%)	AUC(INF) (ng·h/mL) Geometric Mean (CV%)	AUC(0-T) (ng·h/mL) Geometric Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
A (n = 48)	26.68 (57)	117.95 (80)	108.05 (74)	1.50 (0.50, 8.00)	6.65 (3.00)
B (n = 48)	36.53 (57)	141.29 (68)	132.97 (66)	1.00 (1.00, 5.00)	5.16 (2.85)

Treatments:
A = simvastatin 80 mg
B = simvastatin 80 mg + dasatinib 100 mg

Table 11.2.2A: Summary Statistics for Simvastatin Acid Pharmacokinetic Parameters

Treatment	Simvastatin Acid Pharmacokinetic Parameters				
	Cmax (ng/mL) Geometric Mean (CV%)	AUC(INF) (ng·h/mL) Geometric Mean (CV%)	AUC(0-T) (ng·h/mL) Geometric Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
A (n = 48)	5.84 (68)	55.64* (66)	52.26 (65)	5.00 (1.50, 12.00)	4.48* (1.66)
B (n = 48)	8.22 (67)	70.48* (59)	64.64 (60)	4.00 (1.50, 8.00)	4.56* (3.36)

Treatments:
A = simvastatin 80 mg
B = simvastatin 80 mg + dasatinib 100 mg
* n = 47

Table 11.2.3A: Summary Statistics for Dasatinib Pharmacokinetic Parameters

Treatment	Dasatinib Pharmacokinetic Parameters				
	Cmax (ng/mL) Geometric Mean (CV%)	AUC(INF) (ng·h/mL) Geometric Mean (CV%)	AUC(0-T) (ng·h/mL) Geometric Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
B (n = 48)	119.43 (59)	408.24* (51)	383.65 (53)	1.00 (0.50, 5.00)	4.81* (3.15)

Treatment:
B = simvastatin 80 mg + dasatinib 100 mg
* n = 47

The mean plasma concentrations profiles of simvastatin and simvastatin acid with or without dasatinib are below in the sponsors Figure 11.2.1.

Figure 11.2.1 The Mean (SD) Plasma Concentration-time Profiles of Simvastatin With and Without Dasatinib

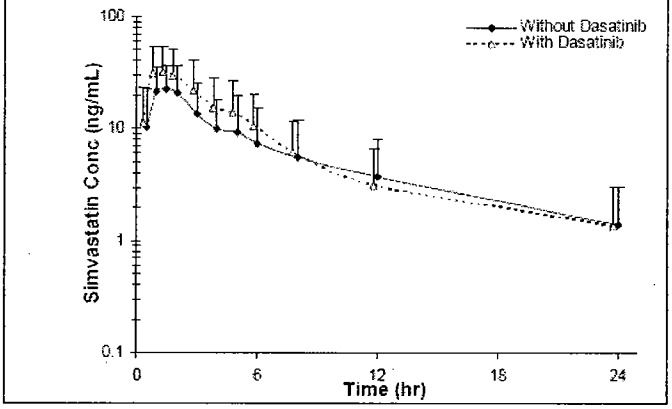
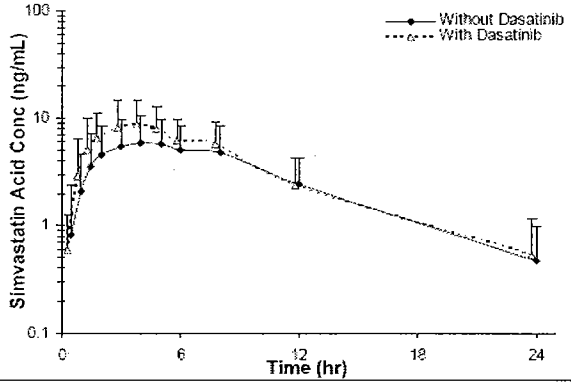


Figure 11.2.2 The Mean (SD) Plasma Concentration-time Profiles of Simvastatin Acid With and Without Dasatinib



STATISTICAL ANALYSIS

To assess the effect of dasatinib on the PK of simvastatin, analysis of variance was performed on log(Cmax), log(AUC0-t) and log(AUCinf). The factors in each analysis were treatment sequence, subject within sequence, treatment period, and treatment. It would be concluded that dasatinib does not increase the exposure of simvastatin if the upper bound of the 90% CI for the B/A ratio of geometric means for both Cmax and AUCinf is less than 125%.

Table 11.2.1B: Results of Statistical Analyses for Simvastatin Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
	Treatment	Adjusted Geometric Means	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	26.68			
	B	36.52	B vs A	1.369	(1.194, 1.569)
AUC(INF) (ng•h/mL)	A	117.95			
	B	141.29	B vs A	1.198	(1.059, 1.355)
AUC(0-T) (ng•h/mL)	A	108.05			
	B	132.97	B vs A	1.231	(1.102, 1.374)

Treatments:
A = simvastatin 80 mg
B = simvastatin 80 mg – dasatinib 100 mg

Table 11.2.2B: Results of Statistical Analyses for Simvastatin Acid Cmax, AUC(INF), and AUC(0-T)

Pharmacokinetic Variable	Adjusted Geometric Means		Ratio of Geometric Means		
	Treatment	Adjusted Geometric Means	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	5.84			
	B	8.22	B vs A	1.409	(1.283, 1.546)
AUC(INF) (ng•h/mL)	A	55.68			
	B	70.44	B vs A	1.265	(1.161, 1.379)
AUC(0-T) (ng•h/mL)	A	52.26			
	B	64.64	B vs A	1.237	(1.134, 1.349)

Treatments:
A = simvastatin 80 mg
B = simvastatin 80 mg – dasatinib 100 mg

PHARMACOKINETICS DISCUSSIONS

- The 90% confidence intervals for ratios of Cmax and AUCinf fell outside the upper bound of 125% for simvastatin and simvastatin acid.
- Dasatinib increased the exposure of simvastatin by 37%, 20% and 23% for Cmax, AUCinf, and AUC_{0-t} respectively.
- Dasatinib also increased the exposure of simvastatin acid by 41%, 27% and 24% for Cmax, AUCinf and AUC0-t, respectively.
- There were no statistically significant period or sequence effects (at the $\alpha = 0.05$ level) in the

analyses of AUCinf and AUC_{0-t} for simvastatin and simvastatin acid.

- A statistically significant period effect was observed in the analysis of simvastatin for Cmax ($p = 0.02$) but is unlikely to impact the general conclusions of the study. This was not seen for simvastatin acid.
- Intra-subject variability estimates were large for simvastatin (41% CV for Cmax, 37% CV for AUCinf, and 33% CV for AUC0-t) and were less variable for simvastatin acid (28% CV for Cmax, 25% CV for AUCinf, and 26% CV for AUC0-t).
- The dasatinib pharmacokinetics characterized in this study were similar in comparison to other results from previous studies.

SAFETY ASSESSMENTS

Data from all 48 subjects were included in the safety data sets. Overall 28 of the 48 subjects had 1 or more treatment-emergent AE's during the study. Overall 50% of subjects had 1 or more AE while on treatment B compared with 20.8% of subjects on Treatment A. The most frequently reported AE across both treatment groups was headache. Twenty-four subjects had a total of 26 events of headache. There were no deaths or SAE's reported in this study. No subject had a QTcF value exceed 450msec. Four subjects had a total of 5 QTcF changes from baseline that exceeded 30msec, 1 of which was 560msec 4 hours after dosing with simvastatin + dasatinib.

CONCLUSIONS

Simvastatin is a substrate of cytochrome P450 3A4. The results of this study indicate that dasatinib is an inhibitor of CYP3A4 due to the increase in the Cmax and AUC of simvastatin when co administered with dasatinib. This reinforces the in-vitro drug interaction studies that concluded dasatinib was a CYP3A4 substrate and potential inhibitor.

4.1.12 Study CA180016 - Formulation Comparison Study

STUDY REVIEWER: Carol Noory, Ph.D.

TITLE OF STUDY: A Formulation Comparability Study of BMS-354825 in Healthy Subjects

INVESTIGATORS:

STUDY PERIOD: Date first subject enrolled: 29-Nov-2004
Date last subject completed: 09-Dec-2004

CLINICAL PHASE: 1

OBJECTIVES

Primary:

- Estimate the comparability of the 5 mg Phase I clinical formulation (Treatment B), and the 20 mg (Treatment C), and 50 mg (Treatment D) Phase II clinical (commercial) formulations of BMS-354825 (dasatinib) to the 50 mg Phase I clinical formulation (Treatment A)

Secondary:

- Assess the pharmacokinetics (PK) of a single 100 mg dose of dasatinib in a healthy volunteer population
- Assess the safety and tolerability of a single 100 mg dose of dasatinib in a healthy volunteer population
- Assess the impact of a single 100 mg dose of dasatinib on the QTc interval in a healthy volunteer population

STUDY DESIGN

This was an open-label, randomized, 4-arm, single-dose parallel study in healthy subjects. Subjects were administered a single 100 mg dose of dasatinib on Day 1. The parallel design was chosen to avoid exposing healthy subjects to four doses of 100mg of the drug.

Treatments

Table 1: Test and Reference Formulations

Designation	Phase	Formulation	Studies	Dose	Batch	N=	Batch size
A (Reference)	1	Clinical	CA180002, CA180003	2X 50 mg	4C91969	18	ablets
B (Test)	1	Clinical	CA180002, CA180003	20X 5 mg	4C88975	19	ablets
C (Test)	2	Clinical	CA180005; CA180006;	5X 20 mg	4L77202	19	tablets

			CA180013; CA180015; CA180017				
D (Test)	2	Clinical	CA180005; CA180006; CA180009; CA180013; CA180015; CA180017	2X 50 mg	4L77205	19	tablets

The 20 mg and 50 mg Phase II Clinical formulations are same as the proposed commercial formulation; the only difference is the tablet debossings.

Blood and Urine Sample Collection

Blood was collected on Day 1at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dose. A 24-hour urine was collected on Day 1 for analyses of dasatinib and its N-oxide metabolite, BMS-606181.

Subjects

A total of 75 subjects were enrolled (Treatments A, C, and D, 19 subjects each and Treatment B, 18 subjects). All subjects completed the protocol as designed. Subjects were admitted to the study facility two days prior to the study and remained confined until the end of study procedures.

ANALYTICAL METHODS

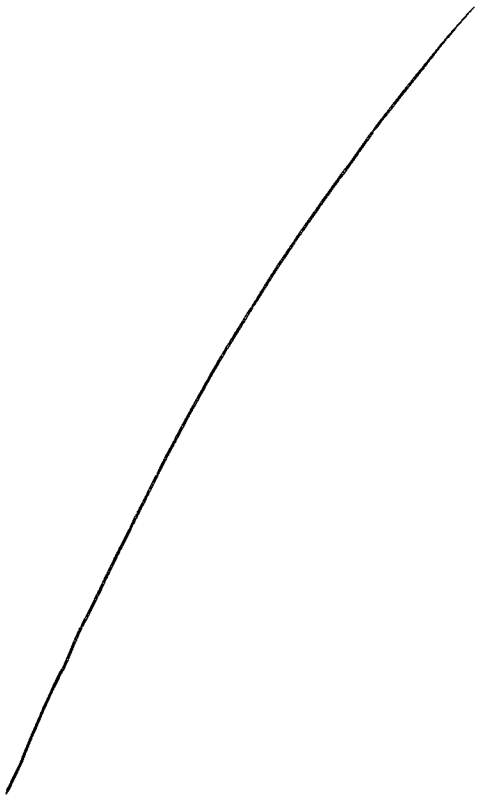
Assay of Dasatinib in Human Plasma

Samples were collected, and plasma samples were frozen and shipped on dry ice to [redacted]. Samples were stored frozen at -20°C prior to analysis. Human plasma samples were analyzed for dasatinib using a validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method in a total of 6 analytical runs. Spiked analytical QC samples were analyzed along with the study samples to assess the accuracy and precision of each analytical run. The standard curves and QC samples parameters are summarized in the following tables.

Table 2: Analytical Method Summary of Parameters

Parameter				
Standard Curve	1, 2, 5, 10, 50, 100, 250, 500, 750, 1000 ng/mL			
Correlation Coefficient	0.9996			
Standard Deviation	0.0015			
% CV	0.2			
LLQ=	1.0 ng/mL			
ULQ =	1000 ng/mL			
N=	6			
BMS 354825: Quality Control Samples: All data	QC3 (3.0 ng/mL)	QC35 (35 ng/mL)	QC400 (400 ng/mL)	QC800 (800 ng/mL)
% Deviation	7.7	4.6	6.8	-5.2
Between run precision %(CV)	1.9	0	0.7	0
Within run Precision (%CV)	5.6	7.4	7.3	5.4
Total variation (%CV)	5.9	7.2	7.3	5.0
N=	19	19	19	19
Number of runs	6	6	6	6

The standard curve and QC data indicate that the dasatinib human plasma assay method was precise and accurate. A sample chromatogram is shown by the following figure:



Assay of Dasatinib and BMS-606181 in Human Urine

At the end of the 24-hour period, the total urine sample was mixed thoroughly and a 4-mL aliquot was stored frozen at or below -20°C. Human urine samples were analyzed for BMS-606181 in a total of 2 analytical runs by a validated LC/MS/MS method. Spiked analytical QC samples were analyzed along with the study samples to assess the accuracy and precision of each analytical run. There were no rejected runs. The standard curves and QC samples are summarized in the following table.

Table 3: Human Urine Analytical Method for BMS-606181: Summary of Parameters

Model: Area Ratio=A* (Concentration **2) + B*(Concentration) + C				
Parameter				
Standard Curve	10, 50, 100, 250, 500 ng/mL			
Correlation Coefficient	0.9966			
Standard Deviation	0.0031			
% CV	0.3			
Between run variability (%CV)	6.7			
Within run Variability (%CV)	3.2			
% Deviation	±3.3			
LLQ=	1.0 ng/mL			
ULQ =	1000 ng/mL			
N=	2			
BMS 354825: Quality Control Samples: All data	QC3 (30.0 ng/mL)	QC35 (75 ng/mL)	QC200 (200 ng/mL)	QC400 (400 ng/mL)

Table 3: Human Urine Analytical Method for BMS-606181: Summary of Parameters				
Model: Area Ratio=A* (Concentration **2) + B*(Concentration) + C				
Parameter				
% Deviation	-0.7	-0.9	-3.6	-4.3
Between run precision %(CV)	N/A	N/A	N/A	N/A
Within run Precision (%CV)	2.0	0.9	1.1	0.9
Total variation (%CV)	N/A	N/A	N/A	N/A
N=	3	3	3	3
Number of runs	1	1	1	1
BMS 606181: Quality Control Samples: All data	QC3 (30.0 ng/mL)	QC35 (75 ng/mL)	QC200 (200 ng/mL)	QC400 (400 ng/mL)
% Deviation	-2.3	-2.4	-3.3	-0.7
Between run precision %(CV)	0.0*	0.0*	6.7	3.3
Within run Precision (%CV)	3.2	1.4	2.0	3.1
Total variation (%CV)	2.8	1.2	7.0	4.5
N=	6	6	6	6
Number of runs	2	2	2	2

The standard curve and QC data indicate that the BMS-606181 human urine assay method was precise and accurate.

PHARMACOKINETIC EVALUATION

Human Plasma Study:

Power: 20 subjects per formulation provided 75% confidence that the estimate of the B:A, C:A, or D:A formulation ratio of geometric means would be within 20% of the true value for dasatinib Cmax, and 80% confidence that the estimate of the B:A, C:A, or D:A ratio of geometric means would be within 20% of the true value for dasatinib AUC(INF).

Results: Summary pharmacokinetic parameters of dasatinib are shown in the following table.

TABLE 4: SUMMARY RESULTS FOR DASATINIB PHARMACOKINETIC PARAMETERS							
Treatment	N	Cmax (ng/mL) Geometric Mean (%CV)	AUC(INF) (ng*h/mL) Geometric Mean (%CV)	AUC(0-t) (ng*h/mL Geometric Mean (%CV)	Tmax (h) Median (min, max)	T-half (h) Mean (SD)	UR (%) Mean (SD)
2 X 50 Clinical (A)	18	90.93 (47)	309.39 (48)	295.15 (49)	1.00 (0.50, 2.00)	3.79 (1.14)	0.14 (0.08)
20 X 5 Clinical (B)	18	97.20 (56)	336.29[a] (47)	283.56 (55)	1.25 (0.50, 5.00)	4.06 (0.97)	0.16[b] (0.07)
5 X 20 Commercial (C)	18	57.32 (60)	308.52[a] (45)	200.95 (59)	1.00 (0.5,4.00)	4.83 (3.00)	0.12b (0.06)
2 X 50 Commercial (D)	18	63.21 (63)	280.15[c] (49)	234.36 (56)	1.00 (0.5, 4.00)	4.45 (1.98)	0.13[a] (0.08)
[a] N=17 [b] N=16 [c] N=18							

Mean dasatinib plasma concentration versus time profiles by treatment are shown below

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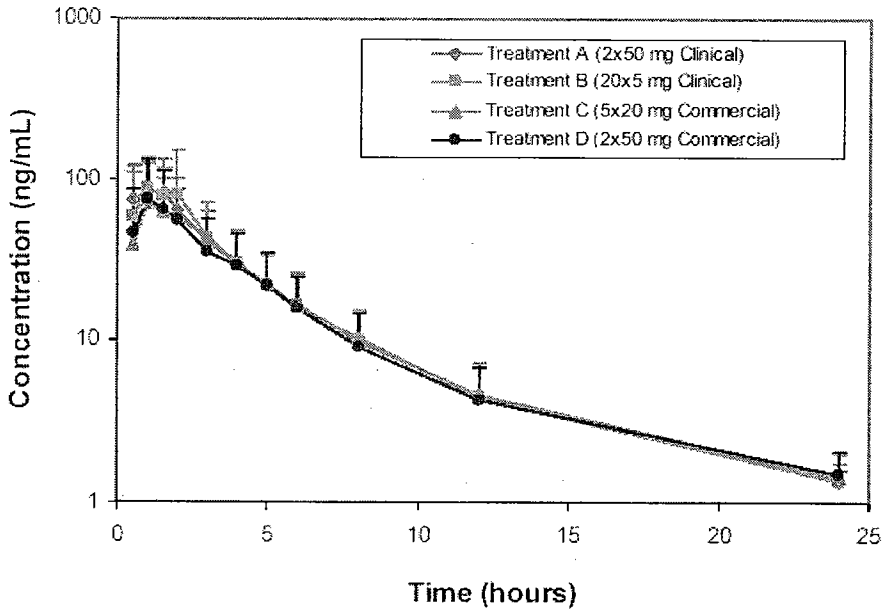


Statistical Analysis:
Analyses of variance were performed for log(Cmax), log(AUC[INF]), and log(AUC[0-T]), and 90% CIs for Cmax, AUC(INF) and AUC(0-T) were calculated for the B:A, C:A, and D:A ratios of geometric means. Summary statistics for the PK parameters of dasatinib tabulated by formulation are presented in the following table.

Results of Statistical Analyses for Dasatinib Cmax, AUC(INF), and AUC(0-T)

Parameter	Formulation	Geometric Mean	Ratio to Reference (90% CI)
Cmax (ng/mL)	2 x 50 mg clinical (A)	90.93	
	20 x 5 mg clinical (B)	97.20	1.069 (0.627, 1.824)
	5 x 20 mg commercial (C)	57.32	0.630 (0.372, 1.068)
	2 x 50 mg commercial (D)	63.21	0.695 (0.410, 1.178)
AUC(INF) (ng•h/mL)	2 x 50 mg clinical (A)	309.39	
	20 x 5 mg clinical (B)	336.29	1.087 (0.811, 1.457)
	5 x 20 mg commercial (C)	308.52	0.997 (0.744, 1.336)
	2 x 50 mg commercial (D)	280.15	0.905 (0.679, 1.208)
AUC(0-T) (ng•h/mL)	2 x 50 mg clinical (A)	295.15	
	20 x 5 mg clinical (B)	283.56	0.961 (0.588, 1.569)
	5 x 20 mg commercial (C)	200.95	0.681 (0.420, 1.105)
	2 x 50 mg commercial (D)	234.36	0.794 (0.489, 1.288)

n = 74 for Cmax and AUC(0-T); n = 70 for AUC(INF)

Discussion:
The following information can be derived from this study:

- 5 mg Phase I Clinical Formulation (B) compared to the 50 mg Phase I clinical formulation (A-Reference):
  - Cmax and AUC(0-T) appeared similar: Cmax increased by 7%, AUC(INF) increased by less than 9% and f AUC(0-T) decreased by less than 4%.
  - Although the 90% CIs for the B:A ratios of Cmax, AUC(INF) and AUC(0-T) are all very wide, the point estimates suggest that the exposure of Formulation B was similar with respect to both Cmax and AUC.

- 20 mg Phase II Clinical Formulation C compared to the 50 mg Phase I clinical formulation (A-reference):
    - Cmax decreased by 37%, AUC(INF) and AUC(0-T) decreased by less than 1% and by 32%, respectively.
    - Although the point estimates for Cmax and AUC(0-T) decreased, the ranges of the Cmax and AUC(0-T) distributions are similar to those of the reference formulation.
- 50 mg Phase II Clinical Formulation D compared to the 50 mg Phase I reference formulation (A):
    - Cmax for decreased by 31%, AUC(INF) and AUC(0-T) decreased by 10% and by 21%, respectively.
    - Although the point estimates for Cmax and AUC(0-T) decreased, the ranges of the Cmax and AUC(0-T) distributions are similar to those of the reference formulation.
- The inter-subject variability estimates calculated from the statistical analysis were high:
    - MSE is 0.9243 for Cmax; 0.2691 for AUC(INF) and 0.7792 for AUC(0-T)
    - Derived CV is 123% for Cmax; 56% for AUC(INF) and 109% for AUC(0-T)
    - DF is 70 for Cmax, 66 for AUC(INF and 70 for AUC(0-T).
- Median Tmax values suggest that the rate of absorption is comparable among the formulations.
- Elimination half-life was fairly consistent across formulations with mean (SD) values of 3.79 (1.14), 4.06 (0.97), 4.83 (3.00), and 4.45 (1.98) hours for Formulations A, B, C, and D, respectively.
- Using Formulation D as the reference, the Phase I formulations, 5 mg (B) and 50 mg (A) and the Phase II 20 mg formulation (C) were compared and the results are given in the following table.

Results of Statistical Analysis for Dasatinib using Treatment D as the reference			
Parameter	Formulation	Geometric Means	Ratio to Reference D
Cmax (ng/mL)	2 X 50 mg commercial (D)	63.,21	
	2 X 50 clinical (A)	90.93	1.439
	20 X 5 mg clinical (B)	97.2	1.538
	5 X 20 mg commercial (C)	57.32	0.907 (0.535 – 1.54)
AUC (INF) (ng*h/mL)	2 X 50 mg commercial (D)	280.15	
	2 X 50 clinical (A)	309.39	1.104
	20 X 5 mg clinical (B)	336.29	1.200
	5 X 20 mg commercial (C)	308.52	1.100 (0.855 -1.475)
AUC(0-T) (ng*h/mL)	2 X 50 mg commercial (D)	234.36	
	2 X 50 clinical (A)	295.15	1.259
	20 X 5 mg clinical (B)	283.56	1.210
	5 X 20 mg commercial (C)	200.95	.8574 (0.529 – 1.976)

- Formulation C meets the bioequivalence criteria compared to Formulation D for Cmax (90.7%), AUC(INF) (110.0%) and AUC(0-T) (85.74%).
- Mean urine excretion of dasatinib within 24 hours post dosing was negligible (less than 0.2% of total administered dose for all the formulations. There was no apparent difference in the excretion between formulations.
- Mean urine excretion of BMS-606181, the N-oxide metabolite of dasatinib, was only about 1% of the administered parent dose.

SAFETY ASSESSMENTS:

Safety assessments included monitoring adverse events (AEs), clinical laboratory tests, vital sign measurements, and electrocardiograms (ECGs). Serial ECG monitoring began one day prior to dose administration and at approximated PK collection time points (predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 hours post dose.

Analysis:

All groups had comparable subject demographic characteristics. All recorded AEs were listed and tabulated by system organ class, preferred term, and formulation. Vital signs and clinical laboratory test results were listed and summarized by formulation. The effect of dasatinib on the QTc interval

was assessed by frequency distributions for maximum QTc and maximum QTc changes from baseline and by summary statistics for maximum QTc and maximum QTc changes from baseline. The effect of dasatinib on the QTc interval was also assessed by linear regressions of QTc outcome measures (Delta QTc at dasatinib Tmax and Delta QTc Avg(0-24)) on measures of dasatinib plasma exposure (Cmax and Cavg[0-T]). In addition to the above analyses on QTc, frequency distribution, summary statistics and plots were provided for maximum heart rate and maximum heart rate change from baseline and for maximum PR and maximum PR change from baseline.

Results:

All AEs were mild or moderate in severity and most were considered possibly related to study medication. Thirty-two (32) cases of headache (82.1% of the total reports of headache) were mild (Grade 1) and 7 (17.9%) were moderate (Grade 2). None of the mild headaches required treatment; all of the moderate headaches required treatment with acetaminophen. All headaches resolved in less than 1 day, except for 3 which lasted between 3 to 5 days.

Eighteen (18) subjects (24.3% of total subjects) had at least 1 laboratory abnormality higher on-treatment relative to pre-study. Of those subjects, the only abnormality reported in more than 2 subjects was lymphocytopenia (6 subjects, 8.1% of total subjects). All of the laboratory abnormalities were mild (Grade 1); none were considered AEs or clinically important by the investigator.

One subject had a maximum QTcLP (log-linear population correction for QT) of 451 msec on Day -1 prior to receiving Formulation C, no subjects had maximum QTcLP greater than 450 msec after dosing. Four subjects had maximum QTcLP changes from baseline between 30 and 60 msec. No increase was detected for QTcLP change from baseline at dasatinib Tmax with increasing dasatinib Cmax. A decrease was observed in change from baseline QTcLP Avg(0-24) with increasing dasatinib Cavg(0-T).

CONCLUSIONS

Pharmacokinetics

A wide degree of inter-subject variability of dasatinib Cmax and AUC was observed in this study. Cmax CV ranged from 47% to 63% across the 4 formulations, while AUC(0-T) CVs ranged from 49% to 59%. The Cmax and AUC(0-T) appeared similar between Phase I Formulations B and A as the estimated ratios of geometric means of Cmax and AUC(0-T) between the 2 formulations were within 10%. The geometric means of Cmax and AUC(0-T) were lower for Phase II Formulations C and D compared with the reference formulation (A); however, the ranges of the distributions of Cmax and AUC(0-T) appeared comparable to those of the reference formulation. This is not surprising given the samples size for this comparability study and the use of a parallel design (instead of a crossover design). The Phase II formulation C was comparable to the Phase II formulation D with respect to Cmax, AUC(INF) and AUC(0-T).

Safety

The effect of a single 100 mg dose of dasatinib on the QTc interval was assessed. The 100 mg dose was safe and tolerable. Forty-eight (48) subjects reported 1 or more AEs, with headache being the most frequently reported AE. All AEs were mild or moderate in intensity; most were considered possibly related to study medication. No trend was seen among the treatment groups in the reporting of AEs. No subjects had an SAE or discontinued from the study. No clinically important abnormalities were identified by the investigator. No increase was observed in QTcLP (QT with log-linear population correction) change from baseline at dasatinib Tmax with increasing dasatinib Cmax. A statistically significant decrease was observed in change from baseline QTc Avg(0-24) with increasing dasatinib Cavg(0-T).

4.1.13 Study CA180009 - Food Effect Study

STUDY REVIEWER: Carol Noory, Ph.D.

TITLE OF STUDY: The Effect of a Light Fat and a High Fat Meal on the Pharmacokinetics Of BMS-354825 in Healthy Subjects

INVESTIGATORS AND CENTERS:

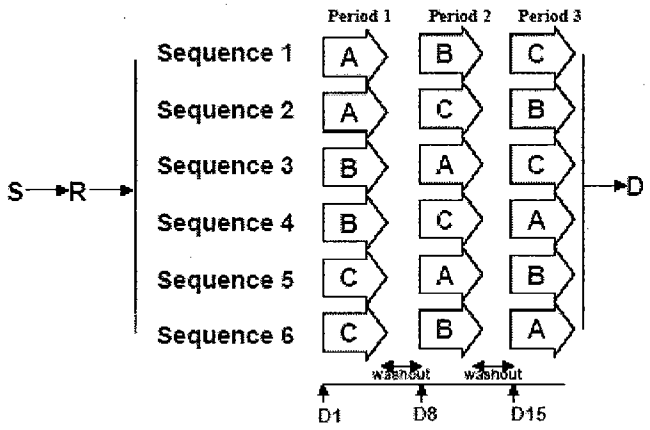
STUDY PERIOD: 7-Mar-2005 to 25-Apr-2005
CLINICAL PHASE: 1
OBJECTIVES:
Primary:

- To determine the effect of a light-fat and a high-fat meal on the pharmacokinetics (PK) of dasatinib in healthy subjects.

Secondary:

- To assess the safety and tolerability of dasatinib in a fasted state or following consumption of a light-fat and high-fat meal

STUDY DESIGN
This was an open-label, randomized, three-period, three-treatment, crossover study. Subjects were admitted to the clinical facility prior to dosing on Day -2 of Period 1. All subjects were to receive each of 3 single dose treatments in 1 of 6 randomly assigned sequences as shown below.



S = screening, R = randomization, D = discharge, A = fasted, B= light-fat meal, C= high-fat meal

There was at least a 7 day washout period between each dose. For each treatment period, subjects were confined to the clinical facility until 24 hours post-dose. Subjects fasted at least 10 hours prior to treatment and 4 hours post-treatment. For Treatments B and C, food was consumed within 30 minutes of dose administration. All tablets were dosed with 240 mL of water. The time of dose administration was called "0" hour. The total calorie content of the light- and high-fat meals was 319 kcal and 985 kcal, respectively. The calories derived from fat, carbohydrates, and protein were 20%, 68%, and 12%, respectively, for the light-fat meal and 52%, 34%, and 14%, respectively, for the high-fat meal.

TREATMENT:
Dasatinib film-coated tablets were dosed at 100 mg. The batches used are listed in the following table.

Strength (Unit)	Label Batch Number	Product Batch Number
50 mg	4K90229.4B	4L77205
	5A09452.5C	5A10537

The treatments are described in the following table.

Treatment	Strength	Total Dose	Meal
A	2 X 50 mg	100 mg	Fasted condition
B	2 X 50 mg	100 mg	**Light Breakfast**: Tablets dosed 30 minutes after the start of a standard light-fat breakfast [319 kcal derived from 20% fat, 68% carbohydrates, and 12% protein])
C	2 X 50 mg	100 mg	**High-fat Breakfast:** Tablets dosed 30 minutes after the start of a standard high-fat breakfast [985 kcal derived from 52% fat, 34%

			carbohydrates, and 14% protein]

SAMPLE COLLECTION:

Blood samples (3 mL) were obtained predose, and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose on Day 1.

SUBJECTS:

A total of 54 subjects were enrolled in the study; 6 discontinued the study early. Reasons for leaving the study are listed below

Subject Identifier	Treatment at Time of Discontinuation	Days in Study	Reason for Discontinuation
CA180009-2-231	Dasatinib 100 mg after high-fat meal	2	Adverse event (Grade 2 urticaria)
CA180009-2-237	Dasatinib 100 mg fasted	9	Adverse event (Grade 1 cough, throat irritation, and pruritus)
CA180009-2-241	Dasatinib 100 mg after high-fat meal	7	No longer met study criteria
CA180009-2-245	Dasatinib 100 mg after light-fat meal	16	No longer met study criteria
CA180009-2-248	Dasatinib 100 mg after high-fat meal	15	No longer met study criteria
CA180009-2-252	Dasatinib 100 mg after high-fat meal	16	No longer met study criteria

SAFETY ASSESSMENTS:

Safety assessments included monitoring adverse events (AEs), clinical laboratory tests, vital sign measurements, and electrocardiograms (ECGs).

ANALYTICAL METHODOLOGY

Assay Method for Dasatinib in Human Plasma

Human EDTA plasma samples were frozen and shipped on dry ice to the — — for analysis. Samples were stored frozen at -20°C prior to analysis for dasatinib and its metabolite, BMS-606181. A validated liquid chromatography tandem mass spectrometry (LC/MS/MS) method was used. The metabolite was included because early animal data indicated that the metabolite was active. Since little activity was shown, further analysis of BMS-606181 was not necessary. Plasma samples were analyzed for dasatinib in a total of 25 analytical runs. The performance parameters of the standard curves and QC samples are summarized in the following table.

Analytical Method Summary of Parameters				
Parameter				
Standard Curve				
Correlation Coefficient	0.9964			
Standard Deviation	0.0015			
% CV	0.2			
LLQ=	1.0 ng/mL			
ULQ =	1000 ng/mL			
N=	25			
BMS 354825 QC Samples: Outliers Excluded	QC3 (3.0 ng/mL)	QC35 (35 ng/mL)	QC400 (400 ng/mL)	QC800 (800 ng/mL)
% Deviation	-2.7	-2.5	-5.2	-6.2
Between run precision %(CV)	2.0	4.9	4.6	5.6
Within run Precision (%CV)	7.2	10.2	5.4	6.2
Total variation (%CV)	7.4	11.3	7.1	8.4
N=	84	83	83	84
Number of runs	26	26	26	26

PHARMACOKINETIC EVALUATION:

The study was designed to have a power of approximately 80% to conclude the absence of a food effect with respect to Cmax and AUC(INF) if data from forty-eight subjects was available. Fifty-four (54) subjects were enrolled to allow for dropouts. Pharmacokinetic parameters of dasatinib were determined using a non-compartmental method and Cmax and Tmax were obtained from experimental observations. The T1/2 was calculated as Ln2/Lz, where Lz was the absolute value of the slope of the terminal log-linear phase. The AUC(0-T) was calculated using the mixed log-linear trapezoidal algorithm in Kinetica. The AUC(INF) was estimated by summing AUC(0-T) and the

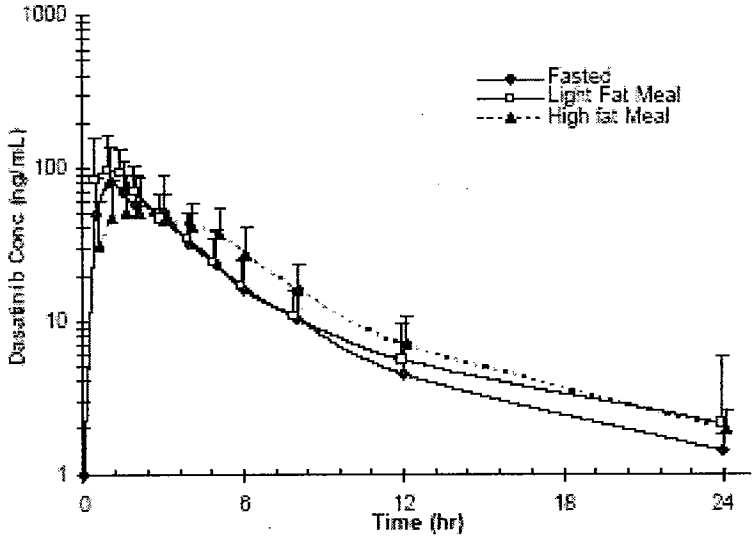
extrapolated area, computed by the quotient of the last observable concentration and Lz. All subjects who received dasatinib were included in the PK data set. However, only subjects with values from Treatment A and at least one of Treatments B and C were included in the summary statistics.

	Dasatinib Pharmacokinetic Parameters				
Treatment	Cmax (ng/mL) Geom Mean (CV%)	AUC(INF) (ng•h/mL) Geom Mean (CV%)	AUC(0-T) (ng•h/mL) Geom Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
A	92.09	304.24	290.57	1	4.84
(n = 49)	(50)	(47)	(49)	(0.50, 3.00)	(2.16)
B	111.78	366.90*	357.46	1.50	4.59*
(n = 49)	(47)	(39)	(42)	(0.50, 4.00)	(1.21)
C	71.03	355.27	341.04	2.00	4.77
(n = 47)	(40)	(32)	(32)	(0.50, 6.00)	(1.34)

*n = 48

A = dasatinib 100 mg fasted; B = dasatinib 100 mg after light-fat meal; C = dasatinib 100 mg after high-fat meal; Geom = geometric

The mean plasma concentration-time profiles of dasatinib following fasted, light-fat meal, and high-fat meal are depicted in the following figure:



Statistical Analysis

To assess the effect of food on the oral bioavailability of 100 mg dasatinib, analysis of variance was performed on log (Cmax), log (AUC[INF]) and log (AUC[0-T]). The factors in each analysis were treatment sequence, subject within sequence, treatment period, and treatment. Additional analyses of variance evaluated the significance of first-order carry over effects.

For Cmax, AUC(INF), and AUC(0-T), ANOVA, models were fitted on a logarithmic scale, and 90% CIs for Cmax, AUC(INF), and AUC(0-T) were calculated for ratios of geometric means. The statistical results are summarized in the following table.

	Adjusted Geometric Means		Ratio of Geometric Means		
Pharmacokinetic Variable	Treatment	Adjusted Geometric Means	Ratio	Point Estimate	90% Confidence Limits
Cmax (ng/mL)	A	92.39			
	B	112.36	B vs A	1.216	(1.047, 1.413)
	C	69.99	C vs A	0.758	(0.651, 0.882)
AUC(INF) (ng•h/mL)	A	304.99			
	B	369.71	B vs A	1.212	(1.100, 1.336)
	C	347.65	C vs A	1.140	(1.034, 1.257)
AUC(0-T) (ng•h/mL)	A	291.19			
	B	359.17	B vs A	1.233	(1.113, 1.367)
	C	333.41	C vs A	1.145	(1.032, 1.270)

Source: Supplemental Tables S.11.2.1C, S.11.2.1D and S.11.2.1E

A = dasatinib 100 mg fasted; B = dasatinib 100 mg after light-fat meal; C = dasatinib 100 mg after high-fat meal; vs = versus

Pharmacokinetics Discussion:

- The 90% confidence intervals for ratios of Cmax and AUC(INF) for the light- or high-fat meal compared to the fasted treatment were not within the equivalence interval of 80% to 125%.
- With a light-fat meal (Treatment B), Cmax and AUC(INF) of dasatinib were increased by 22% to 21%, respectively, compared to the fasted state (Treatment A).
- When dasatinib was administered with a high-fat meal (Treatment C), Cmax was decreased by 24%, and AUC(INF) was increased by 14% compared to the fasted treatment. The upper confidence limit for AUC(INF) and AUC(0-T) ratios for Treatment C to A was slightly over the limit at 125.7% and 127%, respectively.
- There were no statistically significant sequence effects (at the $\alpha = 0.05$ level) and no significant period effects (at the $\alpha = 0.05$ level) in the analyses of Cmax, AUC(INF) and AUC(0-T).
- For both Cmax and AUC(INF), the first order carryover effect was not statistically significant (at the $\alpha = 0.05$ level, although just barely so for AUC(INF) with $P = 0.056$).
- For AUC(0-T), the first order crossover effect was statistically significant at the $\alpha = 0.05$ level (however, the effect appears to be mild with $P = 0.044$).
- The mean half-life for BMS-254825 appears to be in the 4.5 to 5 hour range, with standard deviations ranging approximately from 1.2 to 2.2 hours.
- Intra-subject variability estimates were large, 46%CV for Cmax, 29% CV for AUC(INF) and 31% for AUC(0-T).

SAFETY ASSESSMENTS

Data from all 54 subjects were included in the safety data sets. Overall, 41 (75.9%) of the subjects reported an AE. Headache was the most frequently reported AE. Individual events were infrequent and balanced between treatment groups. The investigator judged 59.3% of the AEs to be probably related to study medication, 29.6% to be possibly related, 25.9% to be unrelated, 14.8% to be unlikely related, and 3.7% to be certainly related. Most of the subjects had AEs that were considered mild (68.5%) or moderate (31.5%) in intensity. Two (2) subjects (3.7%) had severe AEs. There were no deaths in this study or serious adverse events reported in this study. Two (2) subjects discontinued the study because of 1 or more AEs considered probably related to study treatment, 1 subject for Grade 2 urticaria while receiving dasatinib 100 mg with a high-fat meal and the other subject for cough, throat irritation, and pruritus, all Grade 1, while receiving dasatinib 100 mg fasting. The AEs that resulted in discontinuation from the study resolved within 14 hours. Thirty-eight (38) subjects had at least 1 laboratory abnormality higher on-treatment relative to pre-study. Most laboratory abnormalities were observed in only a few subjects each. Four (4) QTcB values exceeded 450 msec, 1 of which occurred pre-study, 2 after Treatment A was administered, and 1 after Treatment C was administered. Fourteen (14) subjects had a total of 26 post-treatment QTcB changes from baseline that exceeded 30 msec, 1 of which was greater than 60 msec. No QTcF values exceeded 450 msec. The maximum change in QTcB from baseline was 65 msec, and occurred in a subject on Treatment C, at 0.5 hours post-treatment. Because the study did not contain a placebo group, the clinical importance of this isolated

prolongation can not be assessed.

CONCLUSIONS:

Pharmacokinetics

Light Fat Meal: The results of this study indicated that a light-fat meal increased the rate as well as the extent of absorption of dasatinib. The Cmax and AUC(INF) values were increased by 22% and 21%, respectively, under fed conditions compared to the fasted treatment. The absence of food effect could not be concluded.

High-Fat Meal: A high-fat meal decreased the rate and marginally impacted the extent of absorption of dasatinib; Cmax decreased by 24%, AUC(INF) increased 14% and Tmax was prolonged by 1 hour compared to fasting conditions. Based on the 90% CI, the absence of food effect could not be established. However, the upper bound of the CI for AUC(INF) (1.257) was slightly above the upper limit of the equivalence criterion (1.25). The change in dasatinib exposure following a high-fat meal is less than 15. Preliminary patient data from CA180002 (the maximum administered dose study in solid tumor patients), suggest that even with dose increases 29%, and > 70% above the recommended 70 mg twice daily dose, there is no increase in severe hematologic or nonhematologic toxicity of dasatinib. Thus, the 22% increase in the average Cmax, and the 21% increase in AUC(INF) following a light-fat meal may be of limited clinical relevance.

Safety

Three single oral doses of dasatinib 100 mg to healthy subjects in a fasted state or following consumption of a light-fat and high-fat meal were safe and tolerable. Forty-one (41, 75.9%) subjects reported 1 or more AEs, with headache being the most frequently reported AE. No clinically important AEs or laboratory abnormalities were identified by the investigator.

4.2 APPENDIX 2 - BIOWAIVER REQUEST

STUDY REVIEWER: Carol Noory, Ph.D.

Dasatinib was formulated as immediate-release, film-coated tablets in strengths of 20 and 50 mg for Phase II clinical trials. The sponsor has requested approval of 20, 50, and 70-mg strength tablets. A waiver for an *in vivo* bioavailability study for the 70-mg strength tablet was requested based on the following:

1. Safety/efficacy at clinical dosing regimen of dasatinib 70 mg (administered as 20 and 50-mg tablets) BID has been established in Phase II clinical trials.
2. Linearity of derived pharmacokinetic measures suggests a dose proportional increase in AUC and linear elimination characteristics over the clinical dose range.
3. The contents of the 70-mg strength tablet are proportionally similar to the contents of the lower strength tablets (i.e., 20 and 50 mg).
4. The *in vitro* dissolution data demonstrate similarity of dissolution profiles between the Reference (20, 50 and 20 + 50 mg) and Test (70 mg) products in three different media: pH 1.2 (USP), pH 4.0 acetate buffer containing 1% Triton X-100 (proposed regulatory method), and pH 4.5 (USP).

Safety/efficacy at clinical dosing regimen

Several clinical studies dosed at 70 mg (50 mg + 20 mg) and support safety and efficacy at this dosing level.

Linear Pharmacokinetics

Approximate dose proportional increases in total daily exposure to dasatinib were observed in clinical study CA180002 within the dose range of 15 to 240 mg daily.

Formulation Proportionality

The compositions of dasatinib tablets are shown in the following table. The proposed 70-mg

strength tablet is manufactured from the same common — , that is used to manufacture the 20 and 50-mg tablets. As indicated in the table, the content of the 70-mg strength tablet (Test product) is proportionally similar to the content of the 20 and 50-mg strength tablets (Reference products) with the exception of the film coat. The slightly higher percentage of the film coat for the lower strength tablets (i.e., 20 and 50 mg) is due to their greater specific surface area resulting from smaller tablet size.

Composition of Proposed Commercial Dasatinib Tablets: 20 mg, 50 mg and 70 mg						
Component	Compendial Reference	Function	% w/w[a]	Amount (mg/tablet)		
				20 mg	50 mg	70 mg
Dasatinib[b]	—	Active	—	20	50	70
Lactose Monohydrate[c]	NF, Ph. Eur.					
Microcrystalline Cellulose	NF, Ph. Eur.					
Hydroxypropyl Cellulose	NF, Ph. Eur.					
Croscarmellose Sodium	NF, Ph. Eur.					
Magnesium Stearate	NF, Ph. Eur.					
White,	—	Film Coat				
	USP, Ph.Eur.		—	—	—	—
Tablet Weight	—	—	—	83.2	207.0	288.4

In vitro profile similarity

Dissolution tests were performed on twelve dosage units of each of the batches described in the following table:

DASATINIB TABLETS BATCHES TESTED FOR DISSOLUTION PROFILE COMPARABILITY								
Dosage Strength (mg)	Batch number	Batch Size	Use of Batch	Designation	pH 1.2[a]	pH 4.0[b]	pH 4.5[a]	pH 6.8[a]
70	5C4345X	—	Commercial site and process	Test	X	X	X	
20	4L77202		Study CA180-016	Reference	X	X	X	X
50	4L77205		Study CA180-016	Reference	X	X	X	
20 + 70[c]	4L77202 and 4L77205		Study CA180-016	Reference	X	X	X	
a: USP Apparatus 2, 60 rpm, 1000 mL of media b: USP Apparatus 2, 60 rpm, 1000 mL of 4.0 acetate buffer with 1% Triton X-100 (proposed registration batches c: 20 and 50 mg film coated tablets added to the same dissolution vessel								

The dissolution results using the paddle apparatus, 60 rpm and 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 4.0 acetate buffer with 1% Triton X-100 are shown in the following table. The Similarity factors (f2) are also given.

Dissolution of Batches (n=12) in Various Media

Sample Description	pH	Average Percent Dissolved					Similarity Factor (f_2)
		10 minutes	15 minutes	30 minutes	45 minutes	60 minutes	
70-mg Test Product	1.2	83	86	90	92	93	--
20 + 50-mg Reference Product		90	92	95	96	97	[b]
20-mg Reference Product		97	98	100	101	101	[b]
50-mg Reference Product		94	96	98	99	99	[b]
70-mg Test Product	4.0 with 1% Triton X-100	73	89	97	97	97	--
20 + 50-mg Reference Product		68	85	95	98	98	66
20-mg Reference Product		75	87	96	97	97	[b]
50-mg Reference Product		70	84	96	97	97	72
70-mg Test Product	4.5	27	34	44	50	53	--
20 + 50-mg Reference Product		23	29	38	43	47	62
20-mg Reference Product		28	37	51	60	65	55
50-mg Reference Product		22	28	38	44	48	63
20-mg Reference Product	6.8[a]	2	2	3	4	4	[c]

[a] Due to the poor solubility at this pH, this dissolution condition was not repeated for any other batches or dosage strengths.
[b] As more than 85% of the labeled amount of drug dissolved in 15 minutes for both the test and reference products, profile comparison with f_2 test is unnecessary.
[c] Dissolution profile at pH 6.8 is irrelevant as less than 5% of the labeled amount of drug was dissolved after 60 minutes for the lowest dosage strength.

Mean dissolution profiles are illustrated in the following figures:

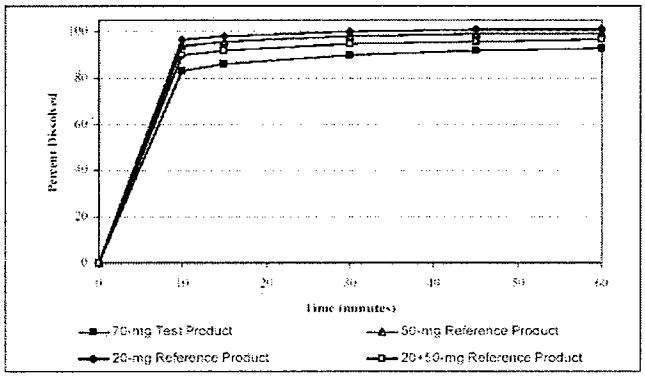


Figure A: Apparatus 2, 60 rpm, Hydrochloric Acid, pH 1.2

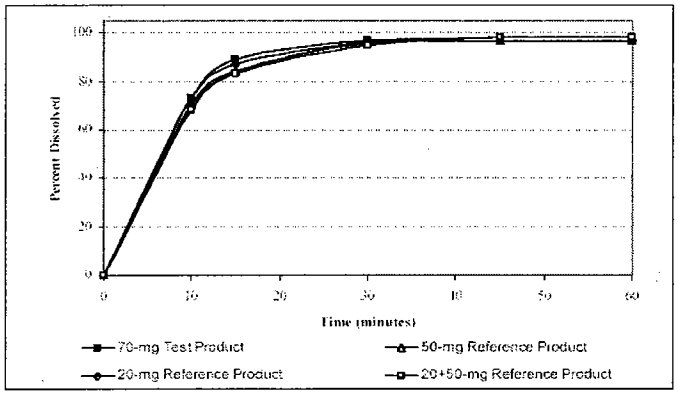


Figure B: Apparatus 2, 60 rpm, pH 4.0 buffer containing 1% Triton X-100

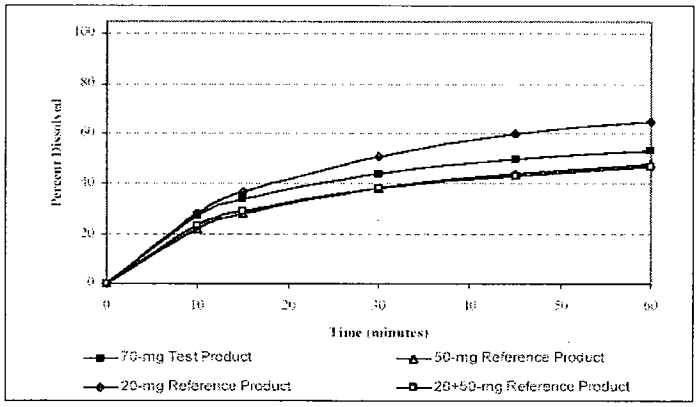


Figure C: Apparatus 2, 60 rpm, pH 4.5 Acetate Buffer

Dissolution in pH 1.2 USP media (USP Apparatus 2, 60 rpm, 1000 mL, 37° C) is considered rapid since more than 85% of the labeled amount was dissolved in fifteen minutes. Therefore f2 determination is unnecessary. Similarity testing is not needed for the dissolution profiles obtained in pH 6.8 USP media (USP Apparatus 2, 60 rpm, 1000mL, 37 °C), since less than five percent was dissolved, even after 60 minutes. The similarity results obtained at pH 4.0 with 1.0% Triton X-100 and pH 4.5 acetate buffer indicate that the dissolution profiles for the 70-mg tablets are similar (f2 value ≥50) to the dissolution profiles for the 20 mg, 50-mg and 20+50-mg film coated tablets tested and suggest that *in vivo* performance of the 70-mg tablets is expected to be similar to the performance of the 20-mg and 50-mg tablets currently utilized in clinical studies.

OVERALL CONCLUSIONS

Elimination characteristics, available safety and efficacy data for the relevant clinical dosing regimen, the *in vitro* dissolution data and formulation proportionality between the strengths, support approval of the sponsor's request for a waiver of the requirement to conduct a bioequivalence study for dasatinib 70 mg strength tablets. The waiver requested for the 70 mg tablets is acceptable.

4.3 APPENDIX 3 - DISSOLUTION ASSESSMENT

STUDY REVIEWER: Carol Noory, Ph.D.

According to the Biopharmaceutics Classification System (BCS), dasatinib is classified as a BCS Class II drug based on its solubility (< 0.001 mg/mL at pH 7.0) and permeability data (102 nm/sec). However, the pH-solubility profile indicates that dasatinib has high solubility at pH 2.6 or below (18.4 mg/mL). The aqueous solubility shows a significant decrease in solubility within a narrow pH range, suggesting that small changes in dissolution media pH could lead to significant differences in the dissolution profile as sink conditions are approached. The maximum recommended dose of dasatinib (70 mg BID) is expected to be highly soluble in physiological gastric conditions.

I. Summary of Method Development

The — ng tablet strength was identified as the highest dosage strength which the sponsor was considering and was used for development of the dissolution procedure. Many of the dissolution screening studies were performed using two or three dissolution vessels as opposed to the typical six-vessel testing for each condition. A summary of the dissolution method development is given in the following tables. The firm evaluated different media and

test conditions to determine a robust test in which the product dissolved less than — in 15 minutes and at least — in 60 minutes.

Table 1: Summary of Dissolution Method Development

Formulation[1]	USP Apparatus	Spindle Rotation Speed	Media Volume (mL)	Medium	Surfactant	Criteria 1 < — dissolved at 20 min	Criteria 1 — dissolved at 60 min	Criteria 2 Is Method robust?[2]
Phase II Commercial	2	50 rpm	900 mL	pH 1.2 (0.1 N HCl)	None	no	YES	---
				pH 4.5 Acetate Buffer		YES	no	---
				pH 6.8 Phosphate Buffer		YES	no	---
Prototype I	2	60 rpm	1000 mL	pH 3.0 Citrate Buffer	None	no	YES	---
				pH 3.2 Citrate Buffer		no	YES	---
				pH 3.4 Citrate Buffer		no	YES	---
				pH 3.5 Citrate Buffer		YES	YES	no
				pH 3.6 Citrate Buffer		YES	no	---
				pH 3.8 Citrate Buffer		YES	no	---
				pH 4.0 Acetate Buffer		YES	no	---
				pH 4.2 Acetate Buffer		YES	no	---
				pH 4.4 Acetate Buffer		YES	no	---
Phase II Commercial	1	60 rpm	1000 mL	pH 3.4 Citrate Buffer	None	no	YES	---
				pH 3.5 Citrate Buffer		no	YES	---
				pH 3.6 Citrate Buffer		YES	YES	no
								robust
Phase II Commercial	1	60 rpm	1000 mL	pH 4.0 Acetate Buffer	1% Triton X-100	YES	YES	YES
				pH 4.2 Acetate Buffer		YES	no	---
				pH 4.4 Acetate Buffer		YES	no	---
				pH 4.8 Acetate Buffer		YES	no	---
				pH 4.1 Acetate Buffer		YES	no	---
Phase II Commercial	2	60 rpm	1000 mL	pH 4.0 Acetate Buffer	0.5% Triton	YES	no	---
					0.75% Triton	YES	no	---
					1.0% Triton	YES	YES	YES
					1.25% Triton	YES	YES	[3]
Phase II Commercial	2	50 rpm	1000 mL	pH 3.2 Citrate Buffer with and w/out sinkers	None	no	no	---
				pH 3.4 Citrate Buffer with and w/out sinkers		YES	no	---
				pH 3.6 Citrate Buffer with and w/out sinkers		YES	no	---

Formulation[1]	USP Apparatus	Spindle Rotation Speed	Media Volume (mL)	Medium	Surfactant	Criteria 1 < — dissolved at 20 min	Criteria 1 — dissolved at 60 min	Criteria 2 Is Method robust?[2]
Phase II Commercial	2	50 rpm	1000 mL	pH 3.6 Acetate Buffer	1% Triton X-100	YES	no	---
				pH 3.8 Acetate Buffer		YES	no	---
				pH 4.0 Acetate Buffer		YES	no	---
Phase II Commercial	1	100 rpm	1000 mL	pH 3.2 Citrate Buffer	None	YES	no	---
				pH 3.4 Citrate Buffer		YES	no	---
				pH 3.6 Citrate Buffer		YES	no	---
Phase II Commercial	1	100 rpm	1000 mL	pH 3.8 Acetate Buffer	1% Triton X-100	YES	no	---
				pH 4.0 Acetate Buffer		YES	no	---

[1] All method development work was performed using the — mg tablet strength as it is the highest dosage strength and presented the most challenges with respect to drug solubility.

[2] Percent dissolved for test method conditions is ≥5% dissolved at all time points after 15 minutes compared to reference method conditions. Robustness was only studied if the dissolution parameters met Criteria 1.

[3] 1.25% Triton X-100 was the highest concentration of Triton X-100 used, therefore this condition was not studied for robustness but rather, was used to establish robustness of media containing 1.0% Triton X-100

The development studies systematically evaluated the effect of media pH, surfactant and surfactant concentration to achieve a sufficiently slow dissolution profile. Results indicate that neither 50 rpm paddle speed (USP Apparatus 2) or 100 rpm baskets (USP Apparatus I) yielded appropriate dissolution profiles due to mounding. The firm was able to remedy this by using the 60 rpm paddle speed. Dissolution in media between pH 3.0 - 4.4 gave a

desirable profile. The use of pH 3.6 citrate buffer was evaluated. However, small changes in media pH dramatically influenced the dissolution profile due to large changes in drug solubility. Therefore, surfactants were evaluated to maintain sink within a pH range where the drug is less soluble. Study results demonstrated dissolution was sufficiently slow, complete, reproducible and robust using pH 4.0 acetate buffer with 1% Triton X-100 as dissolution medium. The parameters for the final dissolution method proposed by the sponsor for dasatinib 20, 50 and 70 mg film coated tablets are:

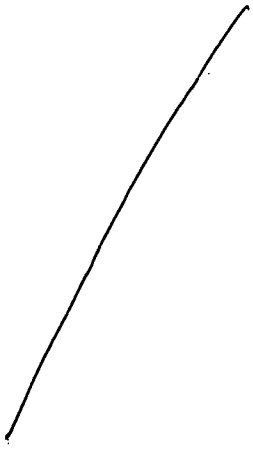
USP Apparatus	Rotation Speed	Media Volume	Temperature	Medium	Surfactant
2	60 rpm	1000 mL	37°C	pH 4.0 acetate buffer	1% Triton X-100

II. Ability to Discriminate

The sponsor evaluated the ability of the dissolution method selected, Paddle Apparatus, 60 rpm, 1000 mL of pH 4.0 acetate buffer with 1% Triton X-100, to discriminate between tablets manufactured using several manufacturing/formulation variables. Tablets manufactured with and without film coating; without — microcrystalline cellulose (MCC); — ablets throughout the potential commercial range of dosage strengths (20 mg to — ng), as well as at an intermediate strength (50 mg) and drug substance particle size were used to evaluate the ability of the method to discriminate. In addition, the method was used to differentiate batches manufactured with different drug substance particle size.

III. Analytical Method

All dissolution aliquots were analyzed by — The analytical parameters are given in the following table:



IV. Determination of Specification

No changes were observed in the dissolution results for all strengths tablets at all storage conditions and packages during the stability studies. Based on this, the sponsor selected a specification of Q= — in 30 minutes. Evaluation of the dissolution results of the following batches was conducted to justify the dissolution specification.

Table 2.3.P.5.T02: Batch Analysis of Dasatinib Tablets, Phase II/Commercial Formulation, Continued

	Dissolution (% of Label, n=6)				
Batch Number (Dosage Strength)	**10 min Mean (Range)**	**15 min Mean (Range)**	**30 min Mean (Range)**	**45 min Mean (Range)**	**60 min Mean (Range)**
4L77202 (20 mg)	76 ( )	89 ( )	98 ( )	99 ( )	99 ( )
4M64169 (20 mg)	81 ( )	90 ( )	96 ( )	97 ( )	97 ( )
5A04130 (20 mg)	81 ( )	89 ( )	94 ( )	95 ( )	96 ( )
5A04132 (20 mg)	77 ( )	88 ( )	95 ( )	98 ( )	98 ( )
5A04134 (20 mg)	90 ( )	96 ( )	98 ( )	98 ( )	98 ( )
5C06213 (20 mg)	75 ( )	90 ( )	97 ( )	98 ( )	99 ( )
5C06214 (20 mg)	72 ( )	88 ( )	95 ( )	96 ( )	96 ( )
5E01515 (20 mg)	78 ( )	94 ( )	102 ( )	102 ( )	101 ( )
5E01517 (20 mg)	75 ( )	91 ( )	98 ( )	99 ( )	99 ( )
5E01519 (20 mg)	74 ( )	89 ( )	97 ( )	97 ( )	98 ( )
5E01521 (20 mg)	71 ( )	88 ( )	97 ( )	97 ( )	98 ( )
5E01522 (20 mg)	82 ( )	95 ( )	100 ( )	100 ( )	99 ( )
5E01523 (20 mg)	70 ( )	87 ( )	97 ( )	98 ( )	98 ( )
5E01524 (20 mg)	71 ( )	87 ( )	96 ( )	97 ( )	98 ( )
5E01525 (20 mg)	77 ( )	96 ( ) [h]	101 ( )	101 ( )	101 ( )
5E01526 (20 mg)	72 ( )	87 ( )	95 ( )	95 ( )	96 ( )
5E01527 (20 mg)	74 ( )	90 ( )	98 ( )	99 ( )	99 ( )
5E01529 (20 mg)	75 ( )	91 ( )	97 ( )	97 ( )	97 ( )
5E01530 (20 mg)	77 ( )	92 ( )	98 ( )	99 ( )	99 ( )
5E01532 (20 mg)	74 ( )	92 ( )	101 ( )	102 ( )	101 ( )
5E01533 (20 mg)	76 ( )	93 ( )	100 ( )	100 ( )	101 ( )
5E01536 (20 mg)	71 ( )	86 ( )	94 ( )	95 ( )	95 ( )
5E01541 (20 mg)	79 ( )	93 ( )	100 ( )	100 ( )	100 ( )
5E01543 (20 mg)	66 ( )	83 ( )	91 ( )	92 ( )	93 ( )
5E01546 (20 mg)	73 ( )	90 ( )	99 ( )	100 ( )	100 ( )

[h] A dissolution result of — Label was obtained for one vessel. As a determinate error could not be established, the result was not removed from the data set and is included in the average.

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Table 2.3.P.5.T02: Batch Analysis of Dasatinib Tablets, Phase II/Commercial Formulation, Continued

Batch Number (Dosage Strength)	Dissolution (% of Label, n=6)				
	10 min Mean (Range)	15 min Mean (Range)	30 min Mean (Range)	45 min Mean (Range)	60 min Mean (Range)
5E01547 (20 mg)	79 ( )	93 ( )	100 ( )	100 ( )	101 ( )
5J02850 (20 mg)	87 ( )	95 ( )	100 ( )	100 ( )	101 ( )
4L77205 (50 mg)	70 ( )	82 ( )	94 ( )	97 ( )	98 ( )
4L85341 (50 mg)	70 ( )	82 ( )	95 ( )	97 ( )	98 ( )
5A10548 (50 mg)	70 ( )	81 ( )	91 ( )	94 ( )	95 ( )
5A10549 (50 mg)	72 ( )	84 ( )	93 ( )	95 ( )	97 ( )
5A10557 (50 mg)	70 ( )	80 ( )	89 ( )	92 ( )	94 ( )
5C05064 (50 mg)	68 ( )	83 ( )	94 ( )	96 ( )	96 ( )
5C05065 (50 mg)	69 ( )	87 ( )	97 ( )	98 ( )	98 ( )
5C08599 (50 mg)	85 ( )	94 ( )	99 ( )	100 ( )	101 ( )
5C08601 (50 mg)	69 ( )	85 ( )	94 ( )	96 ( )	96 ( )
5C08609 (50 mg)	68 ( )	84 ( )	95 ( )	96 ( )	96 ( )
5H01126 (50 mg)	79 ( )	91 ( )	95 ( )	97 ( )	97 ( )
5H01127 (50 mg)	80 ( )	89 ( )	95 ( )	97 ( )	98 ( )
5H01128 (50 mg)	79 ( )	92 ( )	97 ( )	99 ( )	99 ( )
5J02853 (70 mg)[i]	65 ( )	84 ( )	93 ( )	95 ( )	96 ( )
5A07666 ( )[i]	70 ( )	84 ( )	95 ( )	97 ( )	97 ( )
5A07670 ( )[i]	67 ( )	82 ( )	94 ( )	96 ( )	96 ( )
5A07673 ( )[i]	68 ( )	82 ( )	94 ( )	97 ( )	97 ( )

[i] n=12

APPEARS THIS WAY
ON ORIGINAL

Table 2.3.P.5.T03: Batch Analysis of Dasatinib Tablets, Phase 1 Formulation, Continued

Batch Number (Dosage Strength)	Dissolution (% of Label, n=6)				
	10 min Mean (Range)	20 min Mean (Range)	30 min Mean (Range)	40 min Mean (Range)	60 min Mean (Range)
3C72889 (5 mg)					
4C88975 (5 mg)					
4G78659 (5 mg)					
5A01426 (5 mg)					
5C02739 (5 mg)					
5F02041 (5 mg)[f]					
3C72907 (50 mg)	87 (	97 (	100 (	101	101
4C91969 (50 mg)	74 (	90 (	96 (	99 (	101
4G78663 (50 mg)	80 (	93 (	97 (	98	99
5A01431 (50 mg)	87 (	97 (	99 (	101	102
5C04559 (50 mg)	91 (	97 (	99 (	99 (	100

[f] Method 10251 was used with sampling timepoints of 10, 15, 30, 45 and 60 minutes.

V. Conclusions

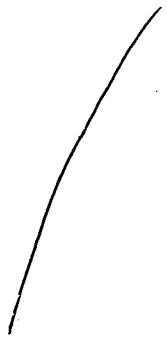
A robust, discriminating dissolution method for dasatinib tablets was developed. This method was used to support (1) clinical release of 20 and 50 mg film coated tablets used in Phase II clinical studies and (2) long term stability studies for 20, 50 and – mg film coated tablets. The method is intended for quality control release testing of commercial 20, 50 and 70 mg film coated tablets.

4.4 APPENDIX 3 - ANALYTICAL METHOD VALIDATION

STUDY REVIEWER: Carol Noory, Ph.D.

The quantitative determination of BMS-354825 and the metabolite, BMS-606181, in human EDTA plasma by LC/MS/MS was developed and validated.

Sample Processing Procedure



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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Assay Validation Summary		
	BMS 354825	BMS 606181
LLOQ	1 ng/mL	1 ng/mL
% deviation at LLOQ	-0.1%	6.7%
Accuracy	-4.5 to 2.1%	-4.5 to -1.9%
Between run precision	0 to 2.9	0 to 3.0
Within run precision	1.9 to 4.9	2.4-4.2
Total Variation %CV	2.1 to 4.5	2.3 to 4.9
N=	18	18
Stability (QC samples)		
0 h @ RT (%dev) 3 ng/mL	0.8%	-8.0%
0 h @ RT (%dev) 800 ng/mL	-1.9%	-7.6%
24 h @ RT (%dev) 3 ng/mL	3.8%	-3.9%
24 h @ RT (%dev) 800 ng/mL	-1.4%	-7.4%
52 weeks @ -20°C (%dev) 3 ng/mL	4.9%	-2.4%
52 weeks @ -20°C (%dev) 800 ng/mL	-3.8%	-2.1%
Freeze/Thaw – 3 cycles (%dev) 3 ng/mL	4.2%	-0.8%
Freeze/Thaw – 3 cycles (%dev) 800 ng/mL	-6.0%	-9.1%
Stability of Processed Samples		
0 h @ RT (%dev) 3 ng/mL	4.2%	4.7
0 h @ RT (%dev) 400 ng/mL	5.7	0.0
0 h @ RT (%dev) 800 ng/mL	-2.9%	-7.4
72 h @ RT (%dev) 3 ng/mL	3.7	3.0
72 h @ RT (%dev) 400 ng/mL	3.4	6.3
72 h @ RT (%dev) 800 ng/mL	0.9	-0.5
Stability in Blood		
1 h @ RT (%dev) 40 ng/mL	3.94	-0.46
1 h @ RT (%dev) 400 ng/mL	1.11	-0.13
2 h @ RT (%dev) 40 ng/mL	5.83	-4.77
2 h @ RT (%dev) 400 ng/mL	10.13	6.47
1 h @ on ice (%dev) 40 ng/mL	6.01	-2.51
1 h @ on ice (%dev) 400 ng/mL	4.34	1.91
2 h @ on ice (%dev) 40 ng/mL	11.42	-3.37
2 h @ on ice (%dev) 400 ng/mL	1.10	-2.62

Conclusion

The analytical method developed is sensitive and specific for dasatinib.

4.5 APPENDIX 5 - QT CONSULT REVIEW

Clinical Pharmacology and Biopharmaceutics Review
QT Consult

1. RECOMMENDATION

The Sponsor's labeling for effect of dasatinib on the QT interval is acceptable.

An analysis of the data from five Phase II studies in patients and a Phase I study in healthy subjects suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QT interval from baseline for subjects receiving therapeutic doses of dasatinib, with associated upper 95% confidence intervals <10 msec.

2. SUMMARY OF FINDINGS

2.1 Preclinical

Preclinical data do not suggest that dasatinib has a high potential to prolong QT interval. The IC_{50} for hERG inhibition by dasatinib is 14.3 microM. The maximum dasatinib concentration observed in

patients receiving 70 mg dasatinib twice daily to steady state was 263 ng/mL in human plasma, or 0.6 microM. This concentration is 24-fold lower than the concentration of free drug that inhibited hERG currents *in vitro*. Protein binding *in vivo* would be expected to increase this margin further. It has been reported that drugs with a 30-fold hERG margin do not seem to prolong QT interval *in vivo*.[1]

2.2. Clinical

2.2.1 Sponsor's Analysis

The Sponsor provided an assessment of dasatinib's effect on QT interval based on data from several Phase 1 studies in healthy subjects and several Phase 1 and 2 studies in patients. Table 1, Table 2, and Table 3 highlight features of the studies performed. Note that there was no placebo control, nor any positive control for QT assay validity, used in any of these studies.

Table 1. Description of Phase 1 Studies in Healthy Subjects with ECG Data.

Study	Purpose	Design	N	Dose	# ECGs/subject	# PK samples/subject
180016	Forml'n	Single Dose	75	100 mg	12/dose	12/dose
180009	Food FX	3-way XO	54	100 mg	4/dose	12/dose
180032	DDI	2 occasions	20	100 mg	4/dose	12/dose
180019	ADME	Single Dose	8	100 mg	4 total	Multiple
180020	pH FX	3-way XO	24	50 mg	1/dose	11/dose
180022	DDI	2-way XO	48	100 mg	4/dose	12/dose

Table 2. Description of Phase 1 Studies in Patients with ECG Data.

Study	Dosage	ECG Days	ECG Hours	N Treated	N with PK
180002	15,30,50,75,105,140,180 mg QD (N=21) or 25,35,50,70 mg BID (N=63)	1,5,26	0,1,2,4,6,8,24	84	84
180003	35, 50, 70, 90, 120, 160 mg BID	1,5,26	0,1,2,3,4,6,8,10	33	33

Table 3. Description of Phase 2 Studies in Patients with ECG data.

Study	Subjects	Design	Dose (mg)	ECG Days	ECG Hours	N Dosed	N with PK data
180005	Patients	BID Dosing	70 mg	1,8	0,1,2,4,6	107	31
180006	Patients	BID Dosing	70 mg	1,8	0,1,2,4,6	74	25
180013	Patients	BID Dosing	70 mg	1,8	0,1,2,4,6	186	0
180015	Patients	BID Dosing	70 mg	1,8	0,1,2,4,6	78	0
180017	Patients	BID Dosing	70 mg	1,8	0,1,2,4,6	22	0

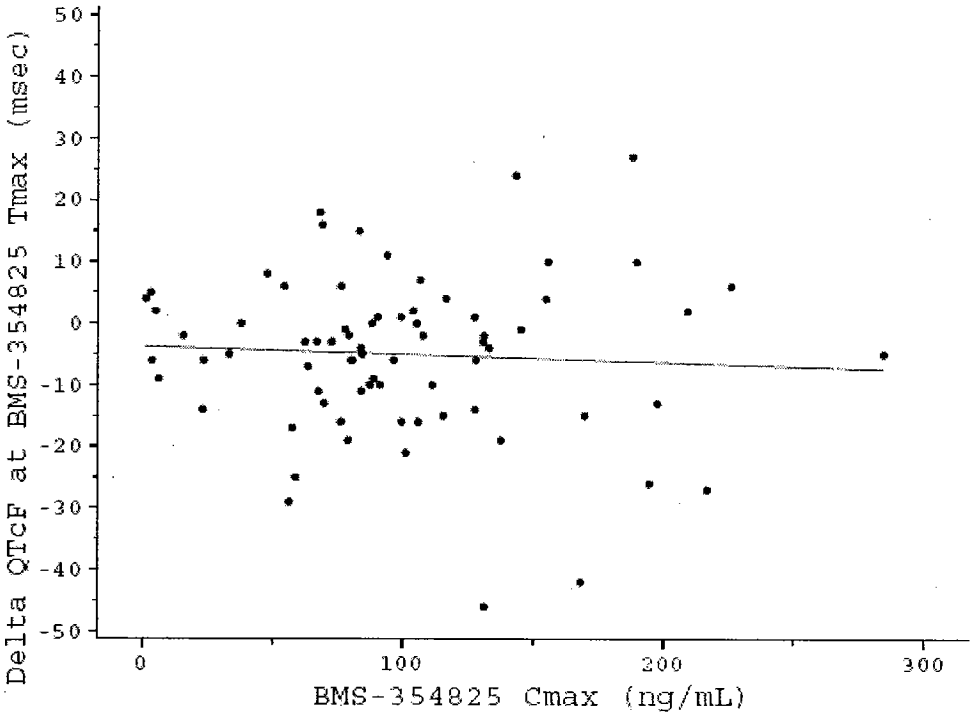
Sponsor's Analysis

The Sponsor's report focused on an analysis of Phase I Study 180016 (Table 1) in healthy subjects and on the five Phase II studies in patients (Table 3). Study 180016 was selected for several reasons:
a) It was the largest Phase 1 healthy subject study.
b) Subjects received only dasatinib, without confounding dietary or concomitant drug administration (single 100 mg doses, fasted).
c) Several correction formulae for QT were compared.
d) It provided the largest number of ECGs and associated PK measurements per subject on one treatment day.
e) The highest Cmax value in this study (284 ng/mL) exceeds the highest Cmax observed with 70 mg BID given chronically in patients (263 ng/mL; in study 180005).

Figure 1 shows the Sponsor's estimated exposure-response relationship for change from baseline in Fridericia corrected QT interval (ΔQTcF) computed using data from Study 180016. The upper 95% confidence interval for the slope is 0.04. This suggests that at a Cmax of 263 ng/mL, the upper 95%

confidence value of change in QTcF from baseline would be 10.5 msec.

Figure 1. Mean time-matched ΔQTcF at maximum concentration (Cmax). The upper 95% confidence interval for the slope is 0.04.

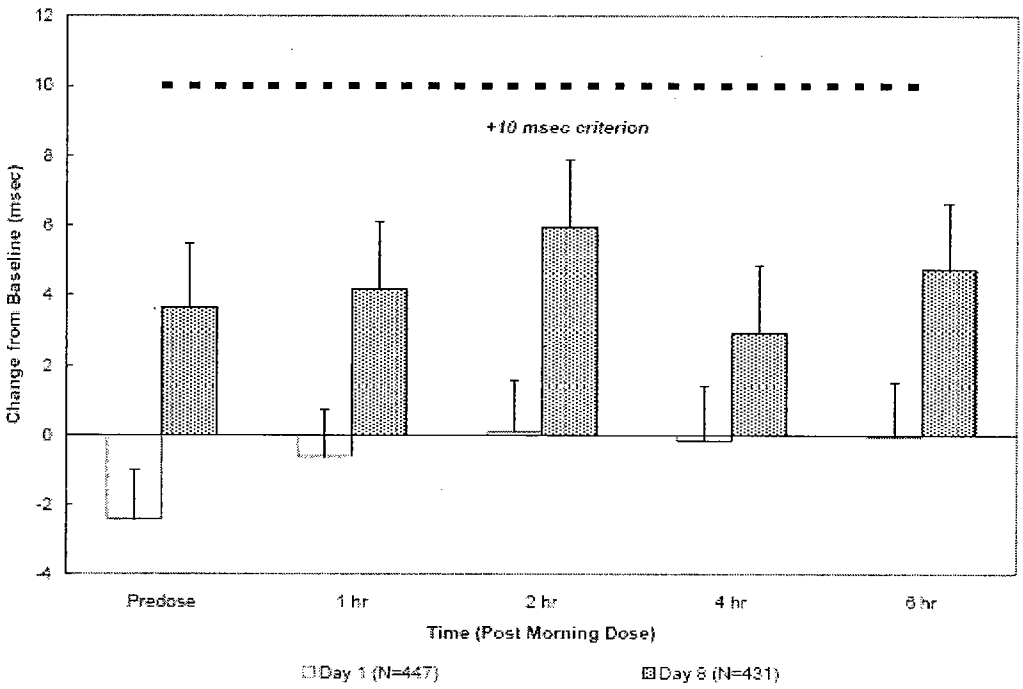


In each of the five Phase II studies performed, subjects with leukemia were treated with dasatinib 70 mg BID, and ECGs were obtained at similar and standardized time points. The Sponsor performed a grouped analysis of these studies regarding changes from pretreatment values in QTc and other ECG intervals.

Figure 2 shows the mean and upper one-sided 95% confidence interval computed on the data pooled across studies as a function of time after dose. Figure 2 shows that the upper one-sided 95% confidence interval at all measurement time points falls below the +10 msec criterion. The Sponsor notes that the mean hourly ΔQTcF (*i.e.*, from Day -1) to Day 1 were modest in all five Phase II studies, but that on Day 8, the QTcF interval was increased at nearly all time points in all studies. Regardless, the extent of change in QTcF from baseline is less than +10 msec.

In conclusion, the Sponsor notes that dasatinib 70 mg BID, when administered for 8 days to subjects with leukemia, is associated with a 3-6 msec mean increase from baseline in QTc interval. The upper 95% one-sided confidence intervals for the mean changes in QTcF at each time point were all <8 msec.

Figure 2. Mean and Upper One-Sided 95% Confidence Interval Computed on the Data Pooled Across Studies as a Function of Time After Dose.



2.2.2. Reviewer's Comments on the Sponsor's Analysis

It was of interest to explore the Sponsor's analysis of the concentration-response relationship as reported in Figure 1 in further detail. The rationale was that the Sponsor's graphical analysis may underestimate the impact of drug exposure on QT interval in some individuals since the Sponsor's analysis shows the mean slope for the concentration-response analysis. The slope of interest, however, is the upper 95% confidence interval value of slope (0.04) because it reflects the range of possible slope values.

When the change in QTc is computed using this slope at a Cmax of 263 ng/mL (the maximum concentration observed in any subject receiving 70 mg BID), the predicted change in QTcF from baseline is 10.5 msec—a value that does not cross the threshold for declaring an effect of drug on QT interval. The typical Cmax for a 70 mg BID regimen is 100 ng/mL (see Figure 7), thus, the predicted ΔQTcF is 4 milliseconds.

In summary, the Sponsor presents two different methods of analysis to assess QT response. According to either analysis, dasatinib does not increase QT interval more than 10 milliseconds from baseline.

2.2.3. Reviewer's Analysis

Two studies were the focus of the reviewer's analysis: Study 180005 and Study 180002 (see Table 2 and Table 3 for details).

Study 180002 was selected since: (1) a wide range of doses were administered to patients, (2) the highest dose administered exceeds the dose to be used therapeutically (up to 180 mg daily), (3) subjects were dosed for a long period of time (several weeks), (4) ECG data were fairly rich (collected until 24 hours post dose), and, (5) PK and ECG data were collected in all subjects (N=84).

Study 180005 was selected since: (1) the clinically relevant dose was administered for 8 days to patients, and, (2) ECG data and PK data were collected in more subjects than during any other Phase 2 study. Note that only one dose was administered in Study 180005 – 70 mg BID; a 140 mg daily dose.

Maximum Mean Analysis

Figure 3 shows a plot of the maximum value of mean ΔQTcF for each daily dose group and indicates the time at which the maximum value of ΔQTcF was achieved in Study 180002. Figure 3 suggests that there is no clear dose-related or time-related trend with respect to change in QTcF from baseline. Thus, the extreme values are likely due to noise rather than related to drug exposure.

Figure 3. Maximum Mean ΔQTcF (Baseline Corrected QTcF) as a Function of Dose with the Upper 95% Confidence Interval for Study 180002. Time of maximum ΔQTcF for each dose is indicated on the plot.

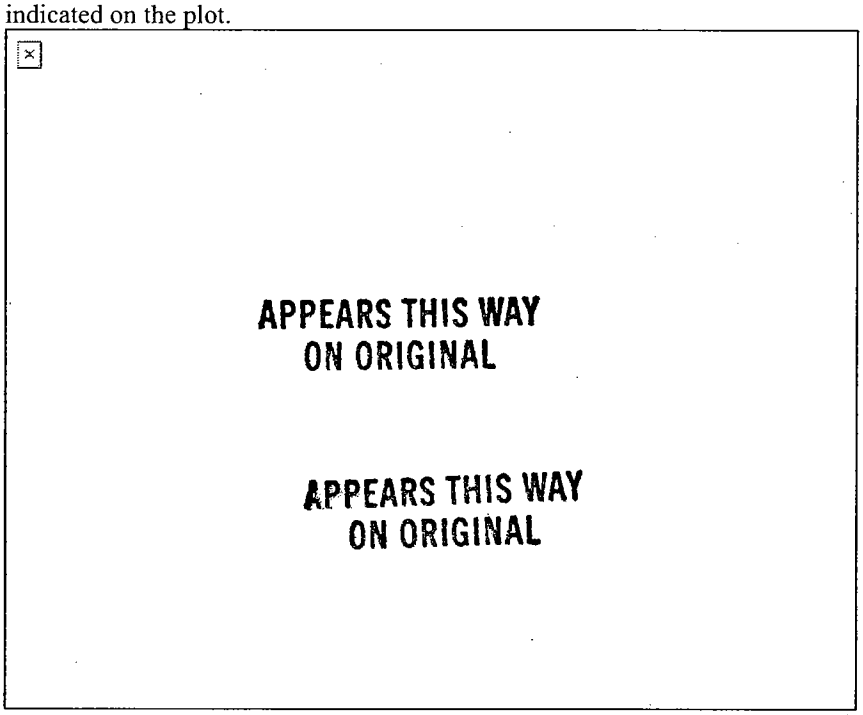
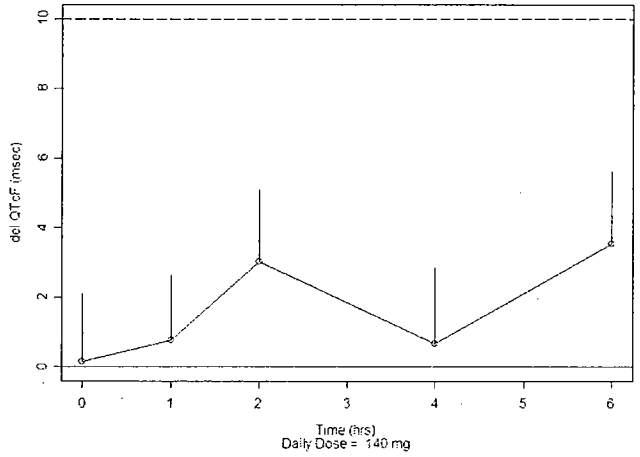


Figure 4 shows a plot of mean ΔQTcF (baseline corrected QTcF) as a function of time with the upper 95% confidence interval above estimates at each time point in Study 180005. As for Study 180002, there is no clear time-related trend in values. All values of ΔQTcF are below 10 msec.

Figure 4. Mean ΔQTcF (Baseline Corrected QTcF) as a Function of Time with the Upper 95% Confidence Interval for Study 180005.



Extreme Values

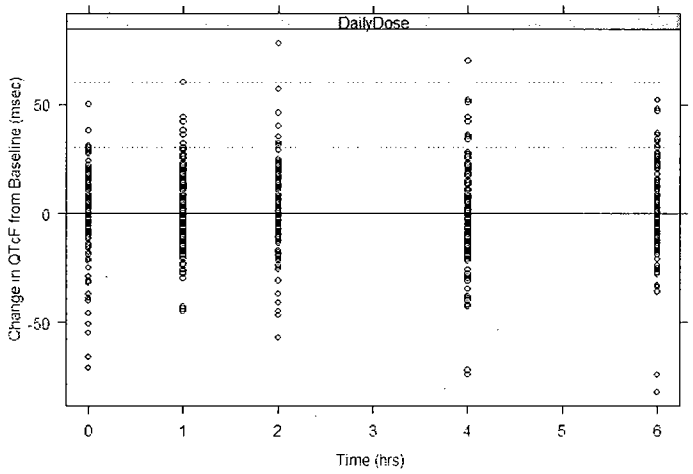
Table 4 shows the number and percent of extreme ΔQTcF values observed in Study 180002. That is, values between 30 and 60 milliseconds, and values exceeding 60 milliseconds. Table 4 does not suggest that there is any dose-related trend in extreme values.

Table 4. Tally of Values of ΔQTcF Exceeding 60 msec and between 30-60 msec by Dose in Study 180002.

ΔQTcF (msec)	Dose (mg)										
	0	**15**	**30**	**50**	**70**	**75**	**100**	**105**	**140**	**180**	**240**
30-60	0 (0%)	7 (9.9%)	3 (4.3%)	3 (2.1%)	2 (1.2%)	4 (5.6%)	6 (3.3%)	2 (3.1%)	35 (8.8%)	8 (3.5%)	4 (4.3%)
>60	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (3.8%)	0 (0%)	1 (0.2%)	0 (0%)	0 (0%)

Figure 5 shows a plot of raw ΔQTcF data as a function of time for Study 180005. This permits viewing any "outlier" values (>30 msec and >60 msec). Lines are drawn at 30 msec and 60 msec to focus on these values. Figure 5 does not suggest any time-related trend in extreme values. Only 2.5% of ΔQTcF values ranged from 30-60 msec and 0.1% of ΔQTcF >60 msec.

Figure 5. Outliers: Raw Values of ΔQTcF for Each Dose Group as a Function of Time After Dose in Study 180005. Lines are drawn on the plot at 30 msec and 60 msec to indicate where values exceed these cutoffs.



Exposure-Response Analysis

An exposure-response analysis was performed on a pooled dataset of ΔQTc and Daily Dose data in studies 180002 and 180005. A linear mixed effects model was fit to the data with patient ID as the grouping variable. The upper 95% confidence value of slope is taken as the slope of interest to predict ΔQTcF.

Figure 6 shows a plot of the upper 95% confidence value of slope for the dasatinib daily dose-time profile. The slope is 0.0258, which means that there is a predicted change of 3.6 milliseconds in QTcF from baseline for the therapeutic dose.

Figure 6. Plot of ΔQTcF vs. Daily Dose of Parent Drug with Mixed Effects Model Predicted Value of 95% Upper Confidence Interval for Slope. The data are pooled from studies 180002 and 180005.

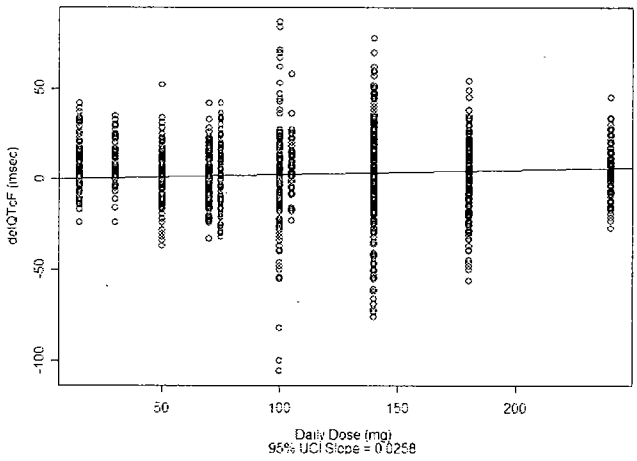
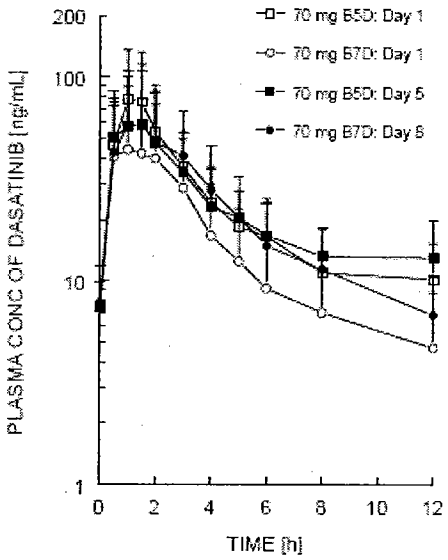


Figure 7 shows a typical dasatinib concentration-time profile following administration of the proposed therapeutic dose at steady state.

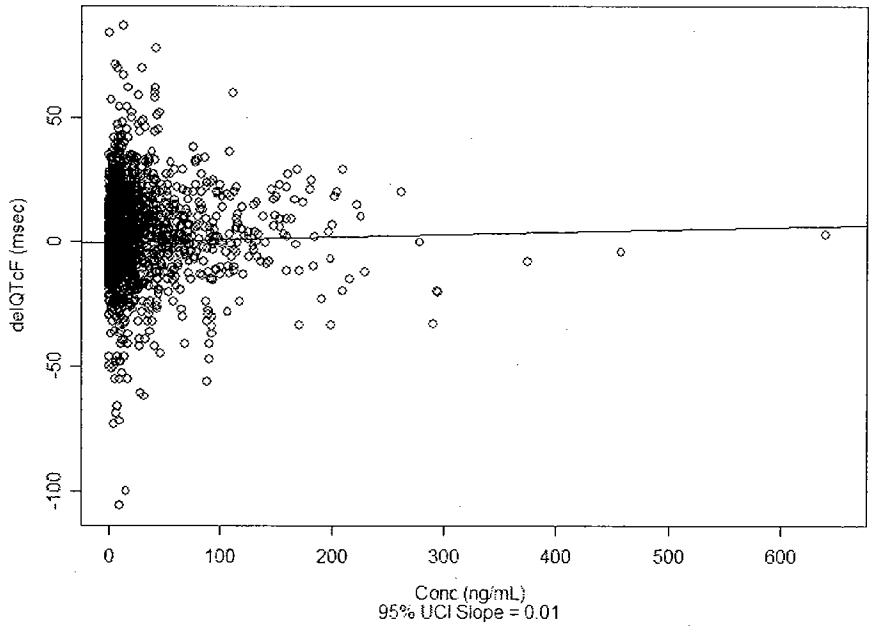
Figure 7. Mean (SD) Dasatinib Plasma Concentration-Time Profiles Following Administration of the Proposed Therapeutic Dose of 70 mg BID Administered as a B5D and B7D Regimen.



A concentration-response analysis was performed on data collected in studies 180002 and 180005. A linear mixed effects model was fit to the data with patient ID as the grouping variable. The upper 95% confidence value of slope is taken as the slope of interest to predict ΔQTcF.

Figure 8 shows the ΔQTcF vs. Concentration data of Parent compound for all subjects with the upper 95% confidence value of slope (slope = 0.01) plotted. According to this model, at the most extreme concentration measured in a subject receiving 70 mg BID to steady state (263 ng/mL), there will be a 2.6 millisecond increase in ΔQTcF. For a typical Cmax of 100 ng/mL, the predicted increase in QT interval is +1 millisecond.

Figure 8. Plot of ΔQTcF vs. Concentration of Parent Drug with Mixed Effects Model Predicted Value of 95% Upper Confidence Interval for Slope. The data are pooled from studies 180002 and 180005.



The Sponsor also measured the concentration of one of dasatinib's metabolites (BMS-606181). Figure 9 shows a plot of ΔQTcF vs. Concentration of metabolite for all subjects with the upper 95% confidence value of slope (slope = -0.034) plotted. According to this model, there is no expected increase in ΔQTcF as a function of metabolite concentration.

Figure 9. Plot of ΔQTcF vs. Concentration of Metabolite with Mixed Effects Model Predicted Value of 95% Upper Confidence Interval for Slope.

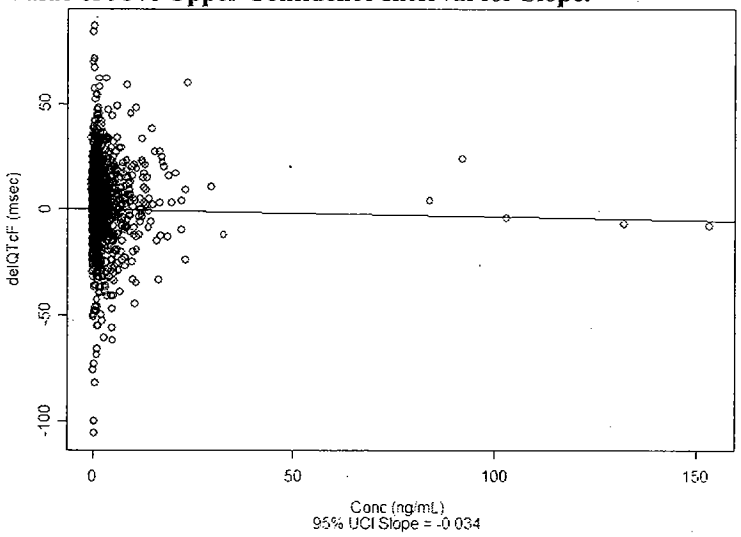


Table 5 summarizes the model predicted effects of exposure to dasatinib on QT interval.

Table 5. Predicted ΔQTcF (With Upper 95% Confidence Interval) by the Population PK-PD Models for Parent Drug.

Dose	Dose Effect (mean + upper 95% CI)	Concentration Effect (mean + upper 95% CI)
70 mg BID	+1.8 msec	+1 msec

140 mg BID	+3.6 msec	+2 mec

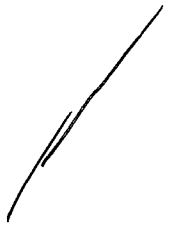
In summary, the reviewer's analysis suggests that the Sponsor's proposed labeling is reasonable.

3. APPENDIX

3.1 References

1. Redfern WS, Carlsson L, Davis AS, Lynch WG, MacKenzie I, Palethorpe S, Siegl PK, Strang I, Sullivan AT, Wallis R, Camm AJ, Hammond TG. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res* (2003) 58(1):32-45.

3.2 Proposed labeling for effect on QT interval



PRECAUTIONS

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In — studies in patients with leukemia treated with SPRYCEL, the mean changes from baseline in QT_cF interval were 3–6 msec; the upper 95% confidence intervals for all mean changes from baseline were <8 msec.

SPRYEL (dasatinib) should be administered with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. (

4.6 APPENDIX 6 - PHARMACOMETRICS REVIEW

Clinical Pharmacology Pharmacometrics Review

Pharmacometric Reviewer Roshni Ramchandani, Ph.D. Angela Men, M.D., Ph.D.
PM Team Leader Jogarao Gobburu, Ph.D.

1. Executive Summary

The applicant conducted five pivotal phase 2 clinical trials without performing a pharmacokinetic-pharmacodynamic (PK-PD) analysis. In order to characterize the PK-PD relationships for effectiveness (cytogenetic response, hematologic response) and toxicity in chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients, the Agency conducted the PK-PD analysis using logistic regression to relate the observed frequency of effectiveness and severe toxicity with dose and C_{trough} of dasatinib. There was no significant correlation identified between the trough level of dasatinib and the probability of effectiveness and severe toxicity. Dose-response relationship was not confirmed because about 50% patients were administrated with combination of 70mg, 50 mg, 40 mg and/or 100 mg BID. In both chronic and

advanced phase studies, about 50% and 30% patients need a dose reduction because of severe toxicities.

2. Introduction

2.1 Summary

The applicant is seeking approval of SPRYCEL™ (dasatinib) for the treatment of chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). The recommended oral dose of dasatinib is 70 mg given every 12 hours (BID) without regard to food.

Five pivotal phase 2 clinical trials are ongoing in CML and PH+ ALL patients. As of the submission cut-off time point, the study population and treated patients are summarized in the Table 1. Endpoints for each of the Phase 2 clinical studies are listed in Table 2.

Table 1. Five Phase 2 Studies

Study (Phase)	Population	Study Design	Dose	N dosed
CA180013 (2)	Chronic phase CML (IM-R only)	Open-label, randomized	70 mg BID	36 (22 Dasatinib: 14 Imatinib)
CA180017 (2)	Chronic phase CML	Open-label, Single-arm	70 mg BID	186
CA180005 (2)	Accelerated phase CML	Open-label, Single-arm	70 mg BID	107
CA180006 (2)	Myeloid blast phase CML	Open-label, Single-arm	70 mg BID	74
CA180015 (2)	Ph+ALL or lymphoid blast CML	Open-label, Single-arm	70 mg BID	78

Table 2. Primary Endpoints for Five Phase 2 Studies

	Studies	Primary Endpoints
Chronic Phase Studies	CA180013 CA180017	Major Cytogenetic Response (MCyR)
Advanced Phase Studies	CA180005 CA180006 CA180015	Overall Hematologic Response (OHR) Major hematologic Response (MaHR)

The most frequently reported (> 10%) adverse events (AEs) included hematological toxicities (neutropenia, thrombocytopenia), gastrointestinal AEs (diarrhea, nausea, and vomiting), fluid retention events, headache, fatigue, asthenia, rash, dyspnea, and pyrexia. No PK/PD analysis was conducted by the applicant.

2.2 Objectives of Analysis

1. To identify the relationship between dose and clinical response.

2. To characterize the relationships between trough level of dasatinib and effectiveness (cytogenetic response, hematologic response) and between trough level of dasatinib and severe toxicity in chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients using logistic regression.

3. Methods

3.1 Clinical Studies:

Dose-response relationships were investigated using study results obtained from 5 Phase 2 studies.

Because some patients did not receive a fixed dose of 70 mg BID during the study period, the average daily dose was used for dose-response analysis. The average daily dose was calculated as: total administrated dose/days (including the days of interruption). All patients enrolled in these Phase 2 studies were included in the dose-response analysis.

For C_{trough}-PD analysis, trough level on Day 8 was used to correlate with the effectiveness and toxicities endpoints. Table 3 and 4 shows the number of subjects who have intensive and sparse PK sampling from the Agency and the Sponsor. Only those subjects with PK data identified by the Agency were included in the C_{trough}-PD analysis.

Table 3. Number of Subjects with PK sampling (Agency)

Study	N with intensive PK		N with sparse PK
	Day 1	Day 8	
CA180005	29	25	10
CA180006	24	21	4
CA1800013	0	0	133
CA1800015	0	0	40
CA1800017	0	0	21

Note: Study CA180013: 18-13070, 31-13038, 31-13081, 38-13124, 44-13003 (no trough level data), 86-13151 trough level on Day 8 were removed because the collection time was not at 0.
Study CA180015: the sponsor report n=41 in the Table above. However, only n=40 data are available. Also CA180015-21-15043 and 140-15055 were removed due to no trough level concentration were collected.
Study CA180005: two patients' data were removed 1-5071 b/c unreliable; 33-5010 b/c pt received 50 mg BID
Study CA180006: the sponsor reported n=22 with sparse PK on Day 8. Only 21 available.

Table 4. Number of Subjects with PK sampling (Sponsor)

Table 2.1: Phase 2 Studies in Subjects with Leukemia				
Study	**Population**	**Subjects with dense PK samples**	**Subjects with sparse PK samples**	**PK[a,b] Assessment Hours**
CA180005	Accelerated CML	29,27[c]	10	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10
CA180006	Blast Phase CML	24,22[d]	4	0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10
CA180013	Chronic CML	0	133	0, 3, 8, 12
CA180015	Ph+ ALL	0	41	0, 3
CA180017	Chronic CML	0	21	0, 3, 8, 12

Source: Individual Study Protocols

[a] Fourteen subjects in studies CA180005 (N=10) and CA180006 (N=4) had sparse samples collected on day 8 at 0 and 3 h.

[b] For studies CA180013, CA180015 and CA180017, there were a total of 195 subjects with sparse samples.

[c] N=29 on day 1 and N=27 on day 8. PK parameters for Subject CA180005-1-5065 and Subject CA180005-1-5071, both on Day 8, were excluded from the summary statistics because these subjects reported 0 and 0.5 h nominal times as 0 h actual times; the data were judged to be unreliable. PK parameters for Subject CA180005-33-5010, Day 8, were excluded from the summary statistics because the subject received 50 mg twice daily.

[d] N=24 on day 1 and N=22 on day 8. PK parameters for Subjects CA180006-1-6063, CA180006-69-6036, CA180006-44-6004, Day 8 were excluded from the summary statistics due to an inadequate number of plasma concentration-time data compared to the other subjects.

Pharmacodynamic (PD) data: Effectiveness and toxicities data were available in 467 patients (Table 1).

Dose-response relationships for effectiveness:

- Analysis was performed to detect the relationship between the probability of effectiveness and average daily dose for chronic and advanced phase studies.
- Average daily dose was calculated using total administrated dose divided by total days (including the days of interruption).
- All patients enrolled in these Phase 2 studies were included in the dose-response analysis.

C_{trough}-Response for Effectiveness:

- Analysis was conducted for chronic (CA180013 and CA180017) and advanced phase studies (CA180005, CA180006 and CA180015) because different primary endpoints were selected.
- Analysis focused on the relationship between the C_{trough} level of dasatinib on Day 8 and the primary endpoints listed in Table 2 using logistic linear regression.
- Only patients with PK data were included in this analysis.

C_{trough}-Response for Toxicity:

- Safety datasets were pooled from 5 phase 2 studies.
- Based on the frequency of toxicities, the toxicities analyzed in the PK-PD analysis included the followings:
    - Neutropenia assessed by absolute neutrophil count (grade 3 and 4)
    - Thrombocytopenia (grade 3 and 4)
    - Anemia assessed by red blood cell count (grade 3 and 4)
    - Pleural effusion (grade 2, 3 and 4)
    - Nausea graded according to NCI CTC v. 3.0 (grade 3 and 4)

- Vomiting graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Diarrhea graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Dyspnea (grade 3 and 4)
- Rash (grade 3 and 4)
- Pyrexia (grade 3 and 4)

Software:

SAS version 9 was used for the logistic regression analyses for cytogenetic response, hematologic response and toxicity measures.

4. Results and Discussion

Dose-Response:

Q: Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant reported that the 70 mg BID dosing regimen employed in the Phase 2 trials proved to be acceptable based on both efficacy and safety. However, as listed in Table 5 and 6, approximately 50% of patients required dose adjustment. Fifty percent and 30% of patients in chronic and advanced phase studies, respectively, had a dose reduction due to toxicities. Furthermore, no significant relationship was identified between response rate in patients with and without dose reduction (Figures 1, 2 and 3). The starting dose of 50 mg BID may deserve to be investigated in the future clinical trials for patients with chronic CML. Such information has been conveyed to the medical officer.

TABLE 5. Percent of Patients in Each Dosing Regimen for Subjects in Chronic Phase Studies (CA180013 and CA180017)

Dose (mg, BID)	Total	% of Patients
40	22	11
50	78	38
70	100	48
90	6	3
drop	2	1
Total	208	100

TABLE 6. Percent of Patients in Each Dosing Regimen for Subjects in Advance Phase Studies (CA18005, CA18006 and CA180015)

Dose (mg, BID)	Total	% of Patients
20	1	0
40	22	8
50	52	20
70	124	48
100	60	23
Drop	1	0
Total	259	100

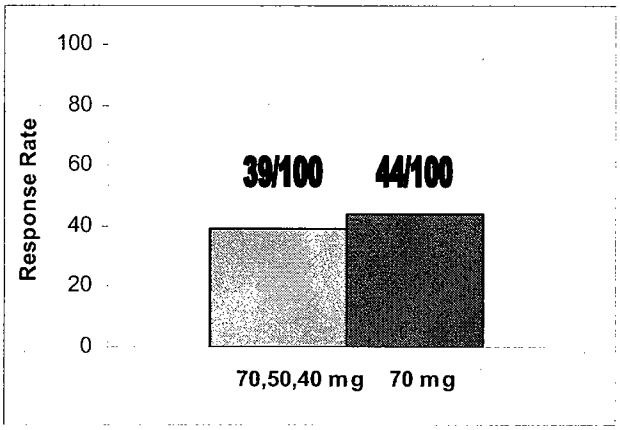


FIGURE 1: Response Rate of MCyR in Chronic Phase Studies

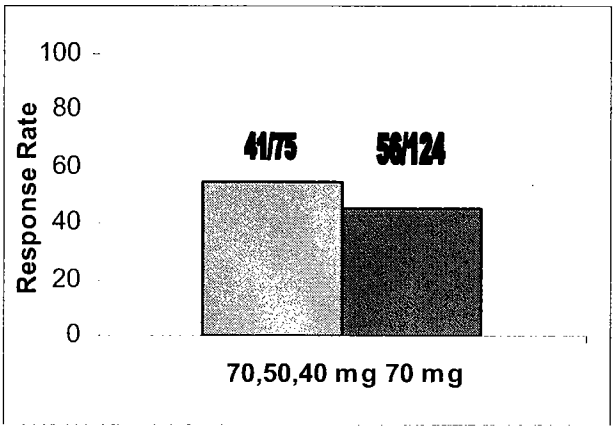


FIGURE 2: Response Rate of MaHR in Advanced Phase Studies

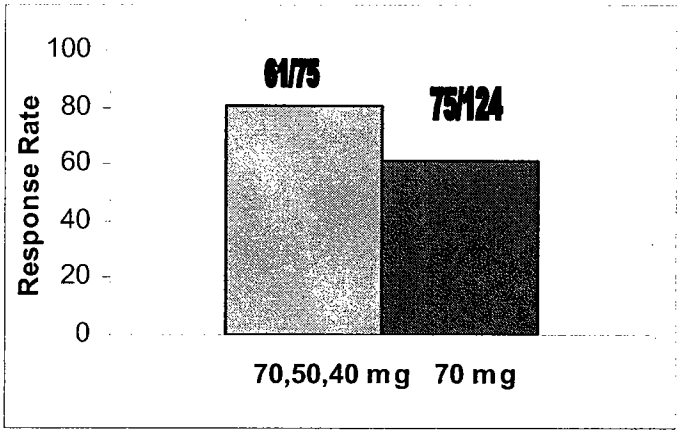


FIGURE 3: Response Rate of OHR in Advanced Phase Studies

Q: What are the characteristics of the exposure-response relationships for efficacy?

Chronic Phase Studies

C_{trough} vs. Response:

Sparse PK samples were obtained in CA180013 and CA180017. A logistic regression of C_{trough} level of dasatinib on Day 8 versus the probability of MCyR (primary endpoint) was performed (Figure 4). The results of the logistic regression model (Pred Prob-MCyR ~ C_{trough}) are listed in Table 7. The probability of MCyR is significantly different from zero (P = 0.0342). However, there is no significant relationship between C_{trough} of dasatinib and probability of MCyR identified in chronic phase studies.

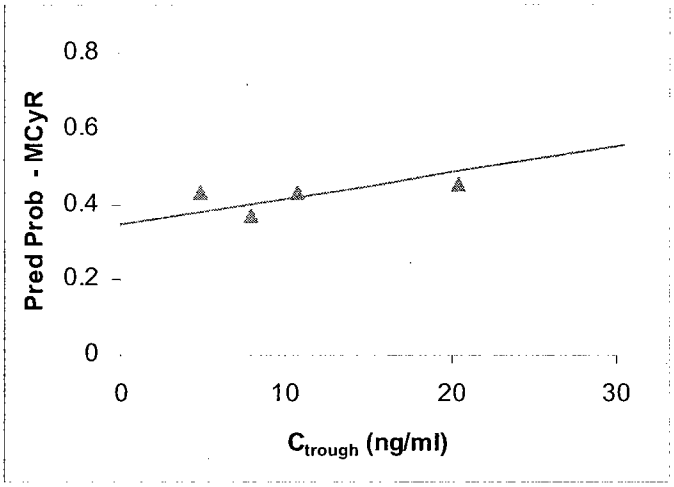


FIGURE 4: Probability of Major Cytogenetic Response (MCyR) vs. C_{trough} in Chronic Phase Studies

TABLE 7. Logistic regression of response (Probability of MCyR) as a function of C_{trough}.

Parameter	Estimate	Pr > ChiSq
Intercept	-0.6252	0.0342
Ctrough	0.0283	0.2186

Dose vs. Response:

There is a significant relationship identified between probability of MCyR and average daily dose for patients with chronic CML (P=0.01) (Figure 5). The median of average daily dose is 100 mg/day for patients. However, because the PD results come from the combination of 70, 50 and 40 mg dosing regimen, the final conclusion regarding this relationship could not be drawn.

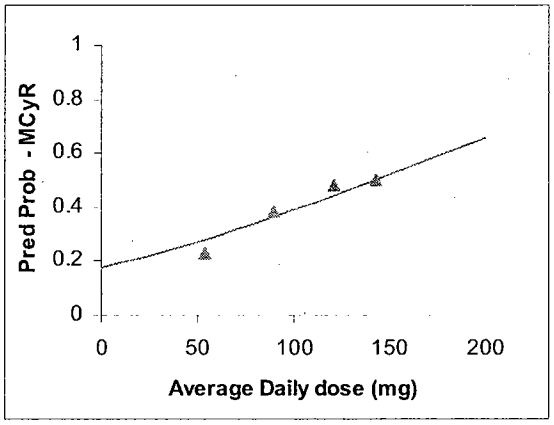


FIGURE 5: Probability of MCyR vs. Average Daily Dose in Chronic Phase Studies

Advanced Phase Studies:

C_{trough} vs. Response:

Both intensive and sparse PK samplings were obtained in CA180005 and CA180006. A linear correlation between exposure (AUC_{0-T}) and C_{trough} of dasatinib is demonstrated in Figure 6. In addition, sparse PK was collected in CA180015. Analysis was performed on the correlation between the C_{trough} level of dasatinib on Day 8 and the primary endpoints, OHR and MaHR (Figures 7 and 8). The results of the logistic regression model (Pred Prob-OHR/MaHR ~ C_{trough}) are listed in Table 8. There are no significant relationships between C_{trough} of dasatinib and OHR and MaHR identified in advanced phase studies.

TABLE 8. Logistic regression of response (Probability of OHR/MaHR) as a function of C_{trough}.

Primary Endpoints	Parameters	Estimate	Pr> ChiSq
OHR	Intercept	0.3585	0.2525
	Ctrough	0.0127	0.5841
MaHR	Intercept	-0.1922	0.5268
	Ctrough	-0.0018	0.9703

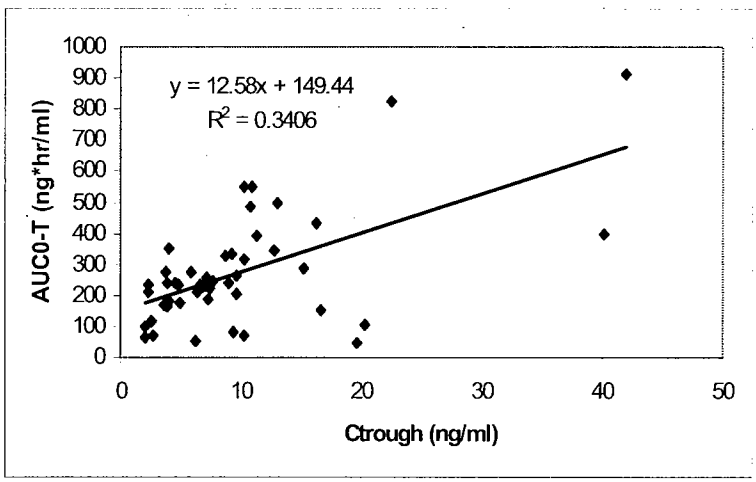


FIGURE 6: AUC_{0-T} vs. C_{trough} (Study CA180005 and CA180006)

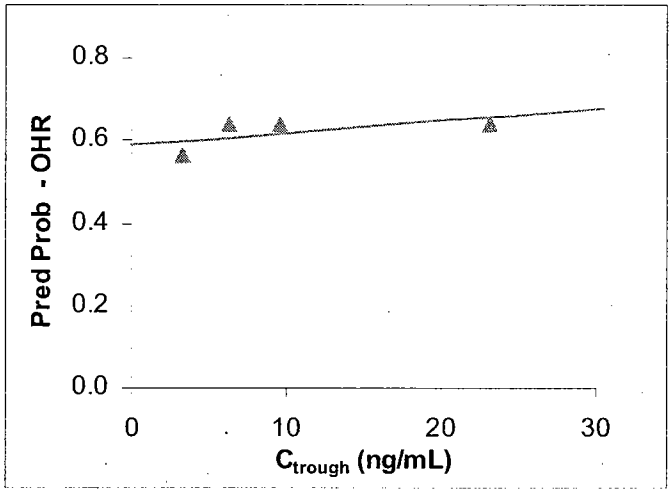


FIGURE 7: Probability of Overall Hematologic Response (OHR) vs. C_{trough} in Advanced Phase Studies

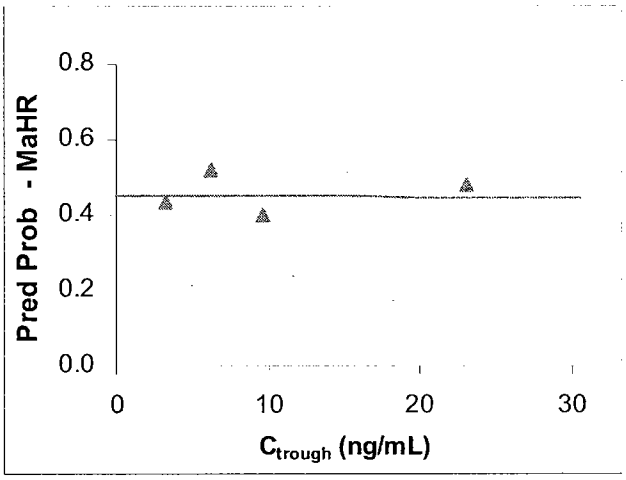


FIGURE 8: Probability of Major Hematologic Response (MaHR) vs. C_{trough} in Advanced Phase Studies

Dose vs. Response:

There is no significant difference identified between probability of MaHR/OHR and average daily doses for patients with advanced disease (P>0.05) (Figures 9 and 10). The median of average daily dose is 133 mg/day for patients.

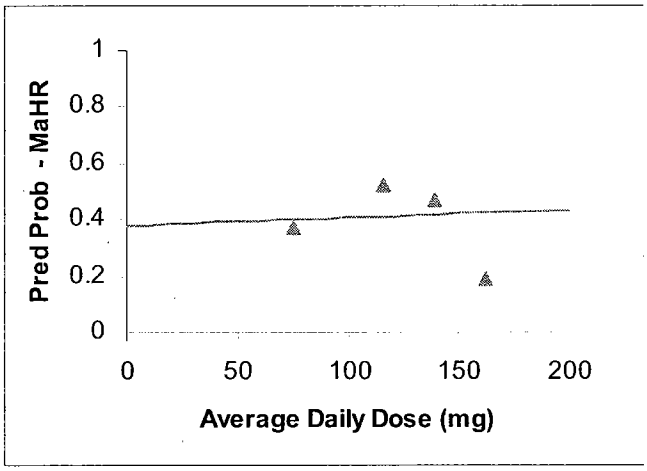


FIGURE 9: Probability of MaHR vs. Average Daily Dose in Advanced Phase Studies

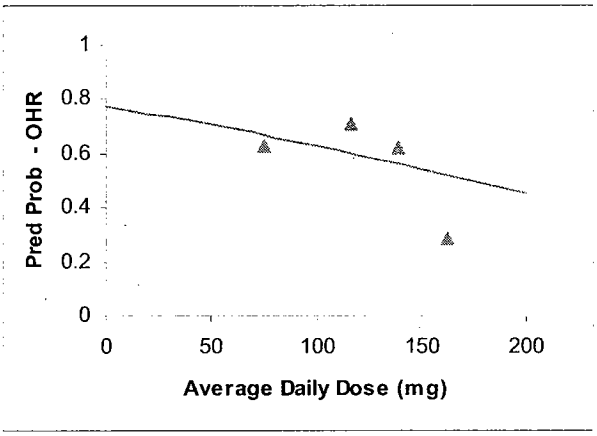


FIGURE 10: Probability of OHR vs. Average Daily Dose in Advanced Phase Studies

In summary, based on the limited data available, no significant correlation between C_{trough} of dasatinib and endpoints of effectiveness could be discerned. Significant relationship between the probability of MCyR and average daily dose was identified in patients with chronic CML.. However, no relationship was found between the probability of MaHR/OHR and average daily dose in patients with advanced disease. Further data is being collected in five ongoing Phase 2 studies, and a population PK model is being developed which could help identify a better relationship between exposure and effectiveness.

Q: What are the characteristics of the exposure-response.relationships (dose-response, concentration-response) for safety?

All drug-related adverse events (AEs) were pooled across all disease phases for the Phase 2 studies. The most frequently reported AEs (> 10%) included hematological toxicities (neutropenia, thrombocytopenia), gastrointestinal AEs (diarrhea, nausea, and vomiting), fluid retention events, headache, fatigue, asthenia, rash, dyspnea, and pyrexia.

Based on the frequency of toxicities, the severe toxicities analyzed in the PK-PD analysis included the following:

- Neutropenia assessed by absolute neutrophil count (grade 3 and 4)
- Thrombocytopenia (grade 3 and 4)
- Anemia assessed by red blood cell count (grade 3 and 4)
- Pleural effusion (grade 2, 3 and 4)
- Nausea graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Vomiting graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Diarrhea graded according to NCI CTC v. 3.0 (grade 3 and 4)
- Dyspnea (grade 3 and 4)
- Rash (grade 3 and 4)
- Pyrexia (grade 3 and 4)

Hematologic Toxicities:

There was no significant correlation identified between severe hematologic toxicities and C_{trough} of dasatinib. Probability of grade 3 and 4 hematologic toxicities, including neutropenia, thrombocytopenia, and anemia, were not significantly correlated with C_{trough} of dasatinib, as indicated in Figure 11.

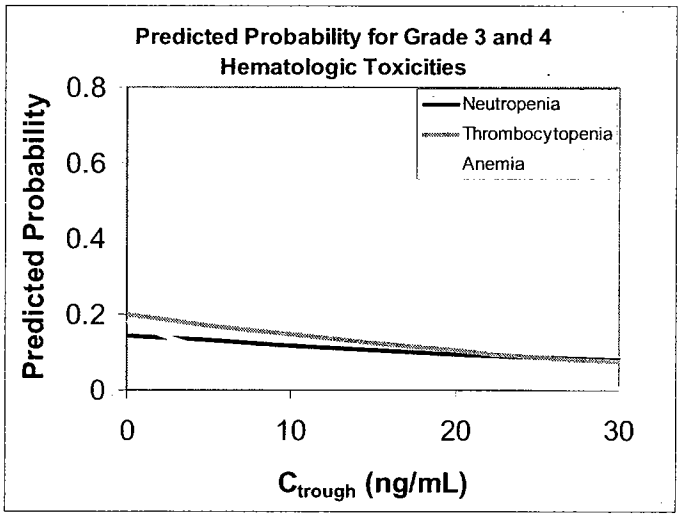


FIGURE 11: Predicted probability of Severe Grade 3/4 Hematologic Toxicities vs. C_{trough}

Gastrointestinal (GI) Toxicities:

Probability of grade 3 and 4 GI toxicities, including nausea, vomiting and diarrhea, did not significantly correlate with C_{trough} of dasatinib, as indicated in Figure 12. Compared with hematologic toxicity, probability of GI severe toxicity is relatively low.

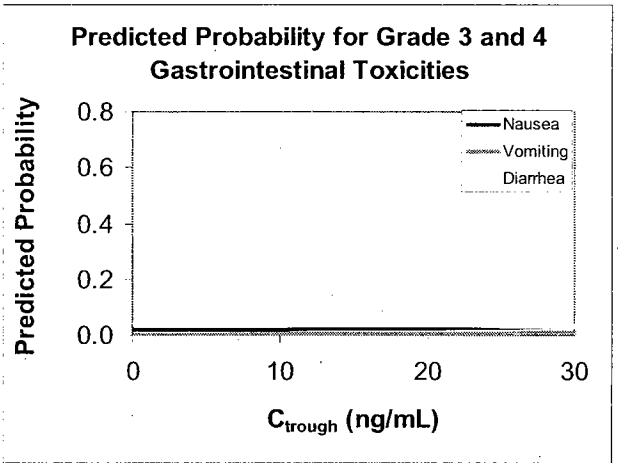


FIGURE 12: Predicted probability of Severe Grade 3/4 Gastrointestinal Toxicities vs. C_{trough}

Edema

Edema is a one of the most frequent toxicities for dasatinib. Grade 2, 3 and 4 are deemed as severe toxicity clinically. A trend shows that probability of pleural effusion increases with increasing C_{trough} of dasatinib. However, no significant correlation was identified from the logistic regression analysis (Figure 13).

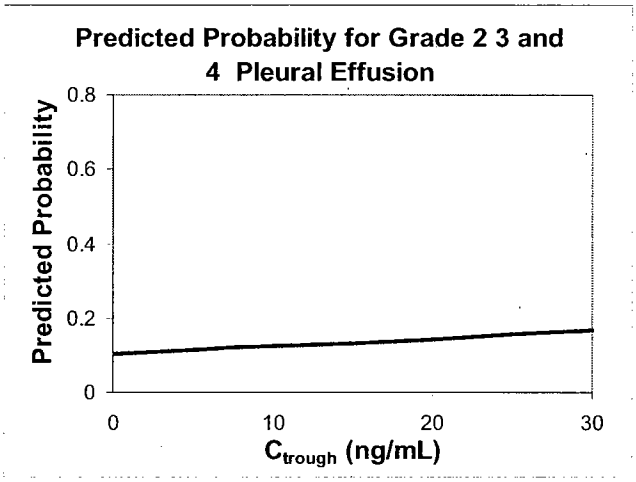


FIGURE 13: Predicted probability of Grade 2/3/4 Pleural effusion vs. C_{trough}

Other Severe Toxicities

Other grade 3 and 4 toxicities, including rash, pyrexia and dyspnea, did not show significant correlation with C_{trough} of dasatinib, as indicated in Figure 14.

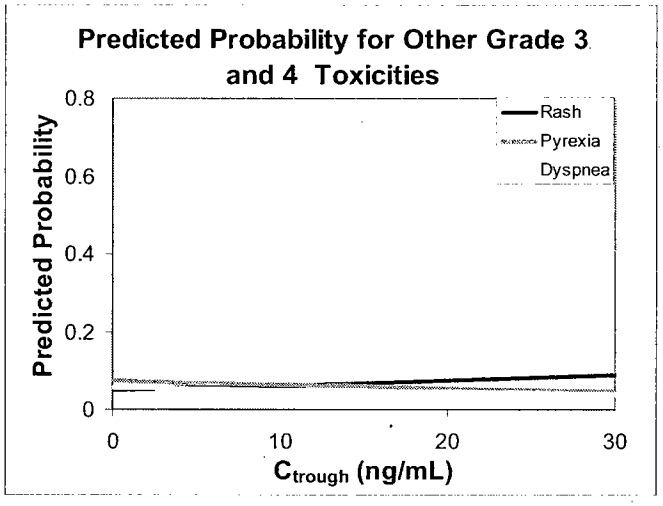


FIGURE 14: Predicted probability of Other Severe Grade 3/4 Toxicities vs. C_{trough}

5. Conclusion

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 five Phase 2 studies, and a population PK model is being developed which could help identify a better relationship between exposure and effectiveness and safety.

4.7 APPENDIX 7 - PHARMACOMETRICS CONSULT FORM

Pharmacometrics Consult Request Form

NDA:	**NDA 21-986**	**Sponsor:**	**BMS**
IND:			
Brand Name:	**Dasatinib**	**Priority Classification:**	**Priority**
Generic Name:	**BMS-354825**	**Indication(s):**	chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL)
Dosage Form:	**70 mg tablet**	**Date of Submission:**	**12/28/05 PK data received on 3/8/06**
Dosing Regimen:	**70 mg BID**	**Due Date of PM Review:**	**Mid-April, 2006**
Division:	**DCP 5**	**Medical Division:**	**DDOP**
Reviewer:	**Angela Men**	**Team Leader:**	**Brian Booth**

Tabular Listing of All Human Studies That Contain PK/PD information:
See attached Table below.

List the following for this compound (if known. The list will be confirmed by PM Scientist during the review):

Clinical endpoint(s):	Cytogenetic response; Hematologic response
Surrogate endpoint(s):	No.
Biomarker(s):	No.
Any reported optimal dose based on PK/PD?:	No.
Any reported dose/concentrations associated with efficacy/ toxicity?:	QTc prolongation
Principal adverse event(s):	Myelosuppression, Fluid retention; QTc prolongation

Pharmacometrics Request: (Jointly filled out with PM Scientist)
The sponsor did integrated analysis for dasatinib of changes in ECG intervals, and of adverse events potentially related to QT/QTc intervals prolongation. The results of this integrated analysis suggest that chronic treatment with dasatinib was associated with a small (3-6 millisecond) prolongation of QTc interval from the pretreatment baseline value and an increased frequency of QTc prolongations. There were no AEs of ventricular arrhythmia (including torsade de pointes), syncope or convulsion that appeared to be attributable to dasatinib treatment. We need check their conclusion.

The ECG-PK summary can be found at \\Cdsesub1\n21986\N_000\2005-12-28\summary\clin-sum.

Due Date to the Reviewer: April 15, 2006

The _x_PM Scientist or the ___Primary Reviewer (select one) will perform the PM Review

PM Briefing ___ or PM Peer Review ___ requested (for criteria see the PM Road Map of QA/QC process)

Primary Reviewer: Angela Men **Signature** _____ **Date:** 3/18/06

PM Scientist: Leslie Kenna **Signature:** _____ **Date:** _____

Table 1.3A: Biopharmaceutics and Clinical Pharmacology Studies in Healthy Volunteers

Study	Question	Study Design	Intervention(s)	Total Treated
CA180009	food effect	3 period, 3 dose, crossover	dasatinib + fasting, dasatinib + high fat meal, dasatinib + low fat meal	54
CA180016	formulation comparability	4 arm, single dose, parallel	2 dasatinib formulations	75
CA180019	ADME	single dose	single dose of 120 μCi of C^{14}-labeled dasatinib	8
CA180020	pH effect	3 period, 6 dose, crossover	dasatinib alone, dasatinib + famotidine, dasatinib + antacid	24
CA180022	simvastatin	2 period, 2 dose, crossover	simvastatin alone, dasatinib + simvastatin	48
CA180032	rifampin	2 period, 2 dose, single-sequence	dasatinib alone, dasatinib + rifampin	20
Total				229

Source: Clinical Pharmacology Summary[19] and Summary of Biopharmaceutics Studies[20]

Table 1.3B: Primary Studies Supporting the Safety and Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Study (Phase)	Population	Accrual Target	CTD Cohort[a]		Total Enrolled[a]
			Enrolled	Treated	
CA180002 (Phase 1)	Chronic, accelerated, blast phase CML and Ph+ ALL (IM-R or IM-I)	60 - 100	85	84	92
CA180013 (Phase 2)	Chronic phase CML (IM-R or IM-I)	100 IM-R	198	186	424
CA180017 (Phase 2)	Chronic phase CML, Randomized, dasatinib vs imatinib (IM-R or IM-I)	150	36[b]	36[b]	166
CA180005 (Phase 2)	Accelerated phase CML (IM-R or IM-I)	60 IM-R	120	107	197
CA180006 (Phase 2)	Myeloid blast phase CML (IM-R or IM-I)	60 IM-R	80	74	124
CA180015 (Phase 2)	Ph+ ALL or lymphoid phase CML (IM-R or IM-I)	60 IM-R	81	78	101
Total			600	565	1,104

IM-R: imatinib-resistant subjects; IM-I: imatinib-intolerant subjects

[a] BMS allowed the studies to additionally enroll subjects until other dasatinib studies could be initiated. The total number of enrolled subjects reflects the enrollment number in the interactive voice response system. All treated subjects were counted once. However, some subjects were counted twice in enrollment numbers because disease status necessitated rolling over from one study to a different study.

[b] In CA180017, the first 36 randomized and treated (with dasatinib [N = 22] or imatinib [N = 14]) subjects were included in the interim analysis.

Source: Dasatinib Clinical Summary of Efficacy[1] and Dasatinib Clinical Summary of Safety[21]

4.8 APPENDIX 8 - OCP FILING REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21,986	Brand Name	SPRYCEL™
OCPB Division (I, II, III, IV, V)	V	Generic Name	dasatinib
Medical Division	Oncology	Drug Class	Inhibitor of multiple oncogenic kinases
OCPB Reviewer	Angela Yuxin Men, M.D., Ph.D.	Indication(s)	chronic myeloid leukemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) patients.
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	Tablets
		Dosing Regimen	70 mg q12h
Date of Submission	Dec 28, 2005; Feb 23,2006	Route of Administration	oral
Estimated Due Date of OCPB Review	Mid-May, 2006	Sponsor	BMS
PDUFA Due Date		Priority Classification	Priority
Division Due Date	June 28, 2006		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling				
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1		
multiple dose:		2		
Patients-				
single dose:	x	1		
multiple dose:	x	6		
Dose proportionality -				
fasting / non-fasting single dose:	x	1		
fasting / non-fasting multiple dose:	x	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	1		
In-vivo effects of primary drug:	x	1		
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:		5		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	x			
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:	x	1		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
In-Vitro Release BE		1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	NA			
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x			
Total Number of Studies		25		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	**Yes**	
Comments sent to firm?		PK raw data and PK summary report for 5 Phase 2 studies are requested
QBR questions (key issues to be considered)	**No P-Gp info. No study is conducted in hepatic impairment patients. Keto study is ongoing.**	
Other comments or information not included above	**Currently, Phase 2 studies' reports include clinical efficacy part. The sponsor said "The PK results will be included in the future report". PK reports and raw PK data have been requested.**	
Primary reviewer Signature and Date	**Angela Men 2/7/06**	
Secondary reviewer Signature and Date		

CC: NDA 21-986, HFD-850(Electronic Entry or Lee), HFD-150(CSO), HFD-860(TL, DD, DDD), CDR (B. Murphy)

Table 1: Clinical Pharmacology Studies

Study Number	Study Characteristics	Dasatinib Dose Formulation Strength Type	Number of Subjects Evaluable for PK Analysis/Total Number of Subjects Treated
CA180002	Single and multiple ascending dose study in subjects with leukemia	15, 30, 50, 75, 105, 140, 180 mg 5 days on and 2 days off QD regimen (Q5D) 25, 35, 50, 70 mg 5 days on and 2 days off q12h regimen (B5D) 35, 50, 70, 90, 120 mg q12h regimen (B7D) 5 and 50 mg Phase 1 clinical tablet	84/91
CA180009[a]	Food effect study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	49/54
CA180016[a]	Formulation comparability study in healthy subjects	100 mg 50 mg Phase 1 clinical tablet 100 mg 5 mg Phase 1 clinical tablet 100 mg 20 mg Phase 2 clinical tablet[b] 100 mg 50 mg Phase 2 clinical tablet[b]	74/75
CA180019	^{14}C ADME study in healthy subjects	100 mg Solution	8/8
CA180020	Famotidine/antacid interaction study in healthy subjects	50 mg Phase 2 clinical tablet[b]	22/24
CA180022	Simvastatin interaction study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	48/48
CA180032	Rifampin interaction study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	20/20

[a] Studies included in the Summary of Biopharmaceutic Studies and Associated Analytical Methods

[b] Composition of the Phase 2 clinical tablet is identical to the proposed 20 and 50 mg commercial film-coated tablet formulation, only the tablet debossings are different.

PK = pharmacokinetics; QD = once daily; q12h = every 12 hours; ADME = absorption, distribution, metabolism, and excretion

Source: Appendix 1 and Summary of Biopharmaceutic Studies and Associated Analytical Methods [1]

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/s/

Julie Bullock
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Angela Men
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