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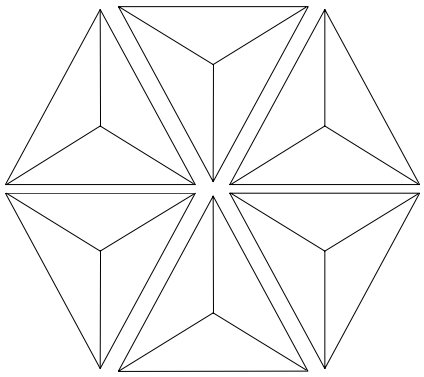
Replaces previous version no. 6 dated 15-Oct-2006



INVESTIGATOR BROCHURE

Dasatinib

BMS-354825

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CHANGES FROM THE PREVIOUS VERSION

Attached is the updated Investigator Brochure [IB] for dasatinib (Version 7, dated 15-Nov-2007). This update replaces Version 6, dated 15-Oct-2006. Apart from minor edits and formatting changes, changes to the IB are summarized in the following table.

Summary of Changes to the Investigator Brochure	
Section	**Change**
Section 1: Summary	Updated to include approval of a new dosing regimen of dasatinib at 100 mg taken orally once daily for the treatment of adults with chronic phase chronic myeloid leukemia (CML) who are resistant or intolerant to imatinib.
Section 2: Introduction	No change
Section 3: Physical/Chemical, and Pharmaceutical Properties and Formulation	Information on 100 mg tablet added to: Section 3.2.1 - Added description for 100 mg tablet Section 3.2.2 - Added 100 mg tablet to list of doses for drug product preparation
Section 4.3: Nonclinical Toxicology	Data from 2 cardiotoxicity studies (1 in rats and 1 in mice) are presented.
Section 5: Effects in Humans	Updated to introduce two Phase 3 studies (CA1800034 and CA180035), which compare alternate doses and administration schedules in imatinib resistant or intolerant subjects with chronic, accelerated, or blast phase CML or Ph+ ALL. Additional studies in the solid tumor program are also introduced.
Section 5.2: Clinical Efficacy	Updated Table 5.2.1A and Table 5.2.1B with study objectives, study design, and subject number for CA180034 and CA180035.
Section 5.2.2: Phase 3 Studies	Section 5.2.2 (Phase 1 Dose-escalation Study) from Version 6 is moved to Section 5.2.3 in Version 7. Data from CA180034 and CA180035 are now presented in Section 5.2.2.
Section 5.2.3: Phase 1 Dose-	No new information; however, section given new

Summary of Changes to the Investigator Brochure	
Section	**Change**
escalation Study	number (was Section 5.2.2 in Version 6).
Section 5.3: Clinical Safety	Introduction of two Phase 3 studies (CA180034 and CA180035), which were designed to assess the safety and efficacy of different dosing schedules and to investigate the optimal dose and schedule of dasatinib. Description of updated clinical safety of dasatinib from the one Phase 1 study, five Phase 2 studies, and two Phase 3 studies with starting dosages of 100 mg QD, 140 mg QD, 50 mg BID, or 70 mg BID in a cohort of 2182 subjects with imatinib resistant/intolerant CML or Ph+ ALL.
Section 5.3.1: Hematologic Toxicity	Updated Table 5.3.1A with hematologic laboratory abnormalities from the overall cohort of 2182 subjects. Added Table 5.3.1B - Hematologic Laboratory Abnormalities in CA180034.
Section 5.3.2: Nonhematologic Adverse Events	Updated adverse event information for the overall cohort of 2182 subjects.
Section 5.3.2.1: Common Drug-related Adverse Events	Updated Table 5.3.2.1A with incidence rates for drug-related adverse events in the overall cohort of 2182 subjects. Added Table 5.3.2.1B - Drug-related AEs Reported in CA180034.
Section 5.3.2.2: Serious Adverse Events	Updated section with data for the overall cohort of 2182 subjects and for the subpopulation of subjects with chronic phase CML in CA180034.
Section 5.3.2.3: Adverse Events Leading to Discontinuation	Updated section with data for the overall cohort of 2182 subjects and for the subpopulation of subjects with chronic phase CML in CA180034.
Section 5.3.2.4: Deaths	Updated section with data for the overall cohort of 2182 subjects. Added Appendix 3: Listing of All Deaths.

Summary of Changes to the Investigator Brochure	
Section	**Change**
Section 5.3.2.5: Laboratory Abnormalities	Updated section with data for the overall cohort of 2182 subjects.
Section 5.3.3: Ongoing Studies	Updated section with data from CA180003 (Phase 1 study in subjects with solid tumors who are refractory to standard therapies).
Section 5.3.4: Expected Adverse Events Updates Since Last Investigator Brochure Revision	A listing of all expected adverse events is provided in Appendix 4.
Section 6: Marketing Experience	Updated the marketing status of SPRYCEL.
Section 7: Guidance for the Investigator	Updated Section 7.2.1 (Product Specific Warnings and Precautions) with data on adverse events of special interest for the overall cohort of 2182 subjects. Updated Section 7.3 (Additional Safety Findings From Clinical Studies) with adverse reactions reported for the overall cohort of 2182 subjects.

LIST OF ABBREVIATIONS

Term	Definition
adm	administration
ALL	acute lymphoblastic leukemia
AML	acute myelogenous leukemia
AUC	area under the concentration-time curve
BCR-ABL	a protein tyrosine kinase
bFGF	basic fibroblast growth factor
BID	twice a day
BMS	Bristol-Myers Squibb
CHR	complete hematologic response
c-KIT	a protein tyrosine kinase
Cmax	maximum observed concentration
CML	chronic myelogenous leukemia
CNS	central nervous system
CP	cyclophosphamide
c-SRC	an alternative form of SRC, a protein tyrosine kinase
CYP	cytochrome P450
ECG	electrocardiogram
EPH	ephrin
ESR	Expedited Safety Report
EU	European Union
FGF	fibroblast growth factor
FYN	A protein tyrosine kinase
GI	gastrointestinal
GIST	gastrointestinal stromal tumor
HCK	protein tyrosine kinase
HUVEC	human umbilical vein endothelial cell
IC_{50}	concentration at which 50% inhibition is observed
LYN	a protein tyrosine kinase
MAD	multi-ascending dose
MTD	maximum tolerated dose
MCyR	major cytogenetic response
mpk	milligrams per kilogram
NA	not assessed
NC	not calculated
NSCLC	non-small cell lung cancer

Term	Definition
PDGF	platelet-derived growth factor
Ph+	Philadelphia chromosome positive
PK	pharmacokinetics
PO	by mouth
PTH	parathyroid hormone
PTK	protein tyrosine kinase
QD	once daily
QT	the interval between the beginning of the Q-wave and the end of the T-wave on an electrocardiogram
QTc	corrected QT interval
SCF	stem-cell factor
SCID	severe combined immunodeficiency
SCLC	small cell lung cancer
SD	standard deviation
SRC	a protein tyrosine kinase
Thalf	half-life
%T/C	percent ratio of tumor weight of treated group to that of control group
Tmax	time of maximum observed concentration
US	United States
VEGF	vascular endothelial growth factor
WBC	white blood cells

1 SUMMARY

1.1 Introduction

SPRYCEL®[1] (dasatinib, Bristol-Myers Squibb [BMS]-354825) is a potent, broad spectrum inhibitor of 5 critical oncogenic tyrosine kinases/kinase families, each of which is linked to multiple forms of human malignancies, and was discovered and developed by BMS. SPRYCEL is approved in the United States (US)[1], Europe (EU)[2], and several other countries for the treatment of subjects with chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to imatinib. The recommended starting dosage for subjects with chronic phase CML is 100 mg administered orally once daily (QD). The recommended starting dosage for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally in 2 divided doses (70 mg twice daily [BID]).

1.2 Nonclinical Studies

In vivo, at doses well below maximum tolerated dose (MTD), dasatinib demonstrated curative activity against several advanced human CML xenograft models in severe combined immunodeficiency (SCID) mice, including an imatinib "acquired-resistance" model completely insensitive to imatinib. Dasatinib also demonstrated antitumor activity against several susceptible cancer models in nude mice and is a potent inhibitor of vascular endothelial growth factor (VEGF)-stimulated proliferation and migration in human umbilical vein endothelial cells (HUVECs).

In cellular assays, dasatinib killed BCR-ABL dependent leukemic cell lines, including those that are resistant to imatinib whether due to mutations that affect drug binding or through overexpression of SRC kinases. Against 4 imatinib-naive CML cell lines, cytotoxic potency was 300-655 times higher for dasatinib than for imatinib. Dasatinib inhibited cellular proliferation of cancer cell lines that express activated SRC or c-KIT.

1.3 Effects in Humans

Bristol-Myers Squibb (BMS) began Phase 1 clinical development of dasatinib in November 2003. Since then, dasatinib has been studied in more than 2000 subjects with CML or Ph+ ALL, resistant or intolerant to imatinib, and with solid tumors. Clinical pharmacokinetic (PK) data indicate that dasatinib has good oral absorption, is > 90% protein bound, and is predicted to have a large volume of distribution. Dasatinib's overall mean terminal half life is around 4 hours in subjects, and it is expected to be eliminated mainly through metabolism.

Dasatinib has an acceptable safety profile.[3] Most subjects had some degree of myelosuppression. Myelosuppression is part of the natural history of most hematologic malignancies and is also a common side effect of most chemotherapeutic agents. Thrombocytopenia, neutropenia, leukopenia, and anemia were frequently reported as Grade 3 to 4 laboratory abnormalities in all subject populations. In cases of severe myelosuppression, recovery generally occurred following brief (2 to 4 week) dose interruptions or reductions. Other severe hematologic toxicities were uncommon. Most subjects continued treatment without further evidence of myelosuppression.

Nearly all subjects reported nonhematologic toxicities, and the majority of subjects treated with dasatinib experienced gastrointestinal AEs, in particular diarrhea, nausea, and vomiting. Most gastrointestinal events were mild to moderate in severity. Safety issues of special interest in the dasatinib program included fluid retention, bleeding-related events, and QT prolongation. The incidence of edema associated with dasatinib treatment was similar across all phases of CML and Ph+ ALL, and pleural effusion in dasatinib-treated subjects mostly occurred in advanced stage CML and Ph+ ALL. Overall, one third of subjects had a bleeding event and of those, half were considered study drug related. These events occurred mostly in subjects with thrombocytopenia. Severe events were uncommon. The mean changes in QTcF with chronic administration of dasatinib were 3 to 6 milliseconds (msec). Three subjects (0.7%) experienced a QTcF > 500 msec. Dasatinib did not affect electrocardiographic heart rate, the PR interval, or the QRS interval.

Treatment with dasatinib resulted in hematologic and cytogenetic responses in all phases of CML and Ph+ ALL and in subjects who were intolerant of or resistant to imatinib.

Hematologic responses were highest in subjects with chronic CML (90%), and cytogenetic responses were highest in subjects with lymphoid blast CML and Ph+ ALL (50% to 58%). Responses were durable in all phases of CML and Ph+ ALL.

In summary, dasatinib has an acceptable safety profile and was active in all phases of CML and Ph+ ALL.

2 INTRODUCTION

Dasatinib (BMS-354825) is a potent, broad spectrum ATP-competitive inhibitor of 5 critical oncogenic tyrosine kinases/kinase families: BCR-ABL, SRC, c-KIT, PDGFR, and ephrin (EPH) receptor kinases, each of which has been linked to multiple forms of human malignancies.

BCR-ABL is a constitutively active protein tyrosine kinase (PTK) present in > 90% of patients with CML and 15% to 30% of adult patients with ALL. BCR-ABL activity is required for the cancer-causing ability of this protein.[4,5] With the approvals of imatinib mesylate (Gleevec®, Glivec®, STI-571), inhibition of BCR-ABL is effective in management of CML, particularly chronic phase where the hematologic response rate is > 90%. However, patients with advanced disease are less sensitive to imatinib and experience less frequent and transient responses.[6] Clinical refractoriness to imatinib is associated with the development of multiple mechanisms of drug resistance, including BCR-ABL gene mutation/over-expression and activation of selected SRC kinases.[7,8] Dasatinib is ~500-fold more potent than imatinib in inhibiting BCR-ABL by binding to both active and inactive conformations of c-ABL, whereas imatinib only binds to the inactive state.[9,10] This difference in binding may be responsible for the increased potency of dasatinib over imatinib.

Dysregulation of SRC function is linked to the pathogenesis of human cancers. Tumor cells with increased metastatic potentials have activated SRC kinase, providing strong evidence linking SRC activation with tumor progression and metastasis.[11] In epithelial cancers, SRC promotes metastasis by disrupting or weakening the normally strong cell-cell adhesions. At the same time, SRC increases the cell-matrix interaction and enhances cell migration.[12,13]

c-KIT is the receptor for stem-cell factor (SCF).[14] Binding of SCF to the KIT receptor results in autophosphorylation and activation of its kinase activity. These initial events trigger several down-stream signaling cascades that regulate cellular activities such as proliferation, apoptosis, and motility.[15,16] Specific somatic mutations in c-KIT resulting in kinase activation cause certain forms of cancer and are implicated in the pathogenesis

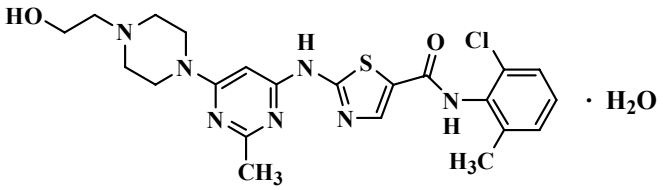
of gastrointestinal stromal tumors (GIST).[17,18] Imatinib, which inhibits mutant forms of c-KIT found in GIST, is effective in the treatment of GIST.[19] Another type of mutation, involving the receptor kinase domain, is found in most cases of adult sporadic mastocytosis, germ cell tumors, acute myelogenous leukemia (AML), and sinonasal natural killer/T-cell lymphoma.[20] This latter form of mutant KIT is insensitive to imatinib. Other types of tumors in which c-KIT dysregulation is implicated include small cell lung cancer (SCLC), neuroblastoma, melanoma, ovarian carcinoma, and breast carcinoma.[20]

Dysregulations of PDGF and PDGFR expression and function are implicated in many forms of solid tumors, including glioblastoma, meningiomas, melanomas, neuroendocrine tumors, ovarian, pancreatic, gastric, lung, and prostate cancer.[21] There is evidence supporting autocrine PDGF stimulation of tumor cell growth and paracrine PDGF stimulation of tumor angiogenesis as the underlying drivers of the oncogenic potential of PDGF and its receptors.[22]

Substantial evidence also implicates EPH kinases in the pathogenesis of cancer. EPH kinases are divided into 2 major groups: EPHA and EPHB.[23] EPHA2 may have important functions in the promotion of angiogenesis,[24] enhanced tumor cell motility, invasion, and metastasis.[25,26] EPHA2 and other EPH kinases are overexpressed in carcinomas of breast, liver, lung, colon, and melanoma.[23]

3 PHYSICAL/CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Physical/Chemical

BMS Number	BMS-354825
Chemical Name	*N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate.
Chemical Structure	
Molecular Formula	$C_{22}H_{26}ClN_7O_2S \bullet H_2O$
Formula Weight	Monohydrate is 506.02 and anhydrous free base is 488.01
Appearance	Dasatinib is a white to off-white powder, which may contain lumps, and has a melting point of 280°C - 286°C.
Solubility	The drug substance is insoluble (United States Pharmacopeia [USP] definition) in water (0.008 mg/mL) at 24 ± 4°C. The solubility (USP definition) of dasatinib in various solvents at 24 ± 4°C is as follows: slightly soluble in ethanol, methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pK_a) (6.8 and 3.1) and 1 weakly acidic pK_a (10.9) were determined.

3.2 Pharmaceutical Properties and Formulation

3.2.1 Description of the Dose Form

Strength	Description
5 mg	white, round, film coated tablet
20 mg	white to off-white, biconvex, round, film coated tablet with either “20” or “BMS” debossed on one side and “527” on the other side
50 mg	white to off-white, biconvex, oval, film coated tablet with either “50” or “BMS” debossed on one side and “528” on the other side
70 mg	white to off-white, biconvex, round, film coated tablet with “BMS” debossed on one side and either “468” or “524”on the other side
100 mg	white to off-white, biconvex, oval, film coated tablet with “BMS 100” debossed on one side and “852” on the other side

3.2.2 Drug Product Preparation

Dasatinib is supplied as 5 mg, 20 mg, 50 mg, 70 mg, and 100 mg film-coated tablets containing dasatinib with lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating contains hydroxypropyl methylcellulose, titanium dioxide, and polyethylene glycol (triacetin in the 5 mg film-coated tablet). Tablets for clinical studies are supplied in high-density polyethylene bottles containing a desiccant and cotton (except the 100-mg tablets, which are packaged without cotton). The bottles are heat-induction sealed with child resistant caps.

3.2.3 Recommended Storage and Use Conditions

The recommended storage condition is 15°C - 25°C.

4 NONCLINICAL STUDIES

4.1 Nonclinical Pharmacology

Drug discovery and nonclinical pharmacology studies showed that dasatinib:

- Kills BCR-ABL dependent leukemic cell lines, including those resistant to imatinib due to kinase domain mutations or overexpression of SRC family kinases
- Is effective against all imatinib-resistant kinase domain mutations tested to date, except T315I
- Has average cytotoxic potency 380-fold higher than imatinib in 4 imatinib naive CML cell lines
- Inhibited proliferation of numerous cancer cell lines that express activated SRC or c-KIT
- Is active against several human CML xenografts in SCID mice at doses below MTD
- Is active against several susceptible human solid cancer models in nude mice
- Potently inhibits VEGF-stimulated proliferation and migration in HUVECs
- Has potent bone anti-resorptive activity

4.1.1 Primary Pharmacodynamics

4.1.1.1 In vitro Molecular Studies

Dasatinib potently inhibits: SRC kinases, BCR-ABL, c-KIT, PDGF receptor β and EPHA and was less potent against 16 other unrelated PTKs, including a number of PTKs and serine/threonine kinases. Imatinib is less potent against several key enzymes: for example, dasatinib was 260-, 8-, 60-, and >1000-fold more potent than imatinib versus BCR-ABL, c-KIT, PDGF receptor β , and SRC kinases, respectively.

4.1.1.2 Cellular and In Vivo Studies

BCR-ABL Dependent Leukemia

In general, dasatinib was 300 to 655 times more potent than imatinib in killing BCR-ABL dependent leukemic cells in cellular assays (Table 4.1.1.2A). Dasatinib inhibits BCR-ABL kinase with an in vitro potency 260-fold greater than imatinib.[9]

Table 4.1.1.2A: In Vitro Cytotoxicity of Dasatinib in Human BCR-ABL Dependent Leukemia Cell Cultures

		Growth Inhibition IC_{50} (nM)		Fold Potency Difference
Cell Line	**Histology**	**Dasatinib**	**Imatinib (STI-571)**	**Dasatinib/STI-571**
K-562	CML (erythromyeloblastoid)	0.77	231	300
KU-812	CML (myeloid)	0.087	57	655
MEG-01	CML (megakaryocytic)	0.28	120	429
SUP-B15	B cell precursor ALL	1.0	350	350

Source: BMS Scientific Report Document Control No. 930003300[9]

Dasatinib demonstrated antitumor activity against several nonclinical and clinically derived models of imatinib resistance. In chronic phase CML, resistance to imatinib occurs frequently through mutations that interfere with drug binding. Dasatinib retained full activity against 14 of 15 imatinib-resistant BCR-ABL mutants.[27] In a model of imatinib resistance associated with over-expression of a SRC kinase, dasatinib was as active against the resistant line as against the sensitive parent (Table 4.1.1.2B).

Table 4.1.1.2B: Acquired Resistance to Imatinib (STI-571) in K562 CML Remains Sensitive to the Cytotoxic Activity of Dasatinib

	Growth Inhibition IC_{50} (nM)	
	K562	**K562/STI-571/R**
Dasatinib	0.7	1.03
STI-571	217	2188

Source: BMS Scientific Report Document Control No. 930003300[9]

Evidence that SRC kinase over-expression plays a role in clinical resistance to imatinib was demonstrated when 3 CML cell lines established from patients who failed imatinib remained sensitive to dasatinib's cytotoxic effects (Table 4.1.1.2C).[28] The highly imatinib resistant WDT-1 line lacks BCR-ABL protein expression completely,[7] which

explains its resistance to imatinib. Dasatinib reduced proliferation or survival of both imatinib sensitive and resistant cells and was not solely dependent on inhibition of BCR-ABL for activity. CML cells obtained from blast crisis patients failing imatinib (progressive disease at 600 to 800 mg daily) expressed high levels or activated forms of SRC-related kinases comparable to levels in imatinib resistant K562-R cells.[28]

Table 4.1.1.2C: Effect of Dasatinib on Imatinib Sensitive and Resistant CML Cells

	Growth Inhibition IC_{50} (nM)				
			CML Cell Lines from Patients		
	K562	K562-R	WDT-1	WDT-2	WDT-3
Dasatinib	0.04	0.01	5.0	0.02	0.04
Imatinib	~200	> 10,000	> 10, 000	~150	~500

Source: BMS Scientific Report Document Control No. 930003300[9]

In vivo, dasatinib demonstrated curative activity, at a wide-range of doses (5-50 milligrams per kilogram [mpk]/administration [adm]) in the advanced-stage SC K562 model in SCID mice. Imatinib was less effective and failed to elicit any cures.[9]

Solid Tumors

Dasatinib inhibited cellular SRC autophosphorylation in several cancer cell lines that highly express c-SRC (Table 4.1.1.2D).

Table 4.1.1.2D: In Vitro Growth Inhibitory Activity of Dasatinib in a Panel of Cancer Cell Lines

	Histology[a]	Growth Inhibition IC_{50} (nM)	
Cell Line	**Type of Cancer**	**Dasatinib**	**Imatinib**
P815	Mastocytoma	5.4	ND
PC3[b]	Prostate	23.2	22,880
PC3/M	Prostate	144	ND
MDA-PCa-2b	Prostate	125	ND
DU145	Prostate	103	ND
WiDr	Colon	257	ND
LOVO	Colon	22.4	ND
SW-480	Colon	389	ND
2C8	Colon	845	ND
GEO	Colon	> 1200	ND
MDA-MB-231	Breast	16.6	ND
RD1	Rhabdomyosarcoma	55.8	ND
A549	Lung	> 1200	ND

Source: BMS Scientific Report Document Control No. 930003300[9]

[a] All cell lines are of human origin except P815 which is murine derived

[b] Effect of dasatinib was determined to be cytostatic in nature, not cytotoxic

ND = not determined

Dasatinib also potently inhibits c-KIT. Assays in SCLC cell lines demonstrated that dasatinib inhibited SCF-driven proliferation with a potency about 10-fold that of imatinib (Table 4.1.1.2E). The concentration range of dasatinib required to inhibit c-KIT phosphorylation was in agreement with that needed to inhibit cellular proliferation.[9]

Table 4.1.1.2E: Cellular Antiproliferative Activity of Dasatinib on SCF Stimulated Proliferation of c-KIT Positive SCLC Cell Lines

	IC_{50} (nM)	
SCLC Cell Lines[a]	**Dasatinib**	**Imatinib**
H526	220	2270
NCI-H69	114	1150
H187	128	1730

Source: BMS Scientific Report Document Control No. 930003300[9]

[a] Cell lines that, under serum deprived cell culture conditions, are dependent on SCF for proliferation

Dasatinib exhibited in vivo antitumor activity in a broad spectrum of solid tumor types. In mice, twice daily (BID) regimens 5-days-on and 2-days-off for 14 to 25 days were well-tolerated with no sign of overt toxicity at doses up to 50 mpk/adm and were equally efficacious as continuous dosing regimens (Table 4.1.1.2F).

Table 4.1.1.2F: Antitumor Activity of Dasatinib in Various Tumor Types Grown in Nude Mice

Tumor		Treatment Regimen			Tumor Response[a]
Name	Type	Dose Range (mpk/adm)	Route	Schedule[b]	(%T/C)
PC3	Prostate cancer	10 - 50	PO	BID x 14	40 - 50
WiDr	Colon cancer	10 - 50	PO	BID x 25	45 - 55
NCI-H69	SCLC	50	PO	BID x 14	40 - 53
H526	SCLC	15 - 50	PO	BID x 14	36 - 59
LOVO	Colon cancer	50	PO	BID x 20	57
RD-1	Rhabdomyosarcoma	50	PO	BID x 15	41
A549	NSCLC	Inactive at 15 - 30	PO	BID x 15	101 - 108

Source: BMS Scientific Report Document Control No. 930003300[9]

[a] Activity is defined as tumor growth inhibition of 50 % T/C at the end of the treatment period. %T/C is the percent ratio of the tumor weight in the treated group to that of the control group

[b] All schedules were 5-days-on and 2-days-off

4.1.2 Secondary Pharmacodynamics

4.1.2.1 Effects on Bone Resorption

SRC kinase plays a major role in osteoclast function.[29] In short-term in vitro studies, dasatinib was a potent inhibitor of bone resorption.[30] In addition, dasatinib inhibited PTH-stimulated release of [^{45}calcium] and, at 5 nM, completely blocks PTH-stimulated bone resorption in thyro-parathyroidectomized rats.[30] The therapeutic utility of SRC inhibition by dasatinib in the treatment of cancer-related hypercalcemic syndromes is at present not fully explored and long-term effects on bone physiology are currently unknown.

4.1.2.2 Immunosuppressive Potential

Dasatinib at 20 or 50 mpk inhibited the T-cell proliferation response in mice following the transfer of lymphocytes from allogeneic donor mice.[31] In addition, treatment of mice with dasatinib 25 mpk BID inhibited the graft-versus-host response in a non-vascularized model of murine heart transplant. Importantly, the 5-days-on and 2-days-off regimen almost completely eliminated immunosuppressive activity in this model.[31]

4.1.2.3 Effects on HUVEC Proliferation and Migration

Dasatinib demonstrated potent antiproliferative activity in HUVECs, the proliferation of which is dependent on either VEGF or basic fibroblast growth factor (bFGF). Dasatinib also inhibited HUVEC migration in a standard in vitro cell migration assay.[32]

4.1.3 Pharmacodynamic Interactions

In combination, dasatinib and paclitaxel produced antitumor effects against the PC3 human prostate carcinoma xenografts that were significantly better than the effects of either single agent alone ($P = 0.05$).[9]

4.2 Nonclinical Pharmacokinetics

The nonclinical pharmacokinetics and ADME of dasatinib were assessed in mice, rats, dogs, and monkeys, and in various in vitro systems. Toxicokinetic assessments were conducted in conjunction with toxicology studies which are discussed in Section 4.3. Plasma samples were analyzed for dasatinib and its metabolites by LC/MS/MS methods. Validated LC/MS/MS methods were used for GLP studies.

The nonclinical pharmacokinetic results are summarized in Table 4.2A and Table 4.2B. Nonclinical studies showed that dasatinib:

- Has the potential for good oral absorption in humans
- Is highly bound to serum proteins
- Has extensive extravascular tissue distribution and is transferred from mother to fetus in rats
- Is eliminated primarily by hepatic metabolism and excreted in feces

- Is excreted in milk in rats
- Is primarily metabolized by cytochrome P450 (CYP) 3A4; therefore its clearance may be decreased when given with drugs that inhibit CYP3A4 and increased when given with CYP3A4 inducers
- Is an inhibitor of CYP3A4 and CYP2C8 and therefore may decrease clearance of drugs significantly metabolized by these enzymes
- Does not induce CYP3A4 and is not likely to increase clearance of drugs significantly metabolized by CYP3A4

Table 4.2A: Summary of Nonclinical Pharmacokinetic Data for Dasatinib in Mice, Rats, Dogs, and Monkeys

Study Design	Species / Strain	Route / Dose / Duration	Animals/ Group (M/F)	Mean Parameters						
				Cmax (μg/mL)	Tmax (h)	AUC(0-∞) (μg·h/mL)	$T_{1/2}$ (h)	Cl (L/h/kg)	Vss (L/kg)	F (%)
Single-dose composite	Mouse/ nude[a]	IV/10mg/kg/6h	F/3	-	-	2.7	0.9	61.7	4.2	-
		PO/5 mg/kg/8h	F/3	0.051	2	0.22	2.5	-	-	17
		PO/15 mg/kg/8h	F/3	0.16	2	0.58	2.0	-	-	14
Single-dose	Rat/ Sprague-Dawley[a]	IA/10mg/kg/10h	M/3	-	-	6.8 ± 2.3	3.3 ± 0.9	26.4 ± 7.8	6.3 ± 2.2	-
		PO/10 mg/kg/10h	M/3	0.24 ± 0.09	2.3 ± 3.3	1.9 ± 1.0	3.1 ± 0.3	-	-	27 ± 15
Single-dose	Dog/ Beagle[b]	IV/1.2 mg/kg/24h	M/3	-	-	0.82 ± 0.20	4.2 ± 2.0	25 ± 6.3	4.7 ± 0.8	-
		PO/3 mg/kg/24h	M/3	0.14 ± 0.04	0.75 ± 0.25	0.68 ± 0.17	5.0 ± 1.8	-	-	34 ± 13
Single-dose	Monkey/ Cynomolgus[b]	IV/2 mg/kg/24h	M/3	-	-	0.98 ± 0.11	2.1 ± 0.1	34 ± 4.1	3.5 ± 0.1	-
		PO/5 mg/kg/24h	M/3	0.17 ± 0.03	0.6 ± 0.1	0.37 ± 0.02	2.2 ± 0.4	-	-	15 ± 2

Abbreviations: IV = intravenous administration; PO = oral administration; C_{max} = maximum plasma concentration; T_{max} = time to reach maximum concentration; AUC = area under the curve; $t_{1/2}$ = half-life; CL = clearance; V_{ss} = steady state volume of distribution; F = absolute bioavailability.

[a] Dosing vehicle was propylene glycol: water (1:1).

[b] Dosing vehicle was 50 mM sodium acetate buffer, pH 4

Source = BMS Study Report Document Control Number 930003190[33]

Table 4.2B: Nonclinical Pharmacokinetics: Summary of Excretion Data after Administration of [^{14}C]Dasatinib to Rats and Monkeys

Study Design	Species / Strain / Route / Dose / Duration	Animals/ Group (M/F)	Percent of Dose Administered (Mean±SD)[a]					Study No./ Ref. No.
			Urine	Bile	Feces	GI Tract	Total	
Single-dose	Rat/Sprague-Dawley/ PO/15 mg/kg (80 μCi/kg)/168 h	M/3	6.4 5 ± 0.82	-[b]	76.39 ± 8.45	-	82.84 ± 9.11[c]	930010421[39]
Single-dose, bile-duct cannulated	Rat/Sprague-Dawley/ PO/10 mg/kg (60 μCi/kg)/24 h	M/2	3.2	35.8	-	53.0	92.0	930010531[36]
Single-dose, bile-duct cannulated	Rat/Sprague-Dawley/ IV/10 mg/kg (60 μCi/kg)/24 h	M/2	12.0	67.4	-	-	79.4	930010531[36]
Single-dose	Monkey/Cynomolgus/ PO/10 mg/kg (30 μCi/kg)/24 h	M/3	2.99 ± 1.55	-	76.82 ± 9.75	-	79.81 ± 11.0[d]	930010419[40]
Single-dose, bile-duct cannulated	Monkey/Cynomolgus/ IV/2 mg/kg (30 μCi/kg)/24 h	M/3	9.89 ± 2.88	67.24 ± 16.40	13.67 ± 12.66	-	90.80 ± 2.56	930010809[41]

Abbreviations: IV = intravenous administration; PO = oral administration.

[a] SD (Standard Deviation) was not determined for the bile-duct cannulated (BDC) rat study, since only 2 animals were evaluated per group.

[b] A dash (-) means that a sample was not collected or not analyzed

[c] In the rat study, an additional 6.70% of the radioactive dose was found in cage rinse, cage wash, and cage wipe samples and approximately 0.31% of the dose remained in the carcass after 168 h, which brought the total recovery of radioactivity for this study to 89.8%.

[d] In the monkey study, approximately 8.84% of additional radioactivity was found in cage debris, cage wash, and cage wipe samples, which brought the total recovery of radioactivity for this study to 88.6%.

4.2.1 Absorption

The extent of oral absorption of dasatinib varied among mouse, rat, dog and monkey; oral bioavailability ranged from 15% (monkey) to 34% (dog).[33] In vitro permeability in Caco-2 cells suggests the potential for good (> 50%) oral absorption in humans.[33] Dasatinib was not an inhibitor of p-glycoprotein and is unlikely to alter absorption characteristics of compounds that are p-glycoprotein substrates.[33]

4.2.2 Distribution

Dasatinib was highly bound (> 91%) to proteins in mouse, rat, dog, monkey, and human sera.[33] In the 4 species tested, mean steady-state volume of distribution values indicated extensive extravascular distribution.[33] After administration of [^{14}C]-dasatinib to Long Evans rats, the tissues with the highest exposure to drug-derived radioactivity were eyes, small intestine, stomach, cecum, liver and adrenal glands.[34] In Sprague-Dawley rats, the tissue distribution profile was similar to Long Evans rats except that drug-derived radioactivity was below the limit of quantitation in eyes.[35] After administration of [^{14}C]-dasatinib to pregnant rats, drug-derived radioactivity was distributed in fetal tissues.[35]

4.2.3 Metabolism

The pathways for metabolism of dasatinib in rats, monkeys, and humans were qualitatively similar. After administration of [^{14}C]-dasatinib, the largest proportion of plasma radioactivity was unchanged dasatinib in all 3 species.[36,37] Metabolites identified in rats, monkeys and humans, included: products of hydroxylation on the phenyl ring (BMS-748730 and BMS-749426), *N*-oxidation on the piperazine ring (BMS-606181), *N*-dealkylation of the hydroxyethyl moiety (BMS-582691), oxidation of the hydroxyethyl moiety to a carboxylic acid (BMS-573188), and glucuronidation and sulfation of dasatinib or its oxidative metabolites.[33,36,37] In vitro data suggest that dasatinib is primarily metabolized by CYP3A4 with smaller contributions from FMO3 and unknown oxidoreductase(s).[38]

4.2.4 Excretion

The results from excretion studies are summarized in Table 4.2B. In rat and monkey, dasatinib was extensively metabolized with drug and drug-related material mainly excreted in the feces.[36,37,39,40,41] Only a small proportion of drug-derived material was excreted in urine. After oral administration of [^{14}C]-dasatinib to lactating female rats, drug-derived radioactivity was excreted in milk.[35]

4.2.5 Pharmacokinetic Drug Interactions

Dasatinib is a time-dependent inhibitor of CYP3A4 (K_I = 1.9 μM, k_{inact} = 0.022 min^{-1}) but not an inducer of CYP3A4.[42,43] Dasatinib may decrease the metabolic clearance of drugs that are primarily metabolized by CYP3A4. Dasatinib is also a competitive inhibitor of CYP2C8 (K_i = 3.6 μM) and may therefore, decrease the metabolic clearance of drugs that are metabolized by CYP2C8.[42]

4.2.6 Other Pharmacokinetic Studies

Not Applicable.

4.3 Nonclinical Toxicology

The nonclinical toxicity profile of dasatinib was characterized in a battery of in vitro and in vivo studies in mice, rats, rabbits, monkeys, and dogs. The nonclinical toxicology and genetic toxicology studies support the repeat oral administration of dasatinib to cancer patients in Phase 1 and Phase 2 clinical studies.

4.3.1 Single- and Repeat-dose Toxicity

Single-dose toxicity studies are summarized in Appendix 1, Table A.[44,45] Repeat-dose toxicity studies are summarized in Appendix 1, Table B.[46,47,48,49,50,51,52,53,54]

4.3.2 Genotoxicity

Dasatinib was not mutagenic in bacterial mutagenicity studies and was not genotoxic in the oral micronucleus study when evaluated up to the MTD. In the in vitro cytogenetics study in CHO cells, dasatinib was clastogenic at concentrations ≥ 5 μg/mL. Genotoxicity studies are summarized in Appendix 1, Table C.[55,56,57,58]

4.3.3 Carcinogenicity

The carcinogenic potential of dasatinib has not been studied.

4.3.4 Reproductive and Developmental Toxicity

Dasatinib caused embryolethality in rats at doses that did not produce maternal toxicity, and skeletal alterations in rabbits at doses that did not produce maternal toxicity. Therefore, dasatinib is a selective developmental toxicant in these 2 species. Reproductive toxicity studies are summarized in Appendix 1, Table D.[59,60,61]

4.3.5 Local Tolerance

Dasatinib was administered orally to humans so no local tolerance studies were necessary.

4.3.6 Other Toxicity Studies

The immunosuppressive potential of dasatinib was demonstrated by inhibition of lymphocyte proliferation in the mouse mixed lymphocyte response study and inhibition of graft rejection in a mouse cardiac transplant model. In these studies, dasatinib-induced immunosuppression demonstrated a threshold effect and could be managed by dose reduction or intermittent dosing.[31]

In mechanistic studies to evaluate the effect of dasatinib on platelets, dasatinib inhibited agonist-induced platelet aggregation in platelet rich plasma from humans, monkeys, and rats. Dasatinib, at concentrations associated with inhibition of platelet aggregation,

prolonged cuticle bleeding time in an anesthetized rat model, but did not cause spontaneous bleeding.[62,63]

Dasatinib absorbs light in the 290 to 700 nm range and had phototoxic potential in an in vitro mouse fibroblast assay.[64]

Dasatinib was not cardiotoxic to prenatal rat cardiomyocytes in vitro at a pharmacologically relevant concentration (0.09 μM).[65] In mice, dasatinib was not cardiotoxic at daily oral doses of up to 14 mg/kg/day (mean AUC ≤ 1,260 ng·hr/mL) for 1 month.[66]

4.3.7 Nonclinical Toxicokinetic Studies

Nonclinical toxicokinetic studies are summarized in Appendix 1, Table E.

4.4 Safety Pharmacology

Based on the intended use of dasatinib in subjects with CML or ALL, safety pharmacology results support the long-term oral administration of dasatinib in this population. Safety pharmacology studies are summarized in Appendix 2.

4.4.1 In Vitro Safety Pharmacology

4.4.1.1 Receptor and Ion-Channel Ligand Binding and Enzyme Activity

In an in vitro receptor and ion-channel ligand binding assay, dasatinib (10 μM) had no biologically relevant inhibitory effect on any of the 42 different receptors or ion channels evaluated (≤ 46% inhibition) or on human-derived acetycholinesterase activity (< 10% inhibition).[67,68]

4.4.1.2 hERG (IKr Current) Assay and Purkinje Fiber Model

Dasatinib activity in vitro in hERG/IKr current and Purkinje fiber assays suggested a risk for prolongation of cardiac ventricular repolarization (QT interval).[69,70] Dasatinib inhibited hERG currents by: 6.1 ± 1.2% at 3 μM, 36.5 ± 6.3% at 10 μM, and 78.6 ± 4.5%

30 μM. In the Purkinje fiber model, dasatinib prolonged time to 50% repolarization (APD_{50}) by 26 ± 5% and time to 90% repolarization (APD_{90}) by 11 ± 0% at 30 μM.

4.4.2 In Vivo Safety Pharmacology

4.4.2.1 Cardiovascular and Respiratory Function

There were no drug-related changes in electrocardiogram (ECG) parameters, heart rate, blood pressure, arterial oxygen saturation, or respiratory rates and sounds in the single-dose, 10-day, 1-month, or 9-month oral toxicity studies in monkeys.[71]

4.4.2.2 Cardiovascular Safety Study

There were minimal, drug-related increases in systolic (5% to15%) and diastolic (8% to 21%) blood pressure in monkeys for approximately 2 hours following a single oral 10 mg/kg dasatinib dose compared with vehicle control.[71] There were no drug-related changes QT interval or in ECG morphology.

4.4.2.3 Neurologic Function

There were no drug-related neurologic observations in rats or monkeys.[72]

5 EFFECTS IN HUMANS

Dasatinib has been administered to more than 2000 subjects, the majority with CML refractory or intolerant to imatinib. Dasatinib's activity has been investigated in eight Phase 1 studies (CA180009, CA180016, CA180019, CA180020, CA180022, CA180032, CA180037, and CA180002) and five Phase 2 studies (CA180005, CA180006, CA180013, CA180015, and CA180017) that supported the approved indication and dosage of dasatinib at 70 mg BID in subjects with CML or Ph+ ALL.[1] Two Phase 3 studies (CA1800034 and CA180035) were designed to compare alternate doses and administration schedules in imatinib resistant or intolerant subjects with chronic, accelerated, or blast phase CML or Ph+ ALL. Efficacy and safety data from CA1800034 and CA180035 are presented in this IB.

Additional ongoing studies in CML include Phase 1/Phase 2 studies in Japan (CA180031, CA180036, and CA180138). Other patient populations studied include metastatic solid tumors. The dasatinib solid tumor clinical program is designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamic profile of dasatinib in subjects with solid tumors and to assess anti-tumor activity. The solid tumor program currently comprises four Phase 1 (CA180003, CA180021, CA180004, CA180086) and three Phase 2 studies (CA180059, CA180088, CA180085). Data are summarized in this IB for CA180003 (subjects with refractory solid tumors; BID schedule) and CA180021 (drug-drug interaction and multi-ascending dose [MAD] study in subjects with solid tumors; QD schedule).

5.1 Clinical Pharmacokinetics

An overview of the clinical pharmacology program for dasatinib and a summary of results are presented in Table 5.1. The clinical pharmacokinetics (PK) of dasatinib were derived from 229 healthy subjects from 6 clinical pharmacology studies along with 84 subjects with leukemia (CML or Ph+ ALL) from a Phase 1 clinical study (CA180002).[75] Although absolute bioavailability was not determined in human, both nonclinical and clinical PK data suggest that dasatinib has reasonable oral bioavailability. Exposure increases in a dose proportional manner and is not affected by intrinsic subject

characteristics. Excretion is primarily through the liver with contribution from the cytochrome p450 enzyme CYP3A4.

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
CA180002 (USA)	Single and multiple ascending dose study in patients with chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who have hematologic resistance to or intolerance of imatinib mesylate	15, 30, 50, 75, 105, 140, 180 mg 5 days on/2 days off QD regimen (Q5D) 25, 35, 50, 70 mg 5 days on/2 days off q12h regimen (B5D) 35, 50, 70, 90, 120 mg q12h regimen (B7D) 5 and 50 mg Phase I clinical tablet	06-Nov-2003 to ongoing (minimum follow up of 3 months for first 84 subjects enrolled by 15-Feb-2005)	84[a] (47, 37) 56 (15, 79)	Maximum tolerated dose, maximum administered dose, dose limiting toxicity, and recommended Phase 2 dose of dasatinib Plasma pharmacokinetics Safety and tolerability of dasatinib Hematologic, cytogenetic and molecular responses	Across dose groups and regimens, following oral administration, dasatinib was rapidly absorbed with the peak plasma concentrations reached at a median Tmax of 1.17 hours. Cmax and AUC(TAU) values for dasatinib increased in a dose related manner. Linear regression analyses suggested that AUC with combined regimens (q12h and QD) increases proportionally to dose over the dose range of 15 to 240 mg/day. Dose proportionality in AUC was also noted for the QD regimen (dose range 15 to 180 mg QD) and for the q12h regimens (dose range 25 to 120 mg q12h). Combining across dose groups and dosing regimens, the mean T-HALF of dasatinib was 3.77 hours on day 1, 4.76 hours on day 5/8, and 5.44 hours on day 26/29, the mean (SD) apparent oral clearance CLo of dasatinib was 403.93 (412.18) L/h on day 5/8 and 532.44 (508.56) hours on day 26/29, the mean (SD) apparent volume of distribution Vz/F for dasatinib was 2723.96 (3020.35) L on day 5/8 and 6208.26 (14234.26) L on day 26/29. CLo was not significantly related to body weight or body surface area. Disease status, age, gender and race appeared to have no clinically relevant effects on CLo, T-HALF and Vz/F of dasatinib. At the current therapeutic dose of 70 mg q12h (across

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
						regimens B5D and B7D), the geometric mean (CV%) Cmax and AUC(TAU) of dasatinib were 33.44 (82) ng/mL and 129.77 (74) ng.h/mL on day 1, 63.21 (60) ng/mL and 236.14 (52) ng.h/mL on day 5/8, 45.87 (65) ng/mL and 162.26 (54) ng.h/mL on day 26/29. Following multiple-dose administration, dasatinib did not show a consistent trend in accumulation on day 5/8 and day 26/29 with geometric mean AI of dasatinib (ratio of AUC(TAU)) of 1.61 and 1.01 on days 5/8 and 26/29, respectively. At the current therapeutic dose of 70 mg q12h (across regimens B5D and B7D), the median Tmax values of dasatinib ranged from 1.00 to 1.42 hours. The mean (SD) T-HALF of dasatinib was 3.77 (1.39), 4.76 (2.74), and 5.44 (3.36) hours on days 1, 5/8 and 26/29, respectively. The mean (SD) CLo of dasatinib was 363.79 (295.68) and 557.93 (539.49) L/h on days 5/8 and 26/29, respectively. 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. Cmax and AUC(0-T) of the dasatinib metabolite BMS-606181 (N-oxide metabolite) appear to increase in a dose related manner. At the current therapeutic dose of 70 mg q12h (across dosing regimens B5D and B7D), the

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
						ratio of the geometric mean AUC values of BMS-606181 to dasatinib, ranged from 6 to 8%, suggesting that BMS-606181 is a minor metabolite of dasatinib.
CA180019 (USA)	Open-label, non-randomized, single-dose study in healthy subjects	Dasatinib 100 mg [^{14}C]dasatinib ([^{14}C]BMS-354825) solution containing 120 µCi of total radioactivity (TRA).	28-Feb-2005 to 24-Mar-2005	8 (8/0) 30 (21, 41)	Mass balance, pharmacokinetics, metabolism, and routes and extent of elimination of a single oral dose of 100 mg (120 µCi) [^{14}C]dasatinib in healthy male subjects Safety of 100 mg (120 µCi) [^{14}C]dasatinib	After administration of a single 100 mg oral dose of [^{14}C]dasatinib, the parent drug was found to be the major drug-related component in plasma. BMS-606181 was a minor circulating metabolite in plasma. Subjects eliminated radioactivity primarily in feces. Mean total recovered through 9 days post dose were approximately 85% in feces and approximately 4% in urine, with a total mean recovery of approximately 89%. Negligible amounts of dasatinib and BMS-606181 were excreted in the urine (approximately 1% of dose), suggesting that no dosage adjustment may be necessary when dasatinib is administered to patients with renal impairment. A single 100 mg dose of [^{14}C] dasatinib was safe and tolerable in healthy subjects.

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
CA180020 (USA)	Open-label, randomized, 3-period, 3-treatment, crossover study in healthy subjects	Dasatinib 100 mg Treatment A: 50 mg dasatinib tablet every 12 hours, first dose in the evening Treatment B: 50 mg dasatinib tablet, every 12 hours, the first dose in the evening, 2 hours prior to a 40 mg oral dose of famotidine (Pepcid®) Treatment C: 50 mg dasatinib tablet, every 12 hours, the first dose in the evening beginning 2 hours after a 30 mL oral dose of an aluminum hydroxide/ magnesium hydroxide antacid	03-Apr-2005 to 30-Apr-2005	24 (24/0) 29 (19, 47)	Effects of a 40 mg oral dose of famotidine, given either 2 hours after or 10 hours before administration of 50 mg dasatinib and effects of a 30 mL dose of aluminum hydroxide/magnesium hydroxide-containing antacid (Maalox®), given 2 hours before, or concomitantly with 50 mg dasatinib, on the PK of a 50 mg oral dose of dasatinib in healthy subjects Safety and tolerability of 2, 50 mg oral doses	When 50 mg of dasatinib was administered 2 hours after a 30 mL dose of an aluminum hydroxide/magnesium hydroxide antacid, dasatinib exposures were similar to those with dasatinib administered alone; however, when the aluminum hydroxide/magnesium hydroxide antacid was coadministered with dasatinib, Cmax and AUC(0-12h) were reduced by 58% and 55%, respectively. When 50 mg of dasatinib was administered 2 hours prior to a 40 mg dose of famotidine, dasatinib exposures were similar to those with dasatinib administered alone; however, when administered 10 hours after the dose of famotidine, dasatinib Cmax and AUC(0-12h) were reduced by 63% and 60%, respectively. Dasatinib, administered as two 50 mg oral doses 12 hours apart, was safe and tolerable in healthy subjects.

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
		(Maalox®) and the second dose in the morning concomitantly with Maalox.			of dasatinib in healthy subjects given 12 hours apart	
CA180022 (USA)	Open-label, randomized, 2-period, 2-treatment, crossover study	Dasatinib 100 mg Treatment A: simvastatin 80 mg (single dose) Treatment B: simvastatin 80 mg + dasatinib 100 mg (both single doses)	13-Apr-2005 to 27-Apr-2005	48 (20/28) 40 (18, 50)	Effect of 100 mg of dasatinib on the single dose PK of 80 mg simvastatin in healthy subjects. Effect of 100 mg dasatinib on the single dose PK of simvastatin acid Safety and tolerability of 100 mg dasatinib coadministered with 80 mg simvastatin.	Coadministration of simvastatin with dasatinib increased the AUC (INF) of simvastatin and simvastatin acid by approximately 20% and 27% compared with simvastatin administered alone. A single dose of 100 mg dasatinib coadministered with 80 mg simvastatin was safe and tolerable in healthy subjects.

Table 5.1: Overview of Clinical Pharmacology Studies

Study Protocol (Country)	Study Design	Dose	Start Date to Stop Date	No. Subjects Sex : (M/F) Age, y: Mean (min, max)	Endpoints	Results
CA180032 (USA)	Open-label, single-sequence study design	Dasatinib 100 mg 2 x 50 mg dasatinib on Day 1 and Day 9 and 2 x 300 mg rifampin QD on Day 2 to Day 9	12-Mar-2005 to 03-Apr-2005	20 (20/0) 32 (20, 50)	Effect of rifampin on the PK of dasatinib in healthy subjects Safety and tolerability of a single dose of dasatinib before and after 8 days of dosing with rifampin	The Cmax, and AUC(INF) of dasatinib were reduced by 81% and 82%, respectively, when a single dose of 100 mg of dasatinib was administered in the presence of rifampin 600 mg once daily at steady state as compared to a single dose of dasatinib alone. There are marked reductions in the Cmax and AUC(INF) for BMS-606181 and BMS-582691with the coadministration of rifampin. A single dose of 100 mg dasatinib coadministered with 600 mg rifampin was safe and tolerable in healthy subjects.

[a] A total of 91 subjects were enrolled and treated in this trial. Data on the first 84 subjects enrolled by 15-Feb-2005 are reported here.

Q12h = every 12 hours; QD = once daily; M/F = males/females; y = years; min, max = minimum. maximum; PK = pharmacokinetics; AUC = area under the concentration versus time curve; AUC(TAU) = AUC in 1 dosing interval; AUC(INF) = AUC from time zero to infinity; AUC(0-T) = AUC from time zero to the last time of measured concentration; Cmax = maximum observed plasma concentration; Tmax = time to maximum plasma concentration; T-HALF = elimination half-life

Source: BMS Study Reports for CA180002, CA180019, CA180020, CA1800022, and CA1800032.[73,74,83,84,85]

5.1.1 Absorption

Dasatinib is rapidly absorbed following oral administration. At the therapeutic dose of 70 mg BID, neither disease status nor study day had a marked influence on the Tmax of dasatinib in subjects with leukemia. The overall mean T-HALF value was 4 to 6 hours.

The geometric mean accumulation index (AI) ranged from 1.01 to 1.61 between days 5/8 and 26/29 and no consistent dose-related trends were observed in the accumulation of dasatinib after repeated administration. This, in conjunction with the short half-life, indicates that dasatinib is likely to reach steady state conditions by the second day of treatment at 70 mg BID. There were no clinically meaningful relationships between steady state CLo and body weight or body surface area. The details of PK parameters of dasatinib on the 70 mg regimen are summarized in Table 5.1.1.[75]

Table 5.1.1: Summary of Pharmacokinetic Parameters for Dasatinib: 70 mg B5D and B7D Regimens

Regimen	Disease Status	Cycle	Study Day (N)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(TAU) (ng.h.mL) Geom. Mean (CV%)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)	CLo (L/h) Mean (SD)	Vz/F (L) Mean (SD)	AI Geom. Mean (CV%)
B5D + B7D	Chronic + Advanced[b]	1	1 (22)	33.44 (82)	129.77 (74)	1.38 (0.50, 6.00)	3.77 (1.39)	--[c]	--	--
B5D + B7D	Chronic + Advanced[b]	1	5/8 (20)	63.21 (60)	236.14 (52)	1.42 (0.17, 3.00)	4.76 (2.74)	363.79 (295.68)	2504.72 (2329.65)	1.61 (147)
B5D + B7D	Chronic + Advanced[b]	1/2	26/29[a] (19)	45.87 (65)	162.26 (54)	1.00 (0.43, 4.17)	5.44 (3.36)	557.93 (529.49)	5018.45 (6531.67)	1.01 (114)

[a] Day 29 is equivalent to Day 1 of Cycle 2.

[b] Subjects with accelerated, myeloid, or lymphoid blast CML

[c] Missing or not calculated

B5D=twice daily (BID) 5 days on/2 days off schedule; B7D=twice daily (BID) continuous schedule; Cmax=maximum plasma concentration; AUC(TAU)=area under the plasma concentration-time curve within the dosing interval (TAU = 12 and 24 hours for the B5D and B7D regimens; Tmax=time to reach Cmax; T-HALF=terminal elimination half-life; CLo=apparent oral clearance; Vz/F=apparent volume of distribution at elimination phase; AI= accumulation index (ratio of AUC(TAU) on Day 5, 8, 26, or 29 and on Day 1); Geom.=geometric; CV%= geometric mean

Source: BMS Scientific Report Document Control No. 930012716[75]

5.1.2 Distribution

Dasatinib is given orally; therefore, there is no direct assessment of distribution. Based on nonclinical data, it is expected to have a large apparent volume of distribution and extensive protein binding.[76]

5.1.3 Metabolism

Dasatinib is extensively metabolized in humans. Unchanged dasatinib represented 29% of circulating radioactivity in plasma after a 100 mg dose of [^{14}C]-labeled dasatinib was administered to 8 healthy subjects in study CA180019.[74] CYP3A4 is the major enzyme responsible for the metabolism of dasatinib.[77,78] In vitro data indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the drug.

5.1.4 Elimination

Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [^{14}C]-labeled dasatinib, approximately 85% of the dose was recovered in the feces within 10 days, and approximately 4% of the administered radioactivity was recovered in the urine. Unchanged dasatinib accounted for 19% and 0.1% of the administered dose in feces and urine, respectively, with the remainder of the dose being metabolites.[74]

5.1.5 Effect of Disease on the Pharmacokinetics of Dasatinib

There were no marked disease-related differences in the PK parameters of dasatinib. In the dose ranges studied, the observed variability does not result in exposures that are expected to be either subtherapeutic or associated with increased drug toxicity either in the total population or in any of the subpopulations.

The observed and dose normalized data (where appropriate) for an analysis of dasatinib PK parameters conducted in healthy subjects (CA180009,[79] CA180016,[80] CA180020,[83] and CA180032[85]) versus subjects with leukemia (CA180002[73]) at comparable doses are presented in Table 5.1.5. Mean Cmax values were approximately 16% to 59% lower, and

mean AUC(0-T) values were approximately 33% lower to 10% higher in subjects with leukemia compared with healthy subjects. The observed variability in these parameters was greater in subjects with leukemia compared with healthy subjects. Possible sources of such variability in exposures include concomitant medications that may alter dasatinib concentration, variability in dosing and sampling times, disease status, and the status of metabolizing organs.

Table 5.1.5: Effect of Disease on the Pharmacokinetics of Dasatinib

Dasatinib Dose on Day 1 (Regimen)	Population (N)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)[a]	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
50 mg	Healthy (22)	41.52 (54)	101.67 (45)[b]	1.00 (0.50, 4.00)	4.01 (0.99)
50 mg (B5D)	Leukemia (3)	34.71 (80)	109.09 (68)	1.00 (0.50, 3.00)	5.20 (1.03)
50 mg (B7D)	Leukemia (8)	17.15 (75)	101.18 (47)	2.33 (1.00, 5.07)	3.87 (1.01)
50 mg (Q5D)	Leukemia (3)	34.55 (40)	111.38 (46)	1.00 (0.92, 1.08)	3.65 (1.11)
100 mg	Healthy (88)	83.49 (50)	275.13 (49)	1.00 (0.50, 4.00)	4.73 (1.99)
70 mg (B5D/B7D)	Leukemia (22)	33.44 (82) (47.77)[c]	129.77 (74) (185.39)	1.38 (0.50, 6.00)	3.77 (1.39)
75 mg (Q5D)	Leukemia (3)	56.50 (59) (75.33)	219.19 (60) (292.25)	1.18 (0.50, 2.08)	2.23 (0.58)
90 mg (B7D)	Leukemia (11)	63.17 (84) (70.19)	219.25 (80) (243.61)	1.22 (0.50, 3.13)	3.56 (1.39)
105 mg (Q5D)	Leukemia (3)	37.92 (20) (36.11)	201.65 (22) (192.05)	3.05 (1.97, 3.17)	3.71 (2.63)
120 mg (B7D)	Leukemia (7)	73.64 (118) (61.37)	290.11 (118) (241.76)	1.52 (0.42, 4.00)	4.26 (1.84)

[a] AUC(0-T)=AUC up to 12 or 24 hours

[b] AUC corrected for residual AUC from the PM dose

[c] Values in square brackets represent geometric mean values normalized to a 100 mg dose

B5D=twice daily (BID) 5 days on/2 days off schedule; B7D=twice daily (BID) continuous schedule; Q5D=once daily (QD) 5 days on/2 days off schedule; SD = standard deviation

Source: BMS Study Reports CA180009, CA180016, CA180020, CA180032, CA180002 (PK).[81,83,85,73]

5.1.6 Drug-Drug Interaction Studies

Dasatinib is extensively metabolized in humans, and the cytochrome p450 enzyme CYP3A4 plays a major role in its metabolism. Dasatinib has little potential to induce CYP3A4 and, at concentrations ≤ 25 μM (1 μM = 488 ng/mL), dasatinib did not induce CYP1A2, CYP2B6, CYP2C9, and CYP3A4 in primary cultures of human hepatocytes.[82] Based on these data and plasma concentrations observed in vivo, dasatinib is unlikely to decrease the exposure of co-administered drugs that are metabolized by CYP1A2, CYP2B6, CYP2C9, or CYP3A4. In human liver microsomes, dasatinib did not inhibit CYP1A2, CYP2B6, CYP2C19, CYP2D6, or CYP2E1 at concentrations up to 50 μM.[42] It inhibited CYP2A6 (IC_{50} = 35 μM), CYP2C8 (IC_{50} = 12 μM), CYP2C9 (IC_{50} = 50 μM), and CYP3A4 (IC_{50} values of 18 and 10 μM for midazolam and testosterone substrates, respectively).[42]

An overview of results obtained from the clinical drug-drug interaction studies conducted with dasatinib is provided below (Table 5.1.6):

(i) CA180020 - This study was conducted with an aluminum hydroxide/magnesium hydroxide-containing antacid (eg, Maalox®) and the H_2-blocker famotidine[83] since these agents increase gastric pH, which may decrease the solubility and thereby impact the bioavailability of dasatinib. A 55% decrease in the AUC of dasatinib was observed when an aluminum hydroxide/magnesium hydroxide containing antacid was coadministered. However, no alteration in dasatinib exposure was observed when aluminum hydroxide/magnesium hydroxide was administered 2 hours prior to dasatinib. Similarly, dasatinib exposure was decreased by > 60% when famotidine was administered 10 hours prior to dasatinib. The concomitant use of H_2 blockers or proton pump inhibitors with dasatinib is not recommended. The use of antacids should be considered in place of H_2 blockers or proton pump inhibitors in patients receiving dasatinib therapy.

(ii) CA180022 - This was a study conducted with a CYP3A4 substrate (simvastatin).[84] While the observed increases in simvastatin concentrations when co-administered with a single dose of dasatinib are modest, results of this study suggest that CYP3A4 substrates

of narrow therapeutic index should be administered with caution in subjects receiving dasatinib.[84]

(iii) CA180032 - This was a study conducted with a CYP3A4 inducer (rifampin).[85] The Cmax and AUC of dasatinib were decreased by > 80% when a single dose of dasatinib was administered following 6 days of continuous dosing with rifampin.[85] For this reason, concomitant use of potent CYP3A4 inducers should be avoided in subjects receiving dasatinib. For those subjects who require treatment with rifampin, or other potent CYP3A4 inducers, alternative therapeutic agents with less potential for CYP3A4 induction should be selected. These results, taken with the nonclinical data, indicate that CYP3A4 is the primary enzyme responsible for dasatinib metabolism.

Table 5.1.6: Summary of Drug-Drug Interaction Studies with Dasatinib

Study Number	Dasatinib Dose	Intervention	Cmax (ng/mL) Geom. Mean	AUC(0-T) (ng•h/mL) Geom. Mean	AUC(0-T) Ratio (90% CI)
CA180020	50 mg pm	Fasting pm	37.57	140.41[a]	reference treatment
	50 mg am	Fasting am	40.86	99.51[a]	reference treatment
	50 mg pm	Famotidine @ T = 2h	40.43	139.45[a]	0.993 (0.895-1.103)
	50 mg am	Famotidine @ T = -10h	15.16	39.28[a]	0.395 (0.255-0.612)
	50 mg pm	antacid @ T = -2h	47.51	147.33[a]	1.049 (0.945-1.165)
	50 mg am	antacid @ T = 0h	17.07	45.20[a]	0.454 (0.293-0.704)
CA180022	100 mg	Simvastatin	26.68	108.05 Simvastatin	reference treatment
	100 mg	Simvastatin + Dasatinib	36.53	132.97 Simvastatin	1.231 (1.102-1.374)
CA180032	100 mg	Fasting	85.56	280.27 T=24h	reference treatment
	100 mg	Rifampin x 6 d	16.16	44.20 T=24h	0.158 (0.132-0.189)

[a] T=12 hours for CA180020

Source: BMS Study Reports CA180020, CA180022, CA180032.[83,84,85]

5.2 Clinical Efficacy

The clinical efficacy for dasatinib was assessed in 1901 subjects with CML or Ph+ ALL resistant or intolerant to imatinib in one Phase 1 study (CA180002),[86] five pivotal Phase 2 studies (CA180005, CA180006, CA180013, CA180015, and CA180017),[87,88,89,90,91,92] and two Phase 3 studies (CA180034 and CA180035) (Table 5.2A).[93,94] An overview of the clinical efficacy of dasatinib is summarized in Table 5.2B.

Table 5.2A: Studies Supporting the Efficacy of Dasatinib in Subjects with CML or Ph+ ALL Resistant or Intolerant to Imatinib

Study (Phase)	Population	Efficacy Cohort	
		Enrolled	Treated
CA180002 (Phase 1)	Chronic, accelerated, blast phase CML and Ph+ ALL (IM-R or IM-I)	85	84
CA180005 (Phase 2)	Accelerated phase CML (IM-R or IM-I)	120	107
CA180006 (Phase 2)	Myeloid blast phase CML (IM-R or IM-I)	80	74
CA180013 (Phase 2)	Chronic phase CML (IM-R or IM-I)	198	186
CA180015 (Phase 2)	Ph+ ALL or lymphoid blast CML (IM-R or IM-I)	81	78
CA180017 (Phase 2)	Chronic phase CML (IM-R only)	150	150 (101 dasatinib-treated)
CA180034 (Phase 3)	Chronic phase CML (IM-R or IM-I)	724 (670)*	662
CA180035 (Phase 3)	Accelerated, blast phase CML and Ph+ ALL (IM-R or IM-I)	638 (611)*	609

* Number randomized

Abbreviations: IM-R - Imatinib-resistant; IM-I - Imatinib-intolerant

Source: Dasatinib Interim Study Report for CA180002, and Dasatinib Efficacy Summary Reports[86,88,89,87,90,91,92], and Dasatinib Phase 3 CSRs[93,94]

Table 5.2B: Overview of Efficacy in Phase 1, 2, and 3 Clinical Studies

Type of Study	Study Objective(s)/ Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Diagnosis of Subjects	Number of Treated Subjects	Duration of Treatment	Study Status	Conclusions
Phase 1 Study							
CA180002 Dose-escalating, open-label; Safety, PK, PD	To establish the maximum tolerated dose (MTD), maximum administered dose (MAD), dose limiting toxicity (DLT) and a recommended Phase 2 dose of dasatinib	Dasatinib 15, 30, 50, 75, 105, 140, and 180 mg PO QD, 5 days on/2 days off every week schedule; Dasatinib 25, 35, 50, and 70 mg PO BID, 5 days on and 2 days off every week schedule; Dasatinib 35, 50, 70, 90, and 120 mg PO BID, continuous daily dosing	Chronic, accelerated or blast phase Ph+ CML or Ph+ ALL who have hematologic resistance to or intolerance of imatinib mesylate	84[a]	Dependent on response; a minimum of 30 days post dosing follow up	Complete	- Hematological and cytogenetic responses were durable across all phases of Ph+ leukemia - None of the subjects with chronic or accelerated phase CML who achieved a MaHR reported disease progression - Four of 11 subjects with blast phase CML or Ph+ ALL who achieved MaHR experienced disease progression (PD)

Table 5.2B: Overview of Efficacy in Phase 1, 2, and 3 Clinical Studies

Type of Study	Study Objective(s)/ Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Diagnosis of Subjects	Number of Treated Subjects	Duration of Treatment	Study Status	Conclusions
Phase 2 Studies - Advanced Phase CML/Ph+ ALL							
CA180005 Open-label; Safety, Efficacy	Assess dasatinib activity by major hematologic response (MaHR) and overall hematologic response (OHR) rates	Dasatinib 70 mg PO BID; dose escalation and reductions were allowed	Accelerated phase Ph+ CML subjects with primary or acquired resistance or intolerance to imatinib mesylate	107	Treated until PD, until intolerable toxicity, or until withdrawal from study; a minimum of 30 days post dosing follow up	Complete	- OHR: 81% (87/107) - MaHR: 64% (69/107) - MCyR: 33% (35/107) - Median time to MaHR: 57 days - PD: 10% (7/69) with MaHR - Longest duration of MaHR: 12.3+ months
CA180006 Open-label; Safety, Efficacy	Assess dasatinib activity by MaHR and OHR rates	Dasatinib 70 mg PO BID; dose escalation and reductions were allowed	Myeloid blast phase Ph+ CML subjects with primary or acquired resistance or intolerance to imatinib mesylate	74	Treated until PD or AE that would preclude additional dasatinib treatment; a minimum of 30 days post dosing follow up	Complete	- OHR: 53% (39/74) - MaHR: 34% (25/74) - MCyR: 31% (23/74) - Median time to MaHR: 56 days - PD: 12% (3/25) with MaHR - Longest duration of MaHR: 9.9+ months

Table 5.2B: Overview of Efficacy in Phase 1, 2, and 3 Clinical Studies

Type of Study	Study Objective(s)/ Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Diagnosis of Subjects	Number of Treated Subjects	Duration of Treatment	Study Status	Conclusions
CA180015 Open-label; Safety, Efficacy	Assess dasatinib activity by MaHR and OHR rates	Dasatinib 70 mg PO BID; dose escalation and reductions were allowed	Lymphoid blast phase Ph+ (or BCR-ABL+) CML or Ph+ ALL subjects resistant or intolerant to imatinib mesylate	78	Treated until PD, until intolerable toxicity, or until withdrawal from study; a minimum of 30 days post dosing follow up	Complete	Lymphoid Blast Phase CML: - OHR: 36% (15/42) - MaHR: 31% (13/42) - MCyR: 50% (21/42) - Median time to MaHR: 35 days - PD: 54% (7/13) with MaHR - Median duration of MaHR was 3.9 months Ph+ ALL: - OHR: 50% (18/36) - MaHR: 42% (15/36) - MCyR: 58% (21/36) - Median time to MaHR: 57 days - PD: 33% (5/15) with MaHR - Longest duration of response: 8.7+ months

Table 5.2B: Overview of Efficacy in Phase 1, 2, and 3 Clinical Studies

Type of Study	Study Objective(s)/ Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Diagnosis of Subjects	Number of Treated Subjects	Duration of Treatment	Study Status	Conclusions
Phase 2 Study - Chronic Phase CML							
CA180013 Open-label; Safety, Efficacy	Assess dasatinib activity by major cytogenetic response (MCyR) rate and complete hematologic response (CHR)	Dasatinib 70 mg PO BID; dose escalation and reductions were allowed	Chronic phase Ph+ CML who have disease that is resistant to high dose imatinib mesylate or who are intolerant of imatinib	186	Treated until PD, unacceptable toxicity, subject withdrawal, or discontinuation; a minimum of 30 days post dosing follow up	Complete	- MCyR: 52% (97/186) -CHR: 90% (168/186) - Median times to MCyR and CHR were 85 and 15 days, respectively - PD: 5% (8/168) with CHR - Longest duration of response: 11.0+ months
CA180017 Randomized (2:1), open-label; Safety, Efficacy	Assess the MCyR rates of dasatinib and imatinib	Dasatinib 70 mg PO BID vs Imatinib Mesylate 400 mg/d PO BID; dose escalation and reductions were allowed	Chronic phase Ph+ CML who have disease that is resistant to imatinib at a dose at 400 - 600 mg/d	101 (dasatinib)	Treated until confirmed PD, unacceptable toxicity, subject withdrawal, or discontinuation; post dosing follow up every 4 weeks until all study related toxicities resolve	Ongoing	Interim efficacy data with a minimum of 3 months of follow-up are reported for this study. - MCyR: 35% (35/101) - Among the 35 dasatinib subjects achieving MCyR, only 1 subject lost partial cytogenetic response (PCyR) after a 5-month dosing interruption due to thrombocytopenia

Table 5.2B: Overview of Efficacy in Phase 1, 2, and 3 Clinical Studies

Type of Study	Study Objective(s)/ Endpoints	Test Product(s); Dosage Regimen; Route of Administration	Diagnosis of Subjects	Number of Treated Subjects	Duration of Treatment	Study Status	Conclusions
Phase 3 Studies							
CA180034 Randomized, 2-by-2, open-label; Safety, Efficacy	To compare dasatinib as defined by MCyR when administered either QD or BID at a total daily dose (TDD) of 100 mg or 140 mg.	Dasatinib 100 or 140 mg PO QD or 50 or 70 mg PO BID	Chronic phase CML imatinib-resistant or imatinib-intolerant subjects who have no prior advanced disease status	662	Treated until PD, unacceptable toxicity, subject withdrawal, or discontinuation; a minimum of 30 days post dosing follow up	Ongoing	- The QD schedule displayed non-inferior MCyR rates compared with the BID schedule - The 100 mg TDD group exhibited non-inferior MCyR rates compared with the 140 mg TDD group - Longest duration of MCyR was > 8 months
CA180035 Randomized, 2-arm, open-label Safety, Efficacy	To estimate the rate of MaHR for 2 dose schedules	Dasatinib 70 mg PO BID or 140 mg PO QD	Accelerated, myeloid blast, or lymphoid blast phase CML, or Ph+ ALL who have primary or acquired resistance or intolerance to imatinib mesylate	609	Treated until PD or AE that would preclude additional dasatinib treatment; a minimum of 30 days post dosing follow up	Ongoing	- The QD group displaying non-inferior MaHR rates compared with the BID group - Median durations of MaHR and MCyR were shorter in QD group vs the BID group - Differences in median response durations were specific to lymphoid blast phase CML or Ph+ ALL

[a] Forty of the 84 subjects were treated with dasatinib BID.

Source: Dasatinib Interim Study Report for CA180002; Dasatinib Efficacy Summary Reports for CA180005, CA180006, CA180013, CA180015, and CA180017; and Dasatinib Clinical Study Reports for CA180034 and CA180035.[86,88,89,87,90,91,92,]

5.2.1 Pivotal Phase 2 Studies

Subjects treated with dasatinib achieved hematologic and cytogenetic responses in the Phase 2 studies. Dasatinib was active in subjects across all phases of CML or Ph+ ALL. Hematologic responses were highest in subjects with chronic CML (CA180013), and cytogenetic responses were highest in subjects with lymphoid blast CML and Ph+ ALL (CA180015). In general, imatinib-intolerant subjects remained on therapy longer than imatinib-resistant subjects.[95] Subjects with 1 or more detectable imatinib-resistant mutations achieved hematologic and cytogenetic responses upon treatment with dasatinib.[96] The duration of therapy and the key efficacy findings in dasatinib-treated subjects for all five Phase 2 studies are summarized in Table 5.2.1A and Table 5.2.1B, respectively.

Table 5.2.1A: Duration of Treatment in Dasatinib Phase 2 Studies - Efficacy Data

	Median Time on Study Therapy, Months (N)					
	CA180013 Chronic CML	**CA180017 Chronic CML**	**CA180005 Accelerated CML**	**CA180006 Myeloid Blast CML**	**CA180015 Lymphoid Blast CML**	**CA180015 Ph+ ALL**
All treated subjects	8.3 (186)	5.5 (101)	8.28 (107)	3.5 (74)	2.8 (42)	3.2 (36)
Subjects still on therapy	8.9 (184)	5.5 (86)	8.64 (67)	9.2 (23)	8.3 (5)	8.3 (9)

Source: Dasatinib Efficacy Summary Reports[92,87,88,89,90,91]

Table 5.2.1B: Efficacy in Dasatinib-treated Subjects in Phase 2 Studies

	CA180013 Chronic (N = 186)	CA180017 Chronic (N = 101)	CA180005 Accelerated (N = 107)	CA180006 Myeloid Blast (N = 74)	CA180015 Lymphoid Blast (N = 42)	CA180015 Ph+ ALL (N = 36)
Hematologic Response (%)[a]						
OHR	NA[c]	NA	81	53	36	50
MaHR	NA	NA	64	34	31	42
CHR	90	92	39	26	26	33
NEL	NA	NA	25	8	5	8
MiHR	NA	NA	17	19	5	8
Cytogenetic Response (%)[b]						
MCyR	52	35	33	31	50	58
CCyR	39	21	24	27	43	58

Shaded boxes = primary endpoints.

[a] Hematologic response criteria (all confirmed responses were maintained at least 4 weeks): **OHR** = MaHR + MiHR; **MaHR** = CHR + NEL; **CHR (chronic):** WBC ≤ institutional ULN, platelets < 450,000/mm^3, no blasts or promyelocytes in PB, < 5% myelocytes plus metamyelocytes in PB, peripheral basophils < 20%, and no extramedullary involvement; **CHR (advanced):** WBC ≤ institutional ULN, ANC ≥ 1000/mm^3, platelets ≥ 100,000/mm^3, no blasts or promyelocytes in PB, bone marrow (BM) blasts ≤ 5%, <5% myelocytes plus metamyelocytes in PB, peripheral basophils < 20%, and no extramedullary involvement; **NEL**: same criteria as for CHR but 500/mm^3 ≤ ANC <1000/mm^3, and/or 20,000/mm^3 ≤ platelets < 100,000/mm^3; **MiHR**: < 15% blasts in BM and in PB, < 30% blasts plus promyelocytes in BM and < 30% blasts plus promyelocytes in PB, < 20% basophils in PB, and no extramedullary disease other than spleen and liver.

[b] Cytogenetic response criteria: **CCyR** (0% Ph+ metaphases) or PCyR (> 0 % - 35%). **MCyR** = CCyR + PCyR.

[c] NA: not applicable

Note: All studies ≥ 8 months follow-up except CA180017 at 3 months follow-up.

Source: Dasatinib Efficacy Summary Reports[92,87,88,89,90,91]

5.2.2 Phase 3 Studies

In CA180034, hematologic and cytogenetic responses were achieved in subjects with chronic phase CML treated with dasatinib either QD or BID at a total daily dose (TDD) of 100 mg or 140 mg. Among the 670 randomized subjects, the median duration of therapy was approximately 8 months (range from 7.9 months to 8.3 months).[93] Limited differences in efficacy were reported between the 4 treatment groups (Table 5.2.2A). There was no difference in progression-free survival between the treatment groups. Overall survival was similar between the 4 treatment groups.

Table 5.2.2A: Hematologic and Cytogenetic Responses in Subjects with Chronic CML (CA180034); Randomized Subjects

	Number (%) of Subjects			
	100 mg QD N = 167	**50 mg BID N = 168**	**140 mg QD N = 167**	**70 mg BID N = 168**
Cytogenetic Response Rate				
MCyR	98 (59)	90 (54)	93 (56)	93 (55)
CCyR	69 (41)	70 (42)	74 (44)	75 (45)
Hematologic Response Rate				
CHR	150 (90)	154 (92)	143 (86)	146 (87)
Progression-free Survival (# Progressed / # Randomized)	14/167 (8)	13/168 (8)	14/167 (8)	18/168 (11)
Overall Survival (# Death / # Randomized)	3/167 (2)	6/168 (4)	4/167 (2)	8/168 (5)

Shaded boxes = primary endpoints
Source: CA180034 Clinical Study Report[93]

In CA180035, hematologic and cytogenetic responses were achieved in subjects with advanced phase CML or Ph+ ALL treated with dasatinib either QD or BID at a TDD of 140 mg. When pooled across disease phase, the median duration of therapy was 8.5 months in the QD group and 8.6 months in the BID group.[94] Efficacy analysis showed that the QD schedule was similar to the BID schedule (Table 5.2.2B). Although a similar difference in overall survival was reported in the 2 groups, a greater number of subjects in the QD group than in the BID group progressed or died.

Table 5.2.2B: Hematologic and Cytogenetic Responses Pooled Across Disease Phase (CA180035); Randomized Subjects

	Number (%) of Subjects	
	QD N = 306	**BID N = 305**
Hematologic Response		
MaHR	147 (48)	146 (48)
CHR	94 (31)	96 (32)
NEL	53 (17)	50 (16)
MiHR	34 (11)	29 (10)
Cytogenetic Response		
MCyR	113 (37)	120 (39)
CCyR	89 (29)	84 (28)
Progression-free Survival (# Progressed / # Randomized)	160/306 (52)	137/305 (45)
Overall Survival (# Death / # Randomized)	108/306 (35)	92/305 (30)

Source: CA180035 Clinical Study Report[94]

5.2.3 Phase 1 Dose-escalation Study (CA180002)

Dasatinib demonstrated clinically relevant hematologic and cytogenetic responses among the first 84 subjects treated in this open-label study in subjects with all phases of CML and Ph+ ALL (Table 5.2.3).[86] Responses were durable across all phases of Ph+ leukemia.

In this study in which subjects had the longest follow-up (up to 19 months, with treatment and follow-up ongoing), none of the chronic or accelerated phase subjects who achieved a MaHR reported disease progression, and only 4 of 11 blast phase and Ph+ ALL responders who achieved MaHR experienced disease progression.

Table 5.2.3: CA180002: Efficacy of Dasatinib in All Phases of CML or Ph+ ALL

Phase of Disease (Dose Schedule)	Hematologic response (%)[a]	Cytogenetic response, MCyR (%)	Number of responders[b]	Number of responders who progressed
Chronic CML (QD)	95	48	20	0
Chronic CML (BID)	89	42	17	0
Accelerated CML (BID)	55	27	6	0
Myeloid blast CML (BID)	30	35	6	1
Lymphoid blast CML/Ph+ ALL (BID)	50	80	5	3

[a] CHR for subjects with chronic CML or MaHR for subjects with advanced stages of CML or Ph+ ALL

[b] Responders with chronic CML have achieved CHR and responders with advanced CML have achieved MaHR.

Source: Dasatinib Interim Study Report CA180002[86]

Subjects treated in CA180002 who received clinical benefit in the opinion of the investigator and who completed a minimum of 3 months on protocol CA180002 were entered in an open-label, roll-over protocol (CA180039). No new data are available.

5.3 CLINICAL SAFETY

The clinical safety and tolerability of dasatinib administered at 70 mg BID was demonstrated in subjects with chronic and advanced phase CML and Ph+ ALL in one Phase 1 study (CA180002) and five pivotal Phase 2 studies (CA180005, CA180006, CA180013, CA180015, CA180017). Besides the expected myelosuppression in these disease populations, fluid retention, in particular pleural effusion, was a common side effect that required medical management with dose interruptions and dose reductions. In an attempt to control these AEs while maintaining dasatinib's efficacy, two Phase 3 studies (CA180034 and CA180035) were designed to assess the safety and efficacy of different dosing schedules and to investigate the optimal dose and schedule of dasatinib. As a result of comparable efficacy and improved safety reported in CA180034, the recommended dose was changed from 70 mg BID to 100 mg QD in subjects with chronic phase CML. The approved dose of 70 mg BID was not changed for subjects with advanced phase CML or Ph+ ALL.

The clinical safety of dasatinib has now been assessed in a cohort of 2182 subjects with imatinib resistant/intolerant CML or Ph+ ALL (Table 5.3). Safety data from the one Phase 1 study, five Phase 2 studies, and two Phase 3 studies with starting dosages of 100 mg QD, 140 mg QD, 50 mg BID, or 70 mg BID are presented in this IB update. Overall, the median duration of therapy was 11 months (range 0.03 - 26 months).[3] Dasatinib continues to show a safe and tolerable safety profile. Incidence rates of fluid retention-related events (including pleural effusion, congestive heart failure, pericardial effusion, pulmonary edema) and of myelosuppression (including neutropenia, thrombocytopenia, and anemia) continue to be of special interest.

Table 5.3: Dasatinib-treated Subjects; Overall Safety Cohort

Study	Number of Subjects				
	Chronic CML	**Accelerated CML**	**Myeloid Blast CML**	**Lymphoid Blast CML/ Ph+ ALL**	**Total**
CA180034	662	-	-	-	**662**
CA180035	-	316	148	145	**609**
CA180017	101[a]	-	-	-	**101**
CA180005	-	174	-	-	**174**
CA180006	-	-	109	-	**109**
CA180013	387	-	-	-	**387**
CA180015	-	-	-	94	**94**
CA180002	-[b]	12	23	11	**46**
Total	**1,150**	**502**	**280**	**250**	**2,182**

[a] 101 subjects were treated with dasatinib and the other 49 subjects were treated with imatinib

[b] 23 chronic CML subjects with BID dosing and 22 subjects with QD dosing were treated. These data remain unpooled because of the different dosing regimens used with respect to the safety cohort

Source: Dasatinib 120-Day Safety Update[3]

5.3.1 Hematologic Toxicity

Myelosuppression is part of the natural history of most hematologic malignancies and is also a common side effect of most chemotherapeutic agents. Thus, the level of hematologic toxicity observed may partly be the result of the underlying leukemic diagnosis. The majority of subjects with CML or Ph+ ALL expressed some degree of hematologic toxicity. Hematologic toxicity was the most common reason for dose reductions or interruptions. In subjects who experienced myelosuppression, recovery occurred following brief (2 to 4 week) dose interruptions and/or reductions**.** Most subjects continued treatment without further evidence of myelosuppression. Neutropenia, thrombocytopenia, and anemia were frequently reported Grade 3 to 4 laboratory abnormalities in all subject populations (Table 5.3.1A).[3]

Table 5.3.1A: CTC Grade 3 to 4 Hematologic Laboratory Abnormalities; Overall Cohort

	Number (%) of Subjects[a] (N = 2182)			
	Chronic Phase (N = 1150)	**Accelerated Phase (N = 502)**	**Myeloid Blast Phase (N = 280)**	**Lymphoid Blast Phase/Ph+ ALL (N = 250)**
Neutropenia	524/1142 (46)	339/499 (68)	220/275 (80)	191/244 (78)
Thrombocytopenia	464/1145 (41)	354/499 (71)	224/275 (82)	192/247 (78)
Anemia	208/1145 (18)	272/499 (55)	206/275 (75)	112/247 (45)

[a] For subjects with values reported at baseline

Source: Dasatinib 120-Day Safety Update[3]

In CA180034 in subjects with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in the 100 mg QD group vs the other treatment groups (Table 5.3.1B).[3]

Table 5.3.1B: CTC Grade 3 to 4 Hematologic Laboratory Abnormalities; CA180034

	Number (%) of Subjects[a] (N = 662)			
	100 mg QD (N = 165)	**140 mg QD (N = 163)**	**50 mg BID (N = 167)**	**70 mg IB (N = 167)**
Neutropenia	56/165 (34)	69/162 (43)	77/166 (46)	70/163 (43)
Thrombocytopenia	37/165 (22)	65/162 (40)	56/166 (34)	62/165 (38)
Anemia	17/165 (10)	31/162 (19)	30/166 (18)	28/165 (17)

[a] For subjects with values reported at baseline

Source: Dasatinib 120-Day Safety Update[3]

5.3.2 Nonhematologic Adverse Events

Dasatinib demonstrated an acceptable safety profile based on safety analyses on data collected from the overall safety cohort of 2182 subjects with CML or Ph+ ALL who were resistant or intolerant to imatinib.[3] Nearly all subjects reported AEs with the most common as fluid-retention related events, diarrhea, headache, and musculoskeletal pain.[3]

5.3.2.1 Common Drug-related Adverse Events

Drug-related AEs (excluding laboratory abnormalities), any grade, reported in ≥ 10% of the subjects in dasatinib clinical studies are shown in Table 5.3.2.1A. The most frequently reported drug-related AEs (reported in ≥ 20% of subjects) included fluid retention events, diarrhea, headache, skin rash, nausea, hemorrhage, fatigue, and dyspnea.

A summary by disease phase of drug-related AEs reported in ≥ 10% of the subjects is in Supplemental Table S.1.

Table 5.3.2.1A: Drug-related Adverse Events Reported in Equal to or Greater Than 10% of All Subjects (All Grades) in Clinical Studies

	All Patients (n=2182)		Chronic Phase (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid/ Ph+ ALL (n=250)
	All Grades	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4	Grades 3/4
Preferred Term	Percent (%) of Subjects					
Fluid Retention	37	8	6	7	13	7
Superficial edema	20	<1	<1	1	1	<1
Pleural effusion	22	5	4	5	10	6
Other fluid retention	10	3	3	3	6	2
Generalized edema	3	<1	<1	1	<1	1
CHF/cardiac dysfunction[a]	2	1	2	<1	2	1
Pericardial effusion	3	1	1	1	2	0
Pulmonary edema	2	1	1	1	1	1
Ascites	<1	<1	0	0	1	<1
Pulmonary hypertension	1	<1	<1	0	1	1
Diarrhea	31	3	3	4	5	4
Headache	24	1	1	1	1	2
Skin Rash[b]	22	1	1	1	1	1
Nausea	22	1	1	1	2	2
Hemorrhage	21	6	2	11	12	8
Gastrointestinal bleeding	7	4	1	8	9	5
CNS bleeding	1	<1	0	<1	<1	2
Fatigue	21	2	2	3	1	2
Dyspnea	20	4	5	4	5	2
Musculoskeletal Pain	14	1	2	1	1	<1
Pyrexia	13	1	1	2	3	1
Vomiting	13	1	1	1	1	2
Abdominal Pain	10	1	1	<1	1	2

[a] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

[b] Includes erythema, erythema multiforme, exfoliative rash, generalized erythema, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, systemic lupus erythematosus rash, urticaria vesiculosa, and rash vesicular.

Source: Supplemental Table S.1

In CA180034 in subjects with chronic phase CML, the rates of drug-related fluid retention events, in particular pleural effusion, were lower in the 100 mg QD group than in the other 3 treatment groups. Selected drug-related AEs are shown by dose regimen in Table 5.3.2.1B. A summary of all drug-related AEs reported in ≥ 10% of the subjects is in Supplemental Table S.4.

Table 5.3.2.1B: Drug-related AEs Reported in CA180034 (Chronic Phase CML)

	100 mg QD n=165		140 mg QD n=163		50 mg BID n=167		70 mg BID n=167	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Preferred Term	**Percent (%) of Patients**							
Diarrhea	23	1	26	3	26	3	25	4
Fluid Retention	24	2	33	4	27	4	32	5
Superficial edema	14	0	14	1	14	0	16	0
Pleural effusion	10	2	20	2	16	3	18	2
Generalized edema	2	0	3	0	0	0	1	0
Congestive heart failure/cardiac dysfunction[a]	0	0	2	1	1	1	4	2
Pericardial effusion	1	1	4	1	2	1	2	1
Pulmonary edema	0	0	0	0	1	0	2	1
Pulmonary hypertension	0	0	0	0	0	0	1	1
Hemorrhage	10	1	12	1	9	2	14	2
Gastrointestinal bleeding	1	1	2	0	4	2	4	2

[a] Includes left ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.
Source: Supplemental Table S.4

5.3.2.2 Serious Adverse Events

Overall, 46% (1008/2182) of subjects across all disease phases reported SAEs (any grade).[3] Notable on-study SAEs (≥ 10%) regardless of relationship to study therapy included pneumonia, infection, sepsis, pleural effusion, pyrexia, hemorrhage (gastrointestinal-related), and febrile neutropenia. A similar profile was reported in CA180034 in subjects with chronic phase CML. Overall, subjects in the 100 mg QD

group (27%) reported fewer SAEs than subjects in the 140 mg QD (37%), 50 mg BID (38%), and 70 mg BID (38%) groups.[3]

5.3.2.3 Treatment Discontinuation Due to Adverse Events

Adverse events (any grade) leading to discontinuation were reported in 11% (249/2182) of subjects across all disease phases.[3] Adverse events leading to discontinuation in any 1 category occurred in ≤ 1 % of the subjects with the exception of pleural effusion (53/2182; 2%). In CA180034, AEs leading to discontinuation in any 1 category occurred in ≤ 1% of the subjects with the exception of pleural effusion (3% in the 140 mg QD and 70 mg BID groups and 2% in the 50 mg BID group), dyspnea (3% in the 140 mg QD), rash (2% in 70 mg BID group), and thrombocytopenia (2% in the 50 mg and 70 mg BID groups).[3]

5.3.2.4 Deaths

A total of 452 (21%) deaths at any time after the last dasatinib dose occurred in the cohort of 2182 subjects pooled across disease phases (Table 5.3.2.4). Progressive disease accounted for 206 of 238 deaths due to disease (Appendix 3). Of the remaining 246 deaths, 52 were reported as "other" and 14 were reported as "unknown".

Table 5.3.2.4: All Deaths Pooled Across Disease Phases

	Number (%) of Subjects	
	Death within 30 Days	**All Death**
Number of deaths	232 (11)	452 (21)
Reason For Death		
Disease	106 (5)	238 (11)
Study Drug Toxicity	6 (< 1)	9 (< 1)
Infection	56 (3)	91 (4)
Cardiovascular Disease	12 (< 1)	17 (< 1)
Fatal Bleeding	23 (1)	31 (1)
Unknown	6 (< 1)	14 (< 1)
Other[a]	23 (1)	52 (2)

[a] Reasons for death due to "other" include (note - more than 1 reason for death can be reported per subject): 6 sepsis, 9 graft vs host disease, 6 respiratory failure, 3 CNS hemorrhage, 2 stem cell transplant complication, 2 respiratory distress syndrome, 2 post stem cell transplant, 2 multiorgan failure, 2 disease progression, 1 GI bleed, 1 fatal bleed, 1 cerebral lesion, 1 pulmonary embolus, 1 pulmonary infiltrate, 1 acute respiratory distress syndrome due to tumor lysis syndrome, 1 acute respiratory distress syndrome due to possible pneumonia and fluid overload, 1 respiratory insufficiency, 1 hypoxia, 1 pleural effusion, 1 pulmonary edema, 1 pericardial effusion, 1 cytopenia, 1 metastatic solid malignancy, 1 'domage' general status, 1 constrictive pericarditis, 1 veno-occlusive disease, 1 accidental oxycodone overdose, 1 relapse of tuberulosis, 1 suicide, 1 status epilepticus, 1 renal failure, 1 hepatic failure, 1 CNS progression, 1 leukoencephalitis, 1 intracranial hypertensive syndrome, 1 sepsis secondary to bacterium, 1 idiopathic pneumonia syndrome, 1 pneumonia secondary to LGL, and 1 fungal pneumonia.

Source: Dasatinib 120-Day Safety Update[3]

5.3.2.5 Laboratory Test Abnormalities

Results of hematologic evaluation are described in Section 5.3.1. There were few clinically meaningful nonhematologic changes in laboratory parameters reported on treatment with dasatinib treatment. Most elevations were mild to moderate, and few subjects (< 1% to 7%) had Grade 3 to 4 elevations.

The most common electrolyte abnormality was hypophosphatemia. The incidence of hypophosphatemia increased with more advanced CML disease. Grade 3 to 4 hypophosphatemia ranged from 10% (chronic phase) to 20% (lymphoid blast phase/Ph+ ALL) of subjects in the various studies. However, none of these subjects experienced associated clinical symptoms and intervention was not required. The majority of these events were transient and subsided spontaneously during treatment.

5.3.3 Other Ongoing Studies

Solid Tumor Program

Ongoing studies in the solid tumor program include four Phase 1 studies (CA180003, CA180021, CA180004, CA180086) and three Phase 2 studies (CA180059, CA180088, CA180085). Data are presented for CA180003 (completed study; CSR in preparation) and CA180021 (ongoing study).

CA180003 is the first Phase 1 study of dasatinib conducted in subjects with solid tumors who are refractory to standard therapies or for which no effective standard therapy exists. Preliminary data are presented in this IB. This study explored 8 dose levels with 2 different dosing schedules. The first schedule assessed 5 days of dasatinib followed by 2 days off-drug each week (5D2), and the second schedule assessed continuous daily dosing (CDD) that was added in Amendment #3 (7-Mar-2005). Sixty-seven subjects were treated at starting TDDs of 70, 100, 140, 180, 200, 240, and 320 mg. Three of 4 subjects and 3 out of 5 treated at the highest dose level on the 5D2 and CDD schedules, respectively experienced DLTs. At the 320 mg dose level on the 5D2 schedule, DLTs consisted of rash, lethargy, prolongation of bleeding time and hypocalcemia, while nausea, fatigue, rash and proteinuria were DLTs at the 240 mg dose level on the CDD schedule. The MTD was established at 240 mg on the 5D2 schedule and 140 mg on the CDD schedule.

All but 1 of the 67 subjects (98.5%) reported at least 1 AE during the study (Table 5.3.3). The most frequent AEs (regardless of relationship) were nausea, anorexia, and fatigue. A total of 64/67 subjects (95%) had at least 1 AE that was considered drug-related by the investigator. Of the 18 deaths, all but 1 of these deaths were due to disease progression; 1 subject died due to gastrointestinal bleeding that the investigator considered most likely due to disease progression, but could not rule out a possible contribution by study drug.

Unlike dasatinib treatment is subjects with leukemia, Grade 3 to 4 myelosuppression in subjects with solid tumors was infrequent. This comparison suggests a minimal direct myelosuppressive effect of dasatinib in normal hemapoietic progenitor cells, which are not driven by the Abl kinase. Preliminary data suggest that the incidence and severity of fluid retention and of pleural effusion, in particular, appear to be less in subjects with solid tumors than in those with leukemia receiving comparable doses of dasatinib.

Table 5.3.3: Overall Summary of Safety

	Number (%) of Subjects	
	Regimen	
	5D2 N=33	CDD N=34
Any AE	33 (100)	33 (97.1)
Most Frequent[a] AEs (regardless of Relationship)		
Nausea	24 (72.7)	23 (67.6)
Anorexia	13 (39.4)	21 (61.8)
Fatigue	16 (48.5)	19 (55.9)
Grade 3-5 AEs (regardless of Relationship)	17 (52)	20 (59)
Drug-related AEs	33 (100)	31 (91.2)
Deaths	12 (36.4)	6 (17.6)
SAEs	18 (54.4)	16 (47.0)
Drug-related SAEs	9 (27.3)	4 (11.8)
AEs that led to discontinuation	9 (27.3)	15 (44.1)
Selected Grade 3-4 On-study Laboratory Abnormalities		
Neutropenia	0	1 (3)
Anemia	2 (3)	1 (3)
Hypocalcemia	3 (9)	0
Phosphate, low	5 (15)	1 (3)

[a] Frequency of adverse events ≥ 50% in either treatment schedule

CA180021 investigated the effect of ketoconazole, a potent inhibitor of CYP3A4, on the PK of dasatinib (Segment 1) and the effect of dasatinib on pharmacodynamic markers in subjects with advanced solid tumors that are refractory to standard therapies or for which no standard therapy exists (Segment 2). Preliminary data are presented in this IB. Segment 1 includes 18 subjects, of which 16 subjects were treated with dasatinib as of 2-Jan-2006. Segment 2 includes approximately 30 additional subjects, of which 14 subjects were treated with dasatinib as of 2-Jan-2006. A total of 4 deaths, all related to

disease progression, were reported. There were 4 subjects with drug-related AEs leading to discontinuation: 1 subject with Grade 1 amnesia, 1 with Grade 2 pleural effusion, 1 with Grade 3 dehydration, and 1 subject with Grade 3 dysphagia and Grade 3 dehydration.

5.3.4 Expected Adverse Events Updates Since Last Investigator Brochure Revision

A listing of all AEs/SAEs that are considered expected adverse events is presented in Appendix 4.

5.3.5 Precautions for Women of Childbearing Potential

Dasatinib is a selective developmental toxicant in rabbits and rats. Whereas the clinical relevance of these data to humans is unknown, women of childbearing potential should be advised to avoid becoming pregnant when taking dasatinib. Also, it is not known how long after stopping dasatinib it would be considered safe for a woman to become pregnant. It is recommended on all dasatinib studies that women of child bearing potential follow specific exclusion criteria. (See Section 7.2.2 Reproduction, Pregnancy, and Lactation).

6 MARKETING EXPERIENCE

The first approval for dasatinib was granted on 28-June-2006 by the US Food and Drug Administration. Additional country approvals include Argentina, Australia, Austria, Canada, Czech Republic, Denmark, Dominican Republic, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, India, Indonesia, Ireland, Italy, Liechtenstein, Macau, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovenia, Sweden, Switzerland, United Kingdom, and Uruguay.[97] Dasatinib has not had any marketing authorizations or registrations denied or withdrawn.

Review of post-marketing data confirm that the safety of dasatinib is consistent with the profile establish in clinical trials. Dasatinib continues to have a favorable risk/benefit profile for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast

phase CML with resistance or intolerance to prior therapy including imatinib and for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.

7 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

7.1 Contraindications

Dasatinib is contraindicated in patients with hypersensitivity to dasatinib or to any other component of dasatinib.

7.2 Warnings and Precautions

7.2.1 Product Specific Warnings and Precautions

Clinical experience in the safety cohort of 2182 subjects has identified several safety concerns with dasatinib. Safety issues of special interest in the dasatinib program included fluid retention, hemorrhage, and QT prolongation. These issues were examined because they are either recognized events in other agents within this drug class or because safety data from nonclinical studies conducted in animals warranted careful evaluation in human studies.

Although nonclinical studies of dasatinib did not identify fluid retention as an important adverse event, imatinib leads to fluid retention in more than 70% of recipients.[3] Thus, AEs related to fluid retention were examined in the dasatinib program.

Myelosuppression

Treatment with dasatinib is associated with severe (Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in subjects with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction. In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported

less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.

Bleeding-related Events

Severe central nervous system (CNS) hemorrhages, including fatalities, occurred in < 1% of subjects receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 4% of subjects and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of subjects. Most bleeding events were associated with severe thrombocytopenia. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution.)

Subjects were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steriodal anti-inflammatory drugs were allowed concurrently with dasatinib if the platelet count was > 50,000. Caution should be exercised if subjects are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

Dasatinib is associated with fluid retention, which was severe in 8% of subjects, including pleural and pericardial effusion reported in 5% and 1% of subjects, respectively. Severe ascites and generalized edema were each reported in ≤ 1%. Severe non-cardiogenic pulmonary edema was reported in 1% of subjects. Subjects who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution.)

In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.

QT Prolongation

In vitro data suggest that dasatinib has the potential to prolong cardiac ventricular repolarization (QT interval). In Phase 2, single-arm clinical studies in subjects with leukemia treated with dasatinib, the mean QTc changes from baseline using Fridericia's method (QTcF) were 3 to 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 8 msec. Three subjects (< 1%) experienced a QTcF > 500 msec.[98]

Dasatinib should be administered with caution to subjects who have or may develop prolongation of QT interval. These include patients with hypokalemia or hypomagnesemia, subjects with congenital long QT syndrome, subjects taking anti arrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy. Hypokalemia or hypomagnesemia should be corrected prior to dasatinib administration.

7.2.2 Reproduction, Pregnancy, and Lactation

Dasatinib may cause fetal harm when administered to a pregnant woman. In nonclinical studies, at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, fetal toxicity was observed in rats and rabbits. Fetal death was observed in rats.

Dasatinib is not recommended for use in women who are pregnant or contemplating pregnancy. If dasatinib is used during pregnancy, or if the patient becomes pregnant while taking dasatinib, the patient should be apprised of the potential hazard to the fetus.

The potential effects of dasatinib on sperm have not been studied. Sexually active male or female patients taking dasatinib should use adequate contraception.

It is unknown whether dasatinib is excreted in human milk. Women who are taking dasatinib should not breast-feed.

7.3 Additional Safety Findings From Clinical Studies

7.3.1 Other Adverse Events Observed During the Evaluation of Dasatinib

Adverse reactions reported in clinical studies of dasatinib that were considered at least possibly related to dasatinib (based on investigator attribution) are listed by system organ class and by frequency. The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100). These events are included based on clinical relevance.

Infections and infestations
Common: infection (including bacterial, viral, fungal, non-specified), pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection
Uncommon: sepsis (including fatal outcomes)

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: tumor lysis syndrome

Blood and lymphatic system disorders
Common: febrile neutropenia
Uncommon: pancytopenia, aplasia pure red cell

Immune system disorders
Uncommon: hypersensitivity (including erythema nodosum)

Metabolism and nutrition disorders
Very Common: anorexia
Common: appetite disturbances
Uncommon: hyperuricemia

Psychiatric disorders
Common: depression, insomnia
Uncommon: anxiety, confusional state, affect lability, libido decreased

Nervous system disorders

Very Common: headache
Common: dizziness, neuropathy (including peripheral neuropathy), dysgeusia, somnolence, CNS bleeding
Uncommon: transient ischemic attack, reversible posterior leukoencephalopathy syndrome, convulsion, amnesia, tremor, syncope, cerebrovascular accident

Eye disorders

Common: dry eye, conjunctivitis, visual disorder

Ear and labyrinth disorders

Uncommon: tinnitus, vertigo

Cardiac disorders

Common: congestive heart failure/cardiac dysfunction, pericardial effusion, arrhythmia (including tachycardia), palpitations
Uncommon: cardiomegaly, angina pectoris, myocardial infarction, pericarditis, acute coronary syndrome, myocarditis, ventricular arrhythmia (including ventricular tachycardia)

Vascular disorders

Very Common: hemorrhage
Common: hypertension, flushing

Uncommon: hypotension, livedo reticulares, thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Very Common: pleural effusion, dyspnea
Common: cough, pulmonary edema, lung infiltration, pneumonitis
Uncommon: pulmonary hypertension, asthma, acute respiratory distress syndrome, bronchospasm

Gastrointestinal disorders

Very Common: diarrhea, nausea, vomiting
Common: abdominal pain, abdominal distension, mucosal inflammation (including mucositis/stomatitis), colitis (including neutropenic colitis), gastritis, oral soft tissue disorder, dyspepsia, constipation, gastrointestinal bleeding
Uncommon: pancreatitis, upper gastrointestinal ulcer, ascites, dysphagia, anal fissure
Rare: esophagitis

Hepatobiliary disorders

Uncommon: hepatitis, cholestasis, cholecystitis

Skin and subcutaneous tissue disorders

Very Common: skin rash[a]
Common: pruritus, alopecia, acne, dry skin, urticaria, hyperhydrosis
Uncommon: dermatitis (including eczema), acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorder, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, panniculitis

Musculoskeletal and connective tissue disorders

Very Common: musculoskeletal pain
Common: arthralgia, myalgia, muscle inflammation, muscular weakness
Uncommon: rhabdomyolysis, musculoskeletal stiffness, blood creatine phosphokinase increased
Rare: tendonitis

Renal and urinary disorders

Uncommon: renal failure, urinary frequency, proteinuria

Reproductive system and breast disorders

Uncommon: gynecomastia, menstruation irregular

General disorders and administration site conditions

Very Common: superficial edema,[b] fatigue, pyrexia,
Common: pain, chest pain, chills, asthenia, generalized edema
Uncommon: malaise
Rare: temperature intolerance

Investigations

Common: weight decreased, weight increased

Injury, poisoning, and procedural complications

Common: contusion

[a] Includes drug eruption, erythema, erythema multiforme, erythrosis, exanthem, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, systemic lupus erythematosus rash, toxic skin eruption, and urticaria vesiculosa.

[b] Includes conjunctival edema, eye edema, eye swelling, eyelid edema, face edema, gravitational edema, localized edema, edema genital, edema mouth, edema peripheral, orbital edema, periorbital edema, swelling face, pitting edema, scrotal edema.

7.4 Overdosage

Experience with overdose in clinical studies is limited to isolated cases. The highest reported dosage ingested was 280 mg per day for 1 week. Since dasatinib is associated with severe myelosuppression, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and appropriate supportive treatment given.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥ 100 mg/kg (600 mg/m^2) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥ 10 mg/kg (120 mg/m^2).

7.5 Drug Interactions

Dasatinib is mainly metabolized through the liver and elimination is predominantly in the feces, mostly as metabolites. Negligible amounts are found in the urine. Drugs were selected for interaction studies (in adult healthy subjects) with dasatinib based upon metabolic considerations. Dasatinib is metabolized primarily by CYP3A4 isoenzyme and, based on in vitro cytochrome P-450 [CYP] inhibition studies, is an inhibitor of CYP3A4. Therefore, the possibility exists for an interaction with other concomitantly administered drugs that are primarily metabolized by or modulate the activity of CYP3A4. At clinically-relevant concentrations, dasatinib does not inhibit the following cytochrome P450 enzymes in vitro: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1.

Drugs that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors: Dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that inhibit CYP3A4 (eg, ketoconazole, itraconazole, erythromycin, clarithromycin,

ritonavir, atazanavir, indinavir, nelfinavir, saquinavir, telithromycin) may increase exposure to dasatinib and should be avoided. Selection of an alternate concomitant medication with no or minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity.

Drugs that may decrease dasatinib plasma concentrations

CYP3A4 Inducers: Drugs that induce CYP3A4 activity (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's wort) may reduce exposure to dasatinib. Concomitant use of potent CYP3A4 inducers with dasatinib should be avoided. In patients for whom CYP3A4 inducers are indicated, alternative agents with no or minimal CYP3A4 induction potential should be selected.

Antacids (aluminum hydroxide/magnesium hydroxide products): Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of dasatinib. Simultaneous administration of dasatinib with antacids should be avoided.

H_2 Blockers/Proton Pump Inhibitors: Long-term suppression of gastric acid secretion by H_2 blockers or proton pump inhibitors (eg, famotidine, omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H_2 blockers or proton pump inhibitors with dasatinib is not recommended. The use of antacids should be considered in place of H_2 blockers or proton pump inhibitors in patients receiving dasatinib therapy.

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: Dasatinib is an inhibitor of CYP3A4. Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib.

7.6 Pediatric Use

The safety and efficacy of dasatinib in subjects < 18 years of age have not been established.

7.7 Geriatric Use

No clinically relevant age-related pharmacokinetic differences have been observed. No specific dose recommendation is necessary in the elderly.

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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%)

Preferred Term	Number of Subjects (N = 2182) Any Grade	Severe (3-4)
FLUID RETENTION	812 (37)	165 (8)
Superficial Edema	428 (20)	9 (<1)
Pleural Effusion	486 (22)	112 (5)
Other Fluid Retention	210 (10)	71 (3)
ASCITES	7 (<1)	3 (<1)
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	52 (2)	29 (1)
GENERALISED OEDEMA	66 (3)	8 (<1)
PERICARDIAL EFFUSION	76 (3)	19 (1)
PULMONARY HYPERTENSION	17 (1)	7 (<1)
PULMONARY OEDEMA	35 (2)	14 (1)
DIARRHOEA	686 (31)	76 (3)
HEADACHE	530 (24)	27 (1)
HEMORRHAGE	448 (21)	129 (6)
Other	321 (15)	38 (2)
Gastrointestinal Bleeding	163 (7)	90 (4)
CNS Bleeding	20 (1)	7 (<1)
NAUSEA	473 (22)	22 (1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%)

	Number of Subjects (N = 2182)	
Preferred Term	Any Grade	Severe (3-4)
FATIGUE	457 (21)	47 (2)
RASH	475 (22)	19 (1)
ABDOMINAL PAIN	213 (10)	15 (1)
DYSPNOEA	439 (20)	89 (4)
MUSCULOSKELETAL PAIN	304 (14)	27 (1)
PYREXIA	287 (13)	28 (1)
VOMITING	274 (13)	21 (1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/us_label/sasprogs/ae-s-pt-grp-indiRUN DATE: 22-AUG-2007 14:09

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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Chronic Phases

	Number of Chronic Subjects (N = 1150)					
	Chronic- QD: 100mg TDD (N = 165)		Chronic- other (N = 985)		Total (N = 1150)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
FLUID RETENTION	40 (24)	4 (2)	370 (38)	70 (7)	410 (36)	74 (6)
Superficial Edema	23 (14)	0	193 (20)	2 (<1)	216 (19)	2 (<1)
Pleural Effusion	17 (10)	3 (2)	219 (22)	42 (4)	236 (21)	45 (4)
Other Fluid Retention	6 (4)	1 (1)	94 (10)	34 (3)	100 (9)	35 (3)
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	0	0	36 (4)	20 (2)	36 (3)	20 (2)
GENERALISED OEDEMA	4 (2)	0	25 (3)	2 (<1)	29 (3)	2 (<1)
PERICARDIAL EFFUSION	2 (1)	1 (1)	33 (3)	6 (1)	35 (3)	7 (1)
PULMONARY HYPERTENSION	0	0	8 (1)	3 (<1)	8 (1)	3 (<1)
PULMONARY OEDEMA	0	0	12 (1)	6 (1)	12 (1)	6 (1)
DIARRHOEA	38 (23)	1 (1)	307 (31)	29 (3)	345 (30)	30 (3)
HEADACHE	53 (32)	1 (1)	278 (28)	14 (1)	331 (29)	15 (1)
HEMORRHAGE	16 (10)	2 (1)	144 (15)	22 (2)	160 (14)	24 (2)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Chronic Phases

	Number of Chronic Subjects (N = 1150)					
	Chronic- QD: 100mg TDD (N = 165)		Chronic- other (N = 985)		Total (N = 1150)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
Other	16 (10)	2 (1)	112 (11)	7 (1)	128 (11)	9 (1)
Gastrointestinal Bleeding	2 (1)	1 (1)	38 (4)	15 (2)	40 (3)	16 (1)
CNS Bleeding	0	0	3 (<1)	0	3 (<1)	0
NAUSEA	30 (18)	1 (1)	229 (23)	6 (1)	259 (23)	7 (1)
FATIGUE	34 (21)	3 (2)	242 (25)	21 (2)	276 (24)	24 (2)
RASH	24 (15)	2 (1)	264 (27)	9 (1)	288 (25)	11 (1)
ABDOMINAL PAIN	16 (10)	1 (1)	112 (11)	5 (1)	128 (11)	6 (1)
DYSPNOEA	25 (15)	3 (2)	246 (25)	49 (5)	271 (24)	52 (5)
MUSCULOSKELETAL PAIN	25 (15)	3 (2)	159 (16)	17 (2)	184 (16)	20 (2)
PYREXIA	7 (4)	1 (1)	125 (13)	6 (1)	132 (11)	7 (1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Chronic Phases

	Number of Chronic Subjects (N = 1150)					
	Chronic- QD: 100mg TDD (N = 165)		Chronic- other (N = 985)		Total (N = 1150)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
VOMITING	11 (7)	1 (1)	100 (10)	6 (1)	111 (10)	7 (1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Disease Phases

	Number of Subjects (N = 1032)					
	Accelerated (N = 502)		Myeloid Blast (N = 280)		Lymphoid Blast/ALL (N = 250)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
FLUID RETENTION	199 (40)	36 (7)	119 (43)	37 (13)	84 (34)	18 (7)
Superficial Edema	109 (22)	3 (1)	58 (21)	3 (1)	45 (18)	1 (<1)
Pleural Effusion	122 (24)	24 (5)	73 (26)	27 (10)	55 (22)	16 (6)
Other Fluid Retention	52 (10)	13 (3)	41 (15)	17 (6)	17 (7)	6 (2)
ASCITES	2 (<1)	0	3 (1)	2 (1)	2 (1)	1 (<1)
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	6 (1)	2 (<1)	8 (3)	5 (2)	2 (1)	2 (1)
GENERALISED OEDEMA	17 (3)	3 (1)	13 (5)	1 (<1)	7 (3)	2 (1)
PERICARDIAL EFFUSION	20 (4)	6 (1)	15 (5)	6 (2)	6 (2)	0
PULMONARY HYPERTENSION	2 (<1)	0	5 (2)	2 (1)	2 (1)	2 (1)
PULMONARY OEDEMA	11 (2)	3 (1)	6 (2)	3 (1)	6 (2)	2 (1)
DIARRHOEA	188 (37)	22 (4)	77 (28)	14 (5)	76 (30)	10 (4)
HEADACHE	131 (26)	3 (1)	34 (12)	4 (1)	34 (14)	5 (2)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Disease Phases

	Number of Subjects (N = 1032)					
	Accelerated (N = 502)		Myeloid Blast (N = 280)		Lymphoid Blast/ALL (N = 250)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
HEMORRHAGE	158 (31)	53 (11)	82 (29)	33 (12)	48 (19)	19 (8)
Other	111 (22)	16 (3)	55 (20)	9 (3)	27 (11)	4 (2)
Gastrointestinal Bleeding	65 (13)	38 (8)	39 (14)	24 (9)	19 (8)	12 (5)
CNS Bleeding	8 (2)	2 (<1)	3 (1)	1 (<1)	6 (2)	4 (2)
NAUSEA	107 (21)	5 (1)	49 (18)	5 (2)	58 (23)	5 (2)
FATIGUE	103 (21)	15 (3)	43 (15)	3 (1)	35 (14)	5 (2)
RASH	98 (20)	3 (1)	47 (17)	2 (1)	42 (17)	3 (1)
ABDOMINAL PAIN	44 (9)	1 (<1)	23 (8)	4 (1)	18 (7)	4 (2)
DYSPNOEA	91 (18)	19 (4)	46 (16)	14 (5)	31 (12)	4 (2)
MUSCULOSKELETAL PAIN	75 (15)	4 (1)	28 (10)	2 (1)	17 (7)	1 (<1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.1:
SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%) by Disease Phases

	Number of Subjects (N = 1032)					
	Accelerated (N = 502)		Myeloid Blast (N = 280)		Lymphoid Blast/ALL (N = 250)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
PYREXIA	74 (15)	12 (2)	43 (15)	7 (3)	38 (15)	2 (1)
VOMITING	78 (16)	7 (1)	41 (15)	3 (1)	44 (18)	4 (2)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
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Table S.4:
CA180-034 SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%)

	Number of Subjects (N = 662)							
	QD: 100mg TDD (N = 165)		QD: 140mg TDD (N = 163)		BID: 100mg TDD (N = 167)		BID: 140mg TDD (N = 167)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
FLUID RETENTION	40 (24)	4 (2)	54 (33)	7 (4)	45 (27)	6 (4)	54 (32)	9 (5)
Superficial Edema	23 (14)	0	23 (14)	1 (1)	24 (14)	0	27 (16)	0
Pleural Effusion	17 (10)	3 (2)	33 (20)	4 (2)	27 (16)	5 (3)	30 (18)	4 (2)
Other Fluid Retention	6 (4)	1 (1)	14 (9)	2 (1)	6 (4)	2 (1)	14 (8)	7 (4)
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	0	0	3 (2)	1 (1)	2 (1)	1 (1)	7 (4)	3 (2)
GENERALISED OEDEMA	4 (2)	0	5 (3)	0	0	0	1 (1)	0
PERICARDIAL EFFUSION	2 (1)	1 (1)	7 (4)	1 (1)	4 (2)	1 (1)	4 (2)	2 (1)
PULMONARY HYPERTENSION	0	0	0	0	0	0	2 (1)	1 (1)
PULMONARY OEDEMA	0	0	0	0	1 (1)	0	3 (2)	1 (1)
DIARRHOEA	38 (23)	1 (1)	42 (26)	5 (3)	44 (26)	5 (3)	41 (25)	6 (4)
HEADACHE	53 (32)	1 (1)	46 (28)	3 (2)	33 (20)	0	48 (29)	5 (3)
HEMORRHAGE	16 (10)	2 (1)	20 (12)	1 (1)	15 (9)	4 (2)	24 (14)	4 (2)
Other	16 (10)	2 (1)	17 (10)	1 (1)	9 (5)	1 (1)	18 (11)	1 (1)
Gastrointestinal Bleeding	2 (1)	1 (1)	3 (2)	0	6 (4)	3 (2)	7 (4)	3 (2)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
MedDRA Version 10

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Table S.4:
CA180-034 SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%)

	Number of Subjects (N = 662)							
	QD: 100mg TDD (N = 165)		QD: 140mg TDD (N = 163)		BID: 100mg TDD (N = 167)		BID: 140mg TDD (N = 167)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
CNS Bleeding	0	0	0	0	1 (1)	0	0	0
NAUSEA	30 (18)	1 (1)	33 (20)	1 (1)	32 (19)	1 (1)	45 (27)	1 (1)
FATIGUE	34 (21)	3 (2)	34 (21)	4 (2)	27 (16)	0	28 (17)	6 (4)
RASH	24 (15)	2 (1)	41 (25)	1 (1)	37 (22)	2 (1)	36 (22)	3 (2)
ABDOMINAL PAIN	16 (10)	1 (1)	21 (13)	1 (1)	16 (10)	0	15 (9)	2 (1)
ARTHRALGIA	18 (11)	1 (1)	15 (9)	0	14 (8)	1 (1)	13 (8)	4 (2)
DYSPNOEA	25 (15)	3 (2)	34 (21)	10 (6)	36 (22)	8 (5)	23 (14)	6 (4)
INFECTION (INCLUDING BACTERIAL, VIRAL, FUNGAL, NON-SPECIFIED)	17 (10)	1 (1)	14 (9)	2 (1)	10 (6)	1 (1)	16 (10)	3 (2)
MUSCULOSKELETAL PAIN	25 (15)	3 (2)	24 (15)	2 (1)	17 (10)	2 (1)	21 (13)	6 (4)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
MedDRA Version 10

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Table S.4:
CA180-034 SU Cohort: Drug-related Adverse Events (Equal to or Greater Than 10%)

	Number of Subjects (N = 662)							
	QD: 100mg TDD (N = 165)		QD: 140mg TDD (N = 163)		BID: 100mg TDD (N = 167)		BID: 140mg TDD (N = 167)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
MYALGIA	20 (12)	0	19 (12)	1 (1)	5 (3)	0	11 (7)	1 (1)

Note: Five percent cut-off not applied to re-grouped AE: FLUID RETENTION and HEMORRHAGE
Preferred terms subsumed/deleted per clinical review
MedDRA Version 10

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Appendix 1: Nonclinical Toxicology

8 page(s) excluding cover page

Table A: Single-Dose Toxicity

Species/ Strain	Method of Administration	Doses (mg/kg)	Animals per group (M/F)	Observed Maximum Non-Lethal Dose (mg/kg); Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Rat / Hsd:Sprague Dawley	Oral, gavage	0 30 100 300	M10, F10	30; < 100	30 mg/kg was generally well tolerated and not associated with severe toxicity (highest non-lethal dose). Doses ≥ 100 mg/kg were severely toxic and associated with mortality. Generally reversible dose-related gastrointestinal (GI), bone marrow, and lymphoid organ toxicities occurred at all doses. At severely toxic doses associated with mortality, cardiac and renal toxicities were also noted.	DS02138 (GLP) 44
Monkey / Cynomolgus	Oral, gavage	0 15 25 45	M2, F2	25; < 45	Systemic exposure to dasatinib dose proportional; no apparent sex-related differences. 25 mg/kg was maximum non-lethal dose; 45 mg/kg was severely toxic & resulted in mortality. Generally reversible drug-related subcutaneous hemorrhage observed at ≥15 mg/kg, GI & lymphoid organ toxicities at ≥ 25 mg/kg, & renal toxicity at 45 mg/kg. Cardiac lesions were not observed.	DS02147 (GLP) 45

Table B: Repeat-dose Toxicity

Species/ Strain	Duration of Dosing; Route (Vehicle/ Formulation)	Doses (mg/kg)	Animals per group (M/F)	NOAEL (mg/kg)	Exposure Multiples (M, F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Rat / Hsd:Sprague Dawley	2 weeks Oral, gavage (Acetate buffer)	0 1 15 30	M6, F6	1	0.2-0.2, 4.7-5.1, 9.4-16.6	Dose-related increases in systemic exposure observed & generally > dose-proportional. Generally well tolerated up to 15 mg/kg. No significant AEs at 1 mg/kg. Severe toxicity & lethality in all animals at 30 mg/kg. Generally dose-dependent lymphoid, hematopoietic, GI toxicities at 15 & 30 mg/kg.	DS02047 (non-GLP) 46
Rat / Hsd:Sprague Dawley	10 to 15 days Oral, gavage (Acetate buffer)	0 3.75 7.5 15 30	F4-5/group	Not deter-mined	Not determine d	Enteropathy occurred at all doses; severity was similar 24 hours after the last dose, regardless of the dosing schedule. However, complete resolution occurred 72 hours after the last dose with the intermittent-dosing schedule, indicating that intermittent dosing was tolerated better than daily dosing.	[None] (non-GLP) 47
Rat / Hsd:Sprague Dawley	5-on/2-off x 1 month (4 cycles); PO (80 mM sodium citrate buffer)	0 0.9 15 25	M15, F15	0.9	0.1-0.1, 3.0-3.0, 4.3-5.6	Generally dose-proportional systemic exposure; no apparent sex-related differences. Generally well tolerated up to 15 mg/kg. No significant AEs at 0.9 mg/kg; maximum non-lethal dose 15 mg/kg. Significant toxicity & lethality at 25 mg/kg. Generally reversible dose-related GI, bone marrow & lymphoid toxicities at ≥ 15 mg/kg. No cardiac lesions.	DS02158 (GLP) 48

Table B: Repeat-dose Toxicity

Species/ Strain	Duration of Dosing; Route (Vehicle/ Formulation)	Doses (mg/kg)	Animals per group (M/F)	NOAEL (mg/kg)	Exposure Multiples (M, F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Rat / Hsd:Sprague Dawley	6 months, PO (80 mM sodium citrate buffer)	0 1.5 4 15/10/8[a]	M25, F25	1.5	0.2-0.4, 1.0-1.4, 4.4-3.5	Approximately dose proportional systemic exposure, no apparent accumulation or reduction in exposure; no apparent sex-related differences. 1.5 & 4 mg/kg tolerated for 26 wks; 15 mg/kg induced GI toxicity & mortality. At all doses, partially reversible GI toxicity & changes in female reproductive tract. Incidence & severity of microscopic changes generally dose-related & minimal at 1.5 mg/kg.	DS03072 (GLP) 49
Dog / Beagle	2 days; Oral, gavage (Acetate buffer)	0 5	M1, F1	Not deter-mined	Not determine d	Study discontinued after 2 days due to severe GI toxicity. Findings reflected heightened sensitivity to GI-tract toxicity & unsuitability for repeat-dose toxicity testing.	DS02050 (non-GLP) 50
Monkey / Cynomolgus	5-on/2-off x 2 weeks; PO; (Acetate buffer)	0 1 10 15 25 62.5	M1, F1	1	0.3-0.1, 4.3-2.7, 5.4-4.2, 23.0-15.3, 27.5-34.5	Greater than dose-proportional dose-related increases in systemic exposure at 1, 10, & 15 mg/kg. Doses up to 10 mg/kg generally well tolerated. Dose-dependent lymphoid, hematopoietic, GI, & renal toxicities at ≥ 10 mg/kg. Highest nonlethal dose was 15 mg/kg.	DS02062 (non-GLP) 51
Monkey / Cynomolgus	5-on/2-off x 1 month (20 doses); PO (80 mM sodium citrate buffer)	0 1 5 15	M4, F4	5 (NOEL= 1)	0.1-0.06, 0.7-0.9 3.8-3.4	Systemic exposure at 1, 5 or 15 mg/kg generally dose-proportional; no apparent sex-related difference; no accumulation. Maximum non-lethal dose 15 mg/kg. Principal repeat-dose related toxicities similar to single-dose toxicities & partially or completely reversible.	DS02159 (GLP) 52

Table B: Repeat-dose Toxicity

Species/ Strain	Duration of Dosing; Route (Vehicle/ Formulation)	Doses (mg/kg)	Animals per group (M/F)	NOAEL (mg/kg)	Exposure Multiples (M, F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Monkey / Cynomolgus	5-on/2-off x 14 d or QD x 14 d; PO (80 mM sodium citrate buffer)	0 10	F5	Not deter-mined	Not determine d	5-on/2-off dosing generally well tolerated. With QD dosing, decreased appetite & dehydration, necessitating dosing interruption or euthanasia.	DS03170 (non-GLP) 53
Monkey / Cynomolgus	5-on/2-off x 9 months, PO (80 mM sodium citrate buffer)	0 1 3/2 10/4.5[b]	M6, F6	Not deter-mined	0.2-0.2, 0.5-0.4, 3.1-2.5	No accumulation or reduction in exposure (41 wks). Near dose-proportional increase in systemic exposure; no sex-related differences. 1 mg/kg generally well tolerated up to 6 months. Dosing interrupted last 3 months due to GI intolerance. Dosing resumed & continued; no significant AEs. 3 mg/kg reduced to 2 mg/kg. 10 mg/kg induced intolerable GI toxicity, mortality; required reductions. 2 animals at 10 mg/kg euthanized due to severe toxicity.	DS03073 (GLP) 54

[a] In surviving animals, the high dose was lowered from 15 to 10 mg/kg/day in Week 8 and then to 8 mg/kg/day in Week 17.

b The high dose was lowered from 10 to 6 mg/kg/day in Week 3 and then to 4.5 mg/kg/day in Week 12; toxicokinetics were not assessed at 6 mg/kg/day. The intermediate dose was lowered from 3 to 2 mg/kg/day in Week 28.

AE = adverse effects

Table C: Genotoxicity Studies

Assay System	Concentration or Dose	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Spiral Ames reverse-mutation assay in Salmonella typhimurium (± S9 activation)	21-5000 µg/plate	No reductions in revertant frequency or bacterial background lawn density were observed. Histidine^{+} revertant values were not significantly elevated in dasatinib-treated cultures with respect to the negative control levels.	DS01124 (non-GLP) 55
Reverse-mutation assay in Salmonella typhimurium and Escherichia coli (± S9 activation)	10-5000 µg/plate	Cytotoxicity was observed in each strain at the highest concentration(s) tested, +/- S9 activation. Mean histidine^{+} and tryptophan^{+} revertant counts did not meet criteria for positive response in cultures treated with dasatinib.	DS02193 (GLP) 56
Cytogenetics in CHO cells	5-60 µg/mL (4 hr without S9), 5-40 µg/mL (4 hr with S9), 2.5-10 µg/mL (20 hr without S9)	Dasatinib was clastogenic to dividing CHO cells with and without metabolic activation when tested to the maximum concentrations recommended by international guidelines.	DS03025 (GLP) 57
Oral micronucleus assay in rats	10, 20, 40 mg/kg PO x 3 days to 3 groups (5/sex); negative control (80 mM citrate buffer) to 1 group (5/sex); CP 7 mg/kg x 3 days to 1 group (5/sex).	Drug-related toxicity at 40 mg/kg included chromorhinorrhea; dark liquid feces; haircoat soiling, chromodacryorrhea and rough haircoat (female); bone marrow toxicity (~44% male, 47% female). Bone-marrow toxicity was seen at 20 mg/kg (15% male, 24% female). Frequencies of MN-PCE were not statistically significantly increased compared to negative-control. A positive micronucleus response was seen in CP-treated rats (2.94% MN-PCE males, 1.97% MN-PCE females).	DS02177 (GLP) 58

CP = cyclophosphamide; MN-PCE = micronucleated polychromatic erythrocytes

Table D: Reproductive and Developmental Toxicity

Species/ Strain	Study Type	Method of Administration (Vehicle/ Formulation); Dosing Period	Doses (mg/kg)	Animals per group (M/F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Rat[Crl:CD® (SD)IGS BR]	Embryo-Fetal Development	Oral (gavage) (80 mM sodium citrate buffer) Gestation Days 6 to 15	0 2.5 5 10 20	F22	Embryolethality with associated decreases in litter size were observed at all doses, and fetal skeletal alterations were observed at 2.5 and 5 mg/kg/day; there were no surviving fetuses at 10 or 20 mg/kg/day. Maternal toxicity was observed at doses ≥ 10 mg/kg/day; mortality occurred at 20 mg/kg/day.	DN04078 (GLP) 59
New Zealand White Rabbit Hra:(NZW) SPF	Range Finding Study in Pregnant Rabbits	Oral (gavage) (80 mM sodium citrate buffer) Gestation Days 7 to 19	GD 7 through 9: 0.5, 2, 5, 4 GD 10 through 19: 1, 3, 6, 10	F7	No drug related changes at 1 and 3 mg/kg/day. At 6 and 10 mg/kg/day, reductions in maternal body weight gain and/or loss, and decreased food consumption. At 10 mg/kg/day, embryolethality with associated decreases in litter size.	DN04062/ (non-GLP) 60
New Zealand White Rabbit Hra:(NZW) SPF	Embryo-Fetal Development	Oral (gavage) (80 mM sodium citrate buffer) Gestation Days 7 to 19	0 0.5 2 6	F27	Fetal skeletal alterations were observed at all doses. Neither embryolethality nor maternal toxicity were observed.	DN04080 (GLP) 61

Table E: Toxicokinetics: Overview of Toxicokinetics Studies

Type of Study	Test System (Species / strain)	Method of Administration	Doses (mg/kg)	AUC (ng•h/mL)	Study No. (GLP Status) Ref. No.
2-week exploratory	Rat	Oral	1, 15, 30	51 - 5,111	DS02047 (non-GLP)[46]
1-month toxicity	Rat	Oral	0.9, 15, 25	34 - 1,737	DS02158 (GLP)[48]
6-month toxicity	Rat	Oral	1.5, 4, 15/10/8[a]	48 - 1,355	DS03072 (GLP)[49]
Single dose toxicity	Monkey	Oral	15, 25, 45	2,225 - 8,745	DS02147 (GLP)[45]
10-day exploratory	Monkey	Oral	1, 10, 15, 25, 62,5	29 - 1,654	DS02062 (non-GLP)[51]
1-month toxicity	Monkey	Oral	1, 5, 15	17 - 1,162	DS02159 (GLP)[52]
9-month toxicity	Monkey	Oral	1, 3/2, 10/6/4.5[b]	54 - 949	DS03073 (GLP)[54]
Embryofetal Development	Rat	Oral	2.5, 5, 10, 20	105 - 1490	DN04078 (GLP)[59]
Embryofetal Development	Rabbit	Oral	0.5, 2, 6	44 - 834	DN04080 (GLP)[61]
Single-dose toxicokinetic study	Rat	Oral	1.5, 4, 15	Dasatinib: 63 - 2,270 BMS-582691[c]: 18 - 108 BMS-748730[c]: 10 - 17 BMS-749426[c]: 9	DS06058 (non-GLP)

Table E: Toxicokinetics: Overview of Toxicokinetics Studies

Type of Study	Test System (Species / strain)	Method of Administration	Doses (mg/kg)	AUC (ng•h/mL)	Study No. (GLP Status) Ref. No.
Single-dose toxicokinetic study	Monkey	Oral	1, 3, 10	Dasatinib: 34 - 1,060 BMS-582691[d]: 8 - 114 BMS-748730[d]: 16 - 18 BMS-749426[d]: 9 - 12	DS06059 (non-GLP)

[a] In surviving animals, the high dose was lowered from 15 to 10 mg/kg/day in Week 8 and then to 8 mg/kg/day in Week 17.

b The high dose was lowered from 10 to 6 mg/kg/day in Week 3 and then to 4.5 mg/kg/day in Week 12; toxicokinetics were not assessed at 6 mg/kg/day. The intermediate dose was lowered from 3 to 2 mg/kg/day in Week 28.

c The concentrations of BMS-582691, BMS-748730, and BMS-749426 following administration of dasatinib at 1.5 or 4 mg/kg were below the lower limit of quantification.

d The concentrations of BMS-582691 following administration of dasatinib at 1 mg/kg , and of BMS-748730 and BMS-749426 following administration of dasatinib at 1 or 3 mg/kg, were below the lower limit of quantification.

Appendix 2: Safety Pharmacology

2 page(s) excluding cover page

Appendix 2: Safety Pharmacology

Systems Evaluated	Species / Strain	Method of Administration; Dose	Animals per Group (M/F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Receptors, ion channels, and enzyme systems	*in vitro*	10 μM	NA	Dasatinib had no biologically significant effect on the binding of any receptor or ion-channel ligands evaluated (≤ 46% inhibition) and no effect on acetylcholinesterase activity (< 10% inhibition).	DS03027 (non-GLP) 67
Human embryonic kidney cell stably transfected with the human hERG channel	*in vitro*	0, 3, 10, 30 μM	NA	Dasatinib inhibited IKr currents by 6.1 ± 1.2%, 36.5 ± 6.3% and 76.8 ± 4.5% (n=3) at 3, 10 and 30 μM, respectively. The calculated IC_{50} was 14.3 μM.	[None]/ (non-GLP) 69
Rabbit Purkinje fibers	*in vitro*	0, 3, 10, 30 μM	NA	Dasatinib prolonged APD_{50} (action potential duration) by 26 ± 5% and APD_{90} by 11 ± 0% at 30 μM.	[None]/ (non-GLP) 69
Cardiovascular	Monkey / Cynomolgus	Oral / gavage: 0, 10 mg/kg	M3, F3	There were no drug-related changes in ECG morphology or QT intervals There were minimal, drug-related increases in systolic (5 to 15%) and diastolic (8 to 21%) blood pressure for approximately 2 hours following a single oral dose of 10 mg/kg dasatinib when compared to vehicle control.	DS03098/ (GLP) 71

Appendix 2: Safety Pharmacology

Systems Evaluated	Species / Strain	Method of Administration; Dose	Animals per Group (M/F)	Noteworthy Findings	Study No. (GLP Status) Ref. No.
Metabolite Studies					
Receptors, ion channels, and enzyme systems	*in vitro*	BMS-573188, BMS-606181, and BMS-582691: 10 μM	NA	Dasatinib, BMS-573188, and BMS-606181 had no biologically relevant effect on binding of any of the ligands to their receptors or ion channels or on any enzyme activities evaluated. BMS-582691 at 10 μM had ≥ 50% effects on 7 of the 34 receptors/channels evaluated (adrenergic β2, non-selective adrenergic α2, non-selective serotonin 5-HT1, serotonin 5-HT1A, norepinephrine transporter, and dopamine transporter receptors, and the sodium channel).	DS05124 (non-GLP) 68
Human embryonic kidney cell stably transfected with the human hERG channel	*in vitro*	BMS-573188: 10, 30 μM BMS-606181: 10, 30 μM and BMS-582691: 3, 10, 30 μM	NA	BMS-573188 inhibited IKr currents by approximately 6 and 11% at 10 and 30 μM; BMS-582691 inhibited IKr currents by 24, 72, and 95% at 3, 10 and 30 μM; and BMS-606181 inhibited IKr currents by 8 and 12% at 10 and 30 μM, respectively.	DT05071/ (non-GLP) 70
Rabbit Purkinje fibers	*in vitro*	BMS-573188, BMS-606181, and BMS-582691: 3, 10, 30 μM	NA	BMS-573188 and BMS-606181 had no biologically relevant effects on APD (action potential duration), whereas BMS-582691 prolonged APD50 and APD90 by 10 and 9%, respectively.	DT05071/ (non-GLP) 70

Appendix 3: Death from SU Cohort

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Appendix 3:
Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Chronic	CA180013-6-13424	20AUG2005	YES	DISEASE	CHRONIC-MYELOGENOUS LEUKEMIA
	CA180013-11-13186	27DEC2005	NO	CARDIOVASCULAR DISEASE	ARRHYTHMIA/CARDIOVASCULAR ARREST
	CA180013-16-13256	14APR2006	NO	INFECTION	CMV PNEUMONIA SEPTIC SHOCK
	CA180013-19-13010	23JUL2005	YES	DISEASE	DISEASE PROGRESSION OF CML, ACCERLERATED PHASE: PNEUMONIA
	CA180013-19-13125	11SEP2005	NO	DISEASE	ACCELERATION OF LEUCEMIA
	CA180013-22-13013	11JAN2006	NO	OTHER	ACUTE RESPIRATORY DISTRESS SYNDROME
	CA180013-38-13124	02JUL2006	NO	DISEASE	PROGRESSION
	CA180013-38-13278	17OCT2005	YES	UNKNOWN	
	CA180013-39-13296	24MAR2006	NO	OTHER	SEPSIS
	CA180013-47-13061	13APR2005	YES	FATAL BLEEDING	CNS BLEED PER SPOUSE REPORT
	CA180013-68-13112	18JUN2006	NO	DISEASE	CHRONIC MYELOID LEUKEMIA
	CA180013-80-13236	15AUG2005	YES	INFECTION	STAPHYLOCCOCUS AUROUS
	CA180013-86-13151	06JUN2005	YES	DISEASE	FAILURE RENAL
	CA180013-105-13336	10SEP2005	NO	CARDIOVASCULAR DISEASE	CARDIOPULMONARY ARREST
	CA180017-128-17047	18FEB2007	YES	OTHER	MULTIORGAN FAILURE
	CA180017-153-17101	17DEC2006	NO	DISEASE	BLAST CRISIS
	CA180034-1-34155	25JUL2006	NO	UNKNOWN	
	CA180034-1-34237	03NOV2006	YES	OTHER	AUTOPSY PENDING. RESULTS ARE FORTHCOMING ACCIDENTIAL OVERDOSE
	CA180034-1-34396	05MAR2006	NO	CARDIOVASCULAR DISEASE	PRE-EXISTING HEART FAILURE (REFACTORY FAILURE)
	CA180034-7-34238	22NOV2006	NO	FATAL BLEEDING	INTRACEREBRAL
	CA180034-7-34264	11FEB2007	NO	UNKNOWN	
	CA180034-7-34266	02JAN2006	YES	CARDIOVASCULAR DISEASE	CARDIAC ARREST

PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/sasprogs_su/dt-l-reason.sas RUN DATE: 01-AUG-2007 13:45

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Appendix 3:
Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Chronic	CA180034-11-34716	28AUG2006	NO	OTHER	IDIOPATHIC PNEUMONIA SYNDROME
	CA180034-17-34706	13SEP2006	NO	DISEASE	CML DISEASE PROGRESSION
	CA180034-19-34445	05OCT2006	NO	DISEASE	CML
	CA180034-22-34022	14SEP2006	NO	OTHER	RELAPSE OF TUBERCULOSIS, LIVER INSUFFICIENCE
	CA180034-22-34513	10DEC2006	NO	DISEASE	CML BLAST CRISIS WITH THROMBOCYTOPENIA SEVERE BLEEDING
	CA180034-27-34372	26MAY2006	NO	INFECTION	SEPSIS DUE TO FEBRILE NEUTROPENIA
	CA180034-34-34362	07DEC2006	NO	OTHER	GRAFT VERSUS HOST DISEASE WITH CYTOPENIA
	CA180034-42-34039	08MAR2007	NO	INFECTION	FUNGIC SEPTICEMIA
	CA180034-54-34443	11NOV2006	NO	OTHER	POST STEM CELL TRANSPLANTATION
	CA180034-62-34718	14APR2006	YES	STUDY DRUG TOXICITY	PULMONARY EDEAM, CHF, NECK PAIN, PLEURAL EFFUSION
	CA180034-74-34074	09MAR2006	NO	DISEASE	CML IN BLASTIC PHASE, DISEASE PROGRESSION. SPECIFY: ACUTE RESPIRATORY FAILURE 2` TO PULMONARY HAEMOR
	CA180034-95-34489	21JUN2006	YES	OTHER	SUICIDE
	CA180034-133-34446	14AUG2006	NO	DISEASE	CHRONIC MYELOID LEUKAMIA
	CA180034-142-34121	24APR2006	YES	STUDY DRUG TOXICITY	NECROSIS COLON
	CA180034-142-34352	10APR2006	YES	FATAL BLEEDING	HEMORRHAGE CNS
	CA180034-144-34059	01SEP2006	NO	INFECTION	PNEUMONIA
	CA180034-144-34631	01APR2006	YES	INFECTION	SEPTIC SHOCK, INFECTIONS COLITIS
	CA180034-149-34416	20AUG2006	NO	INFECTION	E-COLI INFECTION, THE NEUTROPENIA BY BM FIBROSIS NOT TO BE RECOVERED
	CA180034-209-34376	30JUL2006	NO	OTHER	SECONDARY TO STEM CELL TRANSPLANTATION
	CA180034-210-34134	11APR2006	YES	CARDIOVASCULAR DISEASE	CARDIAC INFARCTION

PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/sasprogs_su/dt-l-reason.sas RUN DATE: 01-AUG-2007 13:45

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Chronic	CA180034-210-34139	05AUG2006	NO	DISEASE	LEUKAEMIA EMYELUIDES CHRONICA PROGRESSION
	CA180034-210-34177	23JAN2007	NO	DISEASE	LEUCAEMIA MYELUIDES CHRONICA PROGRESSION
	CA180034-217-34465	03NOV2006	YES	CARDIOVASCULAR DISEASE	1A BIVENTRICULAR FAILURE 1B CORONARY ANTERY ATHEROSCLEROSIS
	CA180034-217-34468	28OCT2006	YES	INFECTION	SEPSIS
	CA180034-224-34298	06MAR2007	YES	UNKNOWN	
	CA180034-225-34635	31JUL2006	YES	DISEASE	PROGRESSION (ACUTE TRANSFORMATION)
Accelerated	CA180002-2-613	30MAY2005	NO	DISEASE	
	CA180002-2-621	11SEP2005	YES	DISEASE	
	CA180005-1-5014	06DEC2005	YES	DISEASE	MYELOID BLAST CRISIS
	CA180005-1-5015	07NOV2005	NO	FATAL BLEEDING	MASSIVE BLEEDING IN THE HEAD
	CA180005-1-5045	29DEC2005	NO	DISEASE	CML BLAST CRISIS, PNEUMONIA
	CA180005-1-5071	08SEP2005	YES	UNKNOWN	
	CA180005-1-5183	22SEP2005	NO	UNKNOWN	
	CA180005-2-5023	16JUN2006	YES	OTHER	PNEUMONIA SECONDARY TO LGL
	CA180005-4-5168	28JUL2006	NO	DISEASE	
	CA180005-7-5105	21AUG2005	YES	DISEASE	RAPID PROGRESSION OF CML
	CA180005-9-5147	17JAN2006	YES	INFECTION	SEPSIS
	CA180005-16-5195	05JUN2006	YES	INFECTION	SEPSIS PELVIC
	CA180005-22-5019	18DEC2005	NO	DISEASE	PROGRESSION OF UNDERLYING DISEASE
	CA180005-23-5099	06NOV2005	NO	DISEASE	CHRONIC MYELOGENOUS LEUKEMIA
	CA180005-24-5166	07APR2006	YES	UNKNOWN	
	CA180005-27-5193	03DEC2005	YES	INFECTION	SEPTIC SHOCK
	CA180005-38-5143	26NOV2005	YES	DISEASE	PROGRESSION

PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/sasprogs_su/dt-l-reason.sas RUN DATE: 01-AUG-2007 13:45

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Accelerated	CA180005-39-5070	08JAN2006	YES	DISEASE	BLAST PHASE
	CA180005-43-5116	30APR2006	NO	DISEASE	PROGRESSION
	CA180005-52-5137	25SEP2005	NO	OTHER	RESPIRATORY INSUFFICIENCY AND CML COMPLICATED
	CA180005-52-5199	27JUL2006	NO	UNKNOWN	
	CA180005-53-5051	15JUN2005	YES	INFECTION	PNEUMONIA (POSSIBLE PNEUMOC CARINII)
	CA180005-54-5098	11SEP2005	NO	UNKNOWN	
	CA180005-56-5178	06SEP2005	YES	INFECTION	PNEUMONITIS
	CA180005-57-5184	06DEC2005	NO	OTHER	GRAFT VS HOST DISEASE, GASTROINTESTINAL BLEED, SEPSIS
	CA180005-69-5025	20AUG2005	NO	INFECTION	PULMONARY INFILTRATES
	CA180005-69-5030	04JUL2005	YES	INFECTION	PULMONARY INFILTRATES
	CA180005-88-5059	18APR2005	YES	OTHER	PULMONARY EMBOLISM
	CA180005-94-5078	11JUN2006	NO	DISEASE	ACCELERATION OF LMC
	CA180005-100-5152	03JUL2005	YES	UNKNOWN	
	CA180005-106-5111	02DEC2005	NO	STUDY DRUG TOXICITY	BONE MARROW FAILURE
	CA180005-112-5141	07JUN2005	YES	OTHER	PULMONARY EDEMA
	CA180005-140-5076	10NOV2005	NO	OTHER	FATAL BLEEDING, CNS BLEEDING
	CA180035-1-35035	22AUG2006	NO	CARDIOVASCULAR DISEASE	CEREBOVASCULAR ACCIDENT
	CA180035-1-35038	06SEP2005	YES	INFECTION	ASPIRATION PNEUMONIA
	CA180035-1-35051	23JAN2006	YES	FATAL BLEEDING	HEMORRHAGE CNS
	CA180035-1-35140	30SEP2006	NO	INFECTION	SEPTIC SHOCK
	CA180035-1-35346	10NOV2006	NO	INFECTION	PNEUMONIA, URINE + YEAST
	CA180035-1-35530	22JAN2007	NO	DISEASE	ACUTE RENAL FAILURE LEADING TO MULTI-ORGAN FAILURE

PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/sasprogs_su/dt-l-reason.sas RUN DATE: 01-AUG-2007 13:45

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Accelerated	CA180035-2-35640	02SEP2006	NO	DISEASE	PROGRESSIVE DISEASE WITH MULTI-ORGAN SYSTEM FAILURE
	CA180035-7-35283	10MAR2007	NO	DISEASE	BLAST PHASE CML
	CA180035-7-35300	13FEB2006	YES	INFECTION	FEBRILE NEUTROPENIA
	CA180035-7-35307	06AUG2006	NO	OTHER	GVHD S/P ALLO BMT
	CA180035-11-35501	22AUG2006	YES	DISEASE	BLAST CRISIS
	CA180035-19-35466	03APR2006	NO	INFECTION	PNEUMONIA-RESPIRATORY FAILURE
	CA180035-20-35094	18JAN2007	NO	INFECTION	CHOLECYSTITIS WITH SEPSIS
	CA180035-20-35606	14MAY2006	NO	DISEASE	CML PROGRESSION
	CA180035-21-35219	07AUG2006	YES	CARDIOVASCULAR DISEASE	CARDIOPULMONARY ARREST
	CA180035-26-35400	22AUG2006	NO	DISEASE	CHRONIC MYELOID LEUKEMIA PROGRESSION
	CA180035-27-35203	05JAN2006	YES	OTHER	STATUS EPILEPTICUS
	CA180035-27-35333	18JAN2006	YES	FATAL BLEEDING	HEMORRHAGIC STROKE
	CA180035-35-35541	10NOV2006	YES	DISEASE	ADENCARCINOMA
	CA180035-39-35608	03JUL2006	YES	OTHER	RESPIRATORY ARREST
	CA180035-40-35120	26SEP2006	NO	DISEASE	CML
	CA180035-42-35004	02MAR2007	NO	INFECTION	SEPTICEMIA
	CA180035-43-35012	22AUG2006	YES	FATAL BLEEDING	CEREBRAL HEMATOMA
	CA180035-47-35407	05JUN2006	NO	DISEASE	CML DISEASE PROGRESSION
	CA180035-56-35322	24JAN2006	YES	INFECTION	PNEUMONIA
	CA180035-62-35402	03OCT2006	NO	DISEASE	CML
	CA180035-62-35418	24JUN2006	YES	DISEASE	CML
	CA180035-68-35119	31DEC2005	YES	DISEASE	CHRONIC MYELOID LEUKEMIA WITH BLAST CRISIS
	CA180035-68-35165	10FEB2006	YES	DISEASE	REFRACTORY CHRONIC MYELOID LEUKEMIA
	CA180035-68-35253	11JUN2006	NO	DISEASE	PROGRESSION OF ACUTE MYELOGENOUS LEUKEMIA

PROGRAM SOURCE: /wwbdm/clin/proj/ca/180/scs01/val/cpp/db_pool/sNDA_120/sasprogs_su/dt-l-reason.sas RUN DATE: 01-AUG-2007 13:45

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Accelerated	CA180035-69-35080	30JAN2006	NO	FATAL BLEEDING	ICH
	CA180035-69-35425	04FEB2007	NO	DISEASE	CHRONIC MYELOID LEUKEMIA PROGRESSIVE DISEASE
	CA180035-69-35601	17JUN2006	YES	INFECTION	PNEUMONIA
	CA180035-80-35123	21NOV2006	NO	DISEASE	ALTERATION OF GENERAL STATUS SEE AE'S C07
	CA180035-80-35147	04JUN2006	YES	DISEASE	PROGRESSION OF DISEASE
	CA180035-84-35249	23OCT2006	NO	INFECTION	SEPSIS
	CA180035-87-35285	25JAN2006	YES	INFECTION	PNEUMONIA
	CA180035-90-35387	09JAN2006	YES	INFECTION	SEPSIS AND PULMONARY INFILTRATE
	CA180035-90-35409	22FEB2007	NO	INFECTION	SEPSIS-MULTIPLE ORGAN FAILURE
	CA180035-94-35003	13JUL2005	YES	INFECTION	SEPTIC SHOCK
	CA180035-94-35018	19FEB2007	NO	OTHER	ACUTE RESPIRAGTORY DISTRESS SYNDROME
	CA180035-99-35058	22FEB2006	NO	DISEASE	BLAST PHASE CML CEREBRAL BLEEDING COAGULAPATHIA
	CA180035-100-35241	14NOV2006	YES	CARDIOVASCULAR DISEASE	CARDIAL INSUFFICIENCY
	CA180035-104-35251	06FEB2006	YES	STUDY DRUG TOXICITY	THE CAUSE OF DEATH WAS PULMONARY INFILTRATE AND PLEURAL EFFUSION. CLOSE INVESTIGATION COULD NOT EXPL
	CA180035-107-35444	16OCT2006	NO	DISEASE	EXTRA MEDULARY INFILTRATION OF CML (MULTIPLE SITES)
	CA180035-118-35311	08AUG2006	NO	INFECTION	PNEUMONIA
	CA180035-118-35314	18AUG2006	YES	FATAL BLEEDING	HEMORRAGE CNS HB03
	CA180035-126-35050	17MAR2007	NO	INFECTION	KLEBSIELLA PNEUMONIAE-CHEST
	CA180035-126-35063	19NOV2005	YES	DISEASE	DISEASE PROGRESSION OF ACCELERATED PHASE CML
	CA180035-128-35304	02FEB2006	YES	FATAL BLEEDING	MASSIVE LUNG BLEEDING

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Accelerated	CA180035-134-35082	14APR2006	YES	DISEASE	DIARRHOEA, ENTERITIS
	CA180035-134-35083	17DEC2005	YES	DISEASE	MYELOID BLAST CRISIS
	CA180035-134-35588	10JUL2006	YES	DISEASE	DISEASE PROGRESSION
	CA180035-138-35620	19MAR2007	YES	OTHER	COMBINATION OF DISEASE+SEPSIS
	CA180035-143-35044	07OCT2005	YES	FATAL BLEEDING	INTRACRANIAL BLEEDING
	CA180035-143-35059	09MAR2006	NO	DISEASE	PROGRESSION OF DISEASE CML
	CA180035-143-35288	08DEC2006	NO	DISEASE	PROGRESSIVE DISEASE
	CA180035-144-35448	20DEC2006	NO	INFECTION	SEPSIS
	CA180035-145-35045	16JUL2006	NO	DISEASE	CML PROGRESSION
	CA180035-146-35074	11SEP2006	NO	OTHER	GRAFT VERSUS HOST POST TRANSPLANT
	CA180035-151-35522	03APR2006	YES	DISEASE	DISEASE PROGRESSION
	CA180035-151-35568	11MAR2006	YES	CARDIOVASCULAR DISEASE	HEMORRAGIC STROKE
	CA180035-187-35277	05DEC2006	YES	CARDIOVASCULAR DISEASE	MYOCARDIAL INFARACTION, HEART FAILURE
	CA180035-187-35328	08SEP2006	NO	FATAL BLEEDING	DISSEMINATED HEMORRHAGIC DIATHESIS
	CA180035-187-35552	12NOV2006	NO	DISEASE	PROGRESSION OF CML
	CA180035-189-35131	02MAR2006	YES	INFECTION	ASPIRATION PNEUMONIA/PULMONARY EDEMA
	CA180035-210-35404	14NOV2006	NO	DISEASE	CML ACCELERATED PHASE, PROGRESSION
	CA180035-225-35337	11MAY2006	YES	UNKNOWN	
Myeloid Blast	CA180002-1-504	19JUN2005	YES	DISEASE	
	CA180002-1-507	15FEB2005	YES	DISEASE	
	CA180002-1-513	03DEC2004	YES	OTHER	DEATH FROM METASTATIC SOLID TUMOR
	CA180002-1-515	24FEB2005	NO	OTHER	BACTERIAL SEPSIS,FUNGAL PNEUMONIA
	CA180002-1-519	15JUL2005	NO	DISEASE	
	CA180002-1-520	30DEC2004	YES	DISEASE	
	CA180002-1-521	08MAY2005	NO	DISEASE	
	CA180002-1-524	02JUN2005	NO	OTHER	CEREBELLAR HEMORRHAGE

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180002-2-603	24DEC2004	YES	DISEASE	
	CA180002-2-614	01FEB2005	YES	DISEASE	
	CA180002-2-616	29JAN2005	YES	DISEASE	
	CA180006-2-6007	25JUL2005	YES	DISEASE	DISEASE PROGRESSION
	CA180006-3-6099	25JAN2006	YES	INFECTION	PNEUMONIA
	CA180006-4-6029	22JUL2005	YES	FATAL BLEEDING	R FRONTAL 1C HEMMORHAGE
	CA180006-4-6037	19APR2005	YES	DISEASE	DISEASE PROGRESSION CML
	CA180006-4-6057	24JUL2005	YES	FATAL BLEEDING	INTRACRANIAL BLEED THROMBOCYTOPENIA SECONDARY TO CML DISEASE PROGRESSION
	CA180006-7-6032	20DEC2005	YES	OTHER	RESPIRATORY FAILURE
	CA180006-10-6123	07AUG2005	YES	OTHER	RENAL FAILURE, HEPATIC FAILURE, RESPIRATORY FAILURE
	CA180006-11-6100	03OCT2005	YES	OTHER	PERICARDIAL EFFUSION
	CA180006-13-6013	24MAY2005	YES	CARDIOVASCULAR DISEASE	ACUTE HEART FAILURE
	CA180006-15-6059	19JUL2006	YES	DISEASE	CNS INVOLVEMENT
	CA180006-18-6061	22JUL2005	YES	DISEASE	CML BLAST CRISIS
	CA180006-19-6068	04MAY2005	YES	FATAL BLEEDING	BRAIN
	CA180006-20-6096	07SEP2005	YES	DISEASE	PROGRESSION OF CML
	CA180006-22-6012	23JAN2006	YES	FATAL BLEEDING	INTRACEREBRAL BLEEDING
	CA180006-22-6028	02APR2005	YES	DISEASE	BLAST CRISIS
	CA180006-23-6014	19APR2005	NO	DISEASE	CML
	CA180006-29-6064	01JAN2006	YES	DISEASE	BLASTIC CRISIS-PROGRESSION OF DISEASE
	CA180006-31-6044	07MAY2005	YES	DISEASE	RELAPSED CML.
	CA180006-31-6093	10JUL2005	YES	DISEASE	PROGRESSIVE BLAST PHASE OF CML
	CA180006-34-6077	20MAR2006	YES	DISEASE	CML BLAST CRISIS
	CA180006-39-6039	12APR2005	YES	DISEASE	CML IN BLAST CRISIS

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180006-42-6020	29MAY2005	YES	DISEASE	DISEASE PROGRESSION
	CA180006-43-6005	25MAR2005	NO	STUDY DRUG TOXICITY	GLOBAL CARDIAC INSUFFICIENCY
	CA180006-44-6006	14SEP2005	NO	DISEASE	BLAST CRISIS
	CA180006-44-6023	12JUL2005	NO	DISEASE	PROGRESSIVE DISEASE
	CA180006-44-6051	11SEP2005	NO	DISEASE	PROGRESSION WITH BRAIN ABCES
	CA180006-51-6081	02OCT2005	NO	INFECTION	PNEUMONIA
	CA180006-51-6084	31JUL2005	YES	INFECTION	SEPSIS
	CA180006-52-6079	06SEP2005	YES	OTHER	DISEASE PROGRESSION/SEPSE/MULTIPLE ORGAN FAILURE
	CA180006-52-6080	31MAY2005	YES	DISEASE	INFECTION - FEBRILE NEUTROPENIA, MULTIPLE ORGAN FAILURE
	CA180006-52-6089	01OCT2005	YES	DISEASE	DISEASE PROGRESSION
	CA180006-53-6050	12NOV2005	YES	DISEASE	REFRACTORY CML-BLACK CRISIS
	CA180006-69-6015	05APR2005	YES	DISEASE	DISEASE PROGRESSION
	CA180006-69-6026	05JUN2005	YES	INFECTION	SEPTICEMIA
	CA180006-69-6027	09APR2005	YES	OTHER	ARDS CAUSED BY TUMOR LYSIS SYNDROME
	CA180006-69-6035	19AUG2005	YES	INFECTION	PULMONARY INFILTRATES AND LIVER MICRO ABSCESS
	CA180006-69-6036	13APR2005	YES	INFECTION	ARDS CAUSED BY WORSENING PNEUMONITIS
	CA180006-69-6067	05SEP2005	YES	DISEASE	DISEASE PROGRESSION OF BLAST CRISIS CML
	CA180006-69-6083	16OCT2005	YES	DISEASE	DISEASE PROGRESSION OF BLAST CRISIS CML
	CA180006-70-6075	21JUN2005	YES	DISEASE	DISEASE PROGRESSION OF MYELOID BLAST PHASE CML
	CA180006-71-6095	07JUN2006	NO	INFECTION	PNEUMONIA, SEPTIC SHOCK
	CA180006-94-6069	02AUG2005	YES	INFECTION	SEPSIS (SEE SAE)
	CA180006-96-6062	01JUL2005	YES	DISEASE	PROGRESSION
	CA180006-96-6066	18AUG2005	YES	DISEASE	CML

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180006-100-6078	04AUG2005	YES	INFECTION	SEPSIS
	CA180006-103-6053	05AUG2005	YES	DISEASE	PROGRESSIVE DISEASE CML
	CA180006-103-6094	26MAY2006	NO	DISEASE	CHRONIC MYOLOID LEUKEMIA
	CA180006-148-6112	16OCT2005	NO	STUDY DRUG TOXICITY	MODERATE PLEURAL EFFUSION
	CA180006-148-6114	13SEP2005	YES	DISEASE	PROGRESSION
	CA180035-1-35040	01DEC2005	NO	DISEASE	CML
	CA180035-1-35043	27JAN2006	NO	DISEASE	LEPTOMENINGEAL DISEASE - PROGRESSION OF CML
	CA180035-1-35079	13OCT2005	YES	FATAL BLEEDING	INTRACRANIAL HEMMORHAGE
	CA180035-1-35153	19MAR2006	NO	DISEASE	CML IN BLAST CRISIS
	CA180035-1-35254	30MAR2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-1-35287	01MAR2006	YES	DISEASE	PROGRESSION DISEASE, LOWER GI HEMMORHAGE
	CA180035-1-35393	12APR2006	NO	DISEASE	CHRONIC MYELOGEROUS LEUKEMIA IN BLAST PHASE
	CA180035-1-35610	03AUG2006	NO	INFECTION	DIFFUSE BILATERAL PNEUMONIA
	CA180035-2-35496	25JUN2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-5-35171	29NOV2005	YES	INFECTION	SEPSIS
	CA180035-5-35205	04FEB2006	NO	DISEASE	PROGRESSIVE DISEASE
	CA180035-5-35280	01SEP2006	NO	OTHER	GVHD WITH PERSISTENT HYPOTENSION LEADING TO RESPIRATORY FAILURE
	CA180035-7-35245	20MAR2007	NO	DISEASE	BLAST PHASE CML
	CA180035-8-35597	11MAY2006	YES	DISEASE	CML BLAST CRISIS PERSISTENT DISEASE
	CA180035-9-35299	03JAN2007	NO	OTHER	DEATH FOLLOW STEM CELL TRANSPLANT COMPLICATIONS
	CA180035-9-35612	14MAR2006	YES	FATAL BLEEDING	INTRACRANIAL HEMORRHAGE
	CA180035-10-35510	01APR2006	YES	DISEASE	RESPIRATORY FAILURE

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180035-15-35445	05NOV2006	NO	DISEASE	PROGRESTION
	CA180035-15-35492	28FEB2006	YES	INFECTION	SEPTIC SHOCK CAUSED BY FEBRILE NEUTROPENIA
	CA180035-15-35516	05JUN2006	YES	DISEASE	CML PROGRESSION
	CA180035-15-35531	12APR2006	YES	OTHER	CEREBRAL LESIONS
	CA180035-19-35386	26MAR2006	YES	INFECTION	PNEUMONIA
	CA180035-19-35529	28DEC2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-22-35046	29SEP2005	YES	DISEASE	IMMUNE SUPPRESSIV DUE TO DISEASE PROGRESSIVE LEADING TO SEPSIS WITH MULTIORGAN FAILURE
	CA180035-22-35106	09FEB2006	NO	DISEASE	LEUCOCYTOSIS
	CA180035-22-35569	23NOV2006	NO	INFECTION	IDIOPATHIC PNEUMONIA SYNDROME AFTER ALLOGENEOUS BONE MARROW TRANSPLANT
	CA180035-23-35342	24FEB2006	YES	DISEASE	CHRONIC MYELOGENOUS LEUKEMIA
	CA180035-23-35636	09JUL2006	NO	DISEASE	PROGRESSIVE CML
	CA180035-27-35481	06JUL2006	NO	DISEASE	MYELOBLASTIC PHASE- CML
	CA180035-31-35442	20MAY2006	NO	INFECTION	ASPERGILLOSIS/PNEUMONITIS
	CA180035-32-35070	22MAR2007	NO	DISEASE	BLAST TRANSFORMATION (AML) OF CML
	CA180035-32-35318	23JAN2006	YES	DISEASE	MYELOID BLAST CRISIS OF CML
	CA180035-33-35415	27FEB2006	YES	INFECTION	RESPIRATORY FAILURE-INTERSTITIAL PNEUMONIA
	CA180035-33-35550	18NOV2006	YES	DISEASE	BLAST CRISIS LEADING TO RENAL FAILURE
	CA180035-34-35487	18NOV2006	YES	DISEASE	CML RELAPSE OF BLAST CRISIS
	CA180035-35-35134	26AUG2006	NO	DISEASE	DISEASE PROGRESSION/BLAST CRISIS.
	CA180035-35-35515	29JUN2006	NO	FATAL BLEEDING	CEREBRAL HAEMATOMA, FOLLOWING FALL
	CA180035-39-35554	28JUL2006	NO	DISEASE	PROGRESSIVE DISEASE
	CA180035-39-35609	25DEC2006	NO	DISEASE	PROGRESSION OF DISEASE

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180035-40-35353	02JAN2006	YES	STUDY DRUG TOXICITY	CARDIO PULMONARY ARREST
	CA180035-42-35086	19JAN2006	YES	DISEASE	PROGRESSION DISEASE OF CML
	CA180035-44-35002	01SEP2005	NO	DISEASE	DISEASE PROGRESSION
	CA180035-44-35579	07MAY2006	NO	DISEASE	PROGRESSIVE DISEASE/ACUTE LYMPHOBLATIC LEUKEMIA)
	CA180035-44-35631	24APR2006	YES	INFECTION	PNEUMOPATHY
	CA180035-53-35148	01JUL2006	YES	DISEASE	DISEASE PROGRESSION
	CA180035-56-35461	15MAY2006	YES	INFECTION	SEPTIC SHOCK
	CA180035-68-35539	29AUG2006	NO	DISEASE	PROGRESSION OF DISEASE
	CA180035-69-35332	20FEB2006	YES	INFECTION	PNEUMONIA
	CA180035-74-35098	07MAR2006	NO	DISEASE	ADULT RESPIRATORY DISTRESS SYNDROME 2` TO HYPERLEUKOCYTOSIS 2` TO LEUKEMIA
	CA180035-74-35145	14MAR2006	YES	DISEASE	CARDIAC-PULMONARY ARREST DUE TO INTRACRANIAL BLEEDING DUE TO CML IN BLASTIC PHASE
	CA180035-74-35365	02OCT2006	NO	DISEASE	INTRACEREBRAL BLEEDING, THROMBOCYTOPENIA SECONDARY TO DISEASE PROGRESSION OF CML
	CA180035-75-35164	24MAR2006	NO	DISEASE	CHRONIC MYELOGENOUS LEUKEMIA
	CA180035-75-35340	02MAY2006	NO	DISEASE	CHRONIC MYELOGENOUS LEUKEMIA
	CA180035-80-35095	27JAN2007	NO	DISEASE	PROGRESSION OF DISEASE
	CA180035-90-35157	22AUG2006	YES	DISEASE	RESPIRATORY FAILURE
	CA180035-90-35178	23APR2006	YES	INFECTION	SEPSIS
	CA180035-95-35010	28AUG2005	YES	FATAL BLEEDING	NTRACEREBRAL HEMATOMAS
	CA180035-96-35006	18JUL2005	YES	STUDY DRUG TOXICITY	CARDIAC ARREST (SEE SAE)
	CA180035-96-35014	17JUL2006	NO	OTHER	GVH
	CA180035-96-35024	16MAY2006	NO	DISEASE	CML PROGRESSION

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Appendix 3:
Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180035-97-35434	14AUG2006	NO	DISEASE	CML
	CA180035-99-35053	15NOV2005	YES	DISEASE	PROGRESSION OF DISEASE
	CA180035-106-35570	12JUL2006	NO	DISEASE	CML BLAST PHASE
	CA180035-116-35483	26OCT2006	YES	DISEASE	CML PROGRESSION
	CA180035-118-35310	04JUN2006	NO	FATAL BLEEDING	CNS HEMORRHAGE
	CA180035-118-35312	17JAN2006	YES	STUDY DRUG TOXICITY	CNS HEMORRHAGE
	CA180035-118-35472	28MAY2006	NO	DISEASE	CML PROGRESSION
	CA180035-123-35293	13SEP2006	NO	DISEASE	CML RISING BLASTS
	CA180035-123-35426	26MAY2006	YES	DISEASE	RELAPSE OF PLASTIC PHASE, CARDIAC FAILURE
	CA180035-123-35427	04AUG2006	YES	FATAL BLEEDING	SPLENIC RUPTURA
	CA180035-123-35463	08APR2006	YES	CARDIOVASCULAR DISEASE	ACUTE CARDIAC INSUFFICIENCY
	CA180035-128-35360	31DEC2005	YES	DISEASE	MULTIORGAN FAILURE DUE TO THE PROGRESSION
	CA180035-134-35096	13MAY2006	YES	DISEASE	PROGRESSIVE DISEASE WITH BONE MARROW FAILURE AND SEVERE ANEMIA
	CA180035-134-35471	07SEP2006	YES	DISEASE	PROGRESSIVE DISEASE - BLAST CRISIS
	CA180035-135-35451	21FEB2006	YES	INFECTION	PNEUMONIA
	CA180035-140-35016	08DEC2005	YES	CARDIOVASCULAR DISEASE	VENTRICULA FIBRILATION
	CA180035-140-35034	28AUG2005	YES	DISEASE	BLAST CRISIS
	CA180035-143-35027	13MAR2007	NO	DISEASE	DISEASE PROGRESSION
	CA180035-143-35336	02APR2006	NO	DISEASE	PROGRESSIVE CML WITH CNS INVOLVEMENT
	CA180035-143-35395	25OCT2006	NO	DISEASE	PROGRESSIVE DISEASE.
	CA180035-143-35507	15FEB2007	NO	DISEASE	DISEASE PROGRESSION
	CA180035-143-35508	16MAY2006	NO	INFECTION	PROGRESSION OF PNEUMONIA
	CA180035-143-35518	30SEP2006	NO	DISEASE	CML-BLAST CRISIS
	CA180035-143-35575	28APR2006	YES	INFECTION	PNEUMONIA

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Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Myeloid Blast	CA180035-145-35036	18DEC2005	NO	DISEASE	PROGRESS OF CML
	CA180035-145-35042	04OCT2005	YES	DISEASE	PROGRESS OF CML
	CA180035-145-35184	09JAN2006	YES	INFECTION	MULTI ORGAN FAILURE DUE TO SEPTIC SHOCK
	CA180035-151-35523	17APR2006	YES	DISEASE	DISEASE PROGRESSION
	CA180035-196-35281	08FEB2006	NO	DISEASE	PROGRESSION OF DISEASE
	CA180035-198-35643	11OCT2006	YES	DISEASE	ACUTE CALL BLAST CRISIS
	CA180035-205-35135	04NOV2006	NO	DISEASE	LEUKEMIA
	CA180035-205-35491	17FEB2006	YES	CARDIOVASCULAR DISEASE	CONGESTIVE HEART FAILURE
	CA180035-208-35252	14JUL2006	NO	INFECTION	VISCENAL TUBERCULOSIS
	CA180035-209-35411	25SEP2006	NO	DISEASE	PROGRESSION OF THE DISEASE
	CA180035-214-35488	09OCT2006	YES	DISEASE	BLAST CRISIS OF CHRONIC MEYLOID LEUKAEMIA
Lymphoid Blast/ALL	CA180002-1-522	20JAN2005	YES	DISEASE	
	CA180002-1-526	11MAR2005	YES	DISEASE	
	CA180002-2-605	28FEB2005	NO	DISEASE	
	CA180002-2-606	01MAR2005	NO	OTHER	MASSIVE BRAIN HEMORRHAGE WHILE UNDERGOING CHEMO
	CA180002-2-609	08JAN2005	YES	DISEASE	RELASPED DISEASE COMPLICATED BY KLEBSIELLA SEPSIS,RESP.FAILURE,ARF,& DIC
	CA180002-2-620	08MAR2005	YES	DISEASE	
	CA180015-1-15058	30SEP2005	NO	DISEASE	PROGRESSION
	CA180015-2-15014	10JUN2005	NO	DISEASE	CML
	CA180015-4-15021	15DEC2005	NO	DISEASE	PROGRESSIVE DISEASE
	CA180015-4-15057	14JUL2005	YES	DISEASE	CML - CNS PROGRESSION

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Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180015-5-15095	15DEC2005	YES	DISEASE	PROGRESSION OF PHILADELPHIA CHROMOSONE (+) ALL
	CA180015-7-15068	03JUN2005	YES	OTHER	RESPIRATORY FAILURE
	CA180015-10-15081	29OCT2005	NO	OTHER	SEPSIS SECONDARY TO BACTEREMIA
	CA180015-11-15100	04SEP2005	YES	DISEASE	CNS BLEED/SEIZURE
	CA180015-13-15011	27OCT2005	YES	OTHER	SUSPECTED CNS PROGRESSION
	CA180015-13-15048	22MAY2005	YES	OTHER	HYPOXIA AND PLEURAL EFFUSION
	CA180015-13-15094	06SEP2005	NO	FATAL BLEEDING	PULMONARY HEMORRAGE
	CA180015-15-15056	26JUN2005	YES	FATAL BLEEDING	CEREBRAL HEMORRAGE
	CA180015-15-15063	28JUL2005	YES	DISEASE	PH-POSITIVE ALL
	CA180015-18-15006	01MAY2005	YES	INFECTION	SEPTIC CHOCK
	CA180015-19-15033	11APR2005	YES	INFECTION	STAPHYLOCOCCAL SEPSIS
	CA180015-21-15019	25JUN2005	NO	INFECTION	SEPSIS
	CA180015-21-15027	26FEB2006	NO	DISEASE	DISEASE PROGRESSION
	CA180015-21-15032	05AUG2005	NO	DISEASE	PROGRESSIVE DISEASE
	CA180015-21-15034	30NOV2005	NO	OTHER	LEUKOENCEPHALITIS (AFTER STEM CELL TRANSPLANTATION)
	CA180015-21-15036	15MAY2005	YES	DISEASE	DISEASE PROGRESSION
	CA180015-21-15043	18MAY2005	YES	INFECTION	SEPTIC SHOCK
	CA180015-21-15061	30DEC2005	NO	DISEASE	DISEASE PROGRESSION
	CA180015-21-15064	28JUN2005	NO	DISEASE	PROGRESSION OF ALL
	CA180015-21-15093	24AUG2005	NO	INFECTION	SEPSIS
	CA180015-22-15070	31AUG2005	YES	DISEASE	
	CA180015-22-15099	15OCT2005	NO	DISEASE	PROGRESSIVE ALL WITH SEPSIS, SUSPECTED ABDOMINAL FOCUS, NO AUTOPSY DONE
	CA180015-23-15085	08DEC2005	NO	OTHER	VENO-OCCLUSIVE DISEASE
	CA180015-23-15091	10AUG2006	NO	DISEASE	PH+ ALL

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180015-24-15101	04AUG2005	YES	DISEASE	ACUTE LYMPHCYTIC LEUKEMIA
	CA180015-31-15040	18AUG2005	YES	FATAL BLEEDING	PROBABLE INTRACRANIAL HEMORRAGE
	CA180015-38-15049	29APR2005	YES	DISEASE	CNS INFILTRATION
	CA180015-39-15050	12MAY2006	NO	DISEASE	CML LYMPHOID BLAST CRISIS
	CA180015-42-15001	24JUL2005	YES	INFECTION	SEPTIC SHOCK RELATED TO DISEASE PROGRESSION AND PANCYTOPENIA
	CA180015-43-15074	20OCT2005	NO	DISEASE	PROGRESSIVE DISEASE
	CA180015-44-15002	18FEB2005	YES	DISEASE	PROGRESSION
	CA180015-44-15003	16FEB2005	YES	DISEASE	PROGRESSION
	CA180015-44-15004	26MAY2005	YES	INFECTION	SEPTIC SHOCK
	CA180015-44-15009	19MAR2005	YES	INFECTION	SEPTIC CHOC + COLLITIC INFECTION
	CA180015-44-15025	20APR2005	YES	OTHER	DOMAGE GENERAL STATUS
	CA180015-44-15059	25DEC2005	NO	DISEASE	PROGRESSIVE DISEASE/COMA
	CA180015-45-15016	14MAR2005	YES	INFECTION	SUSPECTED PULMONARY ASPERGILLOSIS
	CA180015-47-15008	10MAR2005	YES	INFECTION	SEPSIS
	CA180015-51-15077	30OCT2005	NO	INFECTION	SEPTIC SHOCK
	CA180015-52-15053	18SEP2005	NO	OTHER	INTRACRANIUM HYPERTENSIVE SYNDROME
	CA180015-52-15086	11NOV2005	YES	DISEASE	DISEASE PROGRESSION
	CA180015-53-15023	10APR2005	YES	INFECTION	PNEUMONIA PLEURAL EFFUSION
	CA180015-53-15030	07JUL2005	YES	DISEASE	PROGRESSIVE DISEASE (LYMPHOID BLAST CRISIS)
	CA180015-56-15066	01FEB2006	YES	INFECTION	SEPSIS (RESULTING IN MULTI ORGAN FAILURE)
	CA180015-70-15078	14JUN2005	YES	OTHER	CONSTRICTIVE PERICARDITIS
	CA180015-96-15075	20MAR2006	NO	DISEASE	CML PROGRESSION
	CA180015-102-15022	11APR2005	YES	DISEASE	ACUTE LEUKEMIA
	CA180015-103-15028	30NOV2005	NO	DISEASE	PROGRESSIVE DISEASE

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Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180015-140-15044	05MAY2005	YES	INFECTION	ASPARGILLUS INFECTION CAUSING RESPIRATORY FAILURE
	CA180015-140-15069	01SEP2005	YES	FATAL BLEEDING	PULMONARY BLEEDING DUE TO PULMONARY INFECTION
	CA180035-1-35048	31OCT2005	NO	DISEASE	CML BLAST CRISIS
	CA180035-1-35078	28FEB2006	YES	DISEASE	PROGRESSIVE CML IN BLAST PHASE
	CA180035-1-35183	15FEB2006	YES	DISEASE	PROGRESSIVE DISEASE, PERSISTENT BLASTS, MULTIORGAN FAILURE
	CA180035-1-35450	17FEB2006	YES	DISEASE	ALL
	CA180035-2-35185	18APR2006	NO	OTHER	RESPIRATORY FAILURE
	CA180035-2-35563	01JUN2006	NO	UNKNOWN	
	CA180035-5-35499	22MAY2006	YES	INFECTION	SEPSIS
	CA180035-7-35250	12JAN2006	YES	INFECTION	CENTRAL NERVOUS SYSTEM PRESUMED INFECTION
	CA180035-7-35412	05OCT2006	NO	DISEASE	RELAPSED ALL
	CA180035-7-35470	04JUN2006	NO	OTHER	COMPLICATIONS AFTER BONE MARROW TRANSPLANT
	CA180035-7-35594	13APR2006	YES	INFECTION	PNEUMONIA
	CA180035-8-35166	17FEB2006	NO	DISEASE	PH+ ALL
	CA180035-8-35477	14DEC2006	NO	DISEASE	ALL
	CA180035-10-35192	30APR2006	NO	OTHER	GRAFT VERSUS HOST DISEASE
	CA180035-10-35459	01OCT2006	NO	DISEASE	PATIENT REMOVED FROM ALL CML TREATMENT
	CA180035-10-35469	26APR2006	YES	INFECTION	SEPSIS
	CA180035-11-35351	03JAN2006	YES	INFECTION	VRE AND RSV
	CA180035-11-35454	16APR2006	NO	DISEASE	PROGRESSIVE LYMPHO BLASTIC LEUKEMIA
	CA180035-11-35593	12MAY2006	YES	DISEASE	BLAST CRINI CML

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Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180035-13-35364	28APR2006	NO	OTHER	HEPATIC GVHD
	CA180035-13-35432	22JUL2006	YES	DISEASE	DISEASE PROGRESSION
	CA180035-13-35441	27FEB2007	NO	DISEASE	ACUTE RENAL FAILURE
	CA180035-15-35613	12APR2007	NO	DISEASE	DISEASE PROGRESSION
	CA180035-18-35323	08AUG2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-21-35025	20SEP2005	YES	FATAL BLEEDING	INTRACEREBRAL BLEEDING
	CA180035-21-35084	30OCT2006	NO	FATAL BLEEDING	PULMONARY BLEEDING
	CA180035-21-35125	08MAY2006	YES	INFECTION	SEPSIS
	CA180035-21-35151	06FEB2006	NO	DISEASE	PROGRESSION
	CA180035-21-35158	19JAN2006	YES	DISEASE	PROGRESSION
	CA180035-21-35268	12APR2006	NO	INFECTION	CIRCULATORY AREST DUE TO SEPSIS
	CA180035-21-35376	08APR2006	NO	DISEASE	PROGRESSION
	CA180035-21-35480	07OCT2006	NO	DISEASE	MULTIPLE ORGAN FAILURE
	CA180035-21-35543	26SEP2006	NO	INFECTION	PNEUMONIA
	CA180035-21-35553	10MAY2006	NO	DISEASE	PROGRESSION
	CA180035-21-35576	24JUL2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-23-35571	16MAR2006	YES	OTHER	ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) SECONDARY TO POSSIBLE PNEUMONIA AND FLUID OVERLOAD
	CA180035-27-35592	30JUL2006	NO	DISEASE	RELAPSE REFRACTORY ALL
	CA180035-30-35195	23APR2006	NO	DISEASE	PHILADELPHIA CHROMOSOME POSITIVE ALL
	CA180035-30-35595	21SEP2006	YES	FATAL BLEEDING	GI BLEED SECONDARY TO ISCHEMIC COLITIS
	CA180035-31-35607	30MAY2006	NO	DISEASE	ACUTE LYMPHOBLASTIC LEUKEMIA
	CA180035-34-35420	27SEP2006	NO	INFECTION	PNEUMONIA
	CA180035-35-35111	08NOV2005	YES	OTHER	RESPIRATORY FAILURE
	CA180035-35-35187	23MAY2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-43-35007	31MAR2006	NO	DISEASE	DISEASE PROGRESSION (CML)

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Death from SU Cohort

Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180035-43-35022	17NOV2005	YES	FATAL BLEEDING	ENCEPHALOMALACIA AND ISCHEMIA
	CA180035-43-35069	07MAY2006	NO	INFECTION	SEPTICEMIA
	CA180035-44-35072	27JAN2006	NO	DISEASE	STROKE DUE TO THE CNS PROGRESSION OF THE ACUTE LYMPHOTIC LEUKEMIA
	CA180035-44-35535	29NOV2006	NO	DISEASE	NEUROMENINGEAL RELAPSE
	CA180035-46-35359	13JUN2006	NO	DISEASE	ACUTE LYMPHOBLASTIC LEUKAEMIA
	CA180035-46-35383	21NOV2006	NO	DISEASE	PH + VE ACUTE LYMPHOBLASTIC LEUKAEMIA
	CA180035-47-35396	20MAR2006	NO	DISEASE	DISEASE PROGRESSION
	CA180035-51-35331	19MAY2006	NO	INFECTION	SEPTIC SHOCK AFTER STEM CELL TRANSPLANTATION
	CA180035-55-35294	02APR2007	NO	OTHER	GRAFT-VERSUS-HOST DISEASE
	CA180035-56-35255	09DEC2006	NO	UNKNOWN	
	CA180035-69-35503	13MAY2006	YES	INFECTION	PNEUMONIA
	CA180035-70-35410	31MAY2006	NO	DISEASE	PNEUMONIA AND PROGRESSIVE ALL
	CA180035-74-35089	05FEB2006	NO	DISEASE	CHRONIC MYELEGENONS LEUKEMIA IN BLASTIC CRISIS - DISEASE PROGRESSION
	CA180035-75-35548	07MAY2006	YES	DISEASE	ACUTE LYMPHOBLASTIC LEUKEMIA
	CA180035-76-35324	15APR2006	NO	INFECTION	E COLI SEPSIS, VANCOMYCIN - RESISTANT ENTEROCOCCI PNEUMONIA
	CA180035-79-35173	18FEB2006	NO	DISEASE	PH+ VC ALL
	CA180035-80-35416	03OCT2006	NO	DISEASE	PROGRESSION OF DISEASE
	CA180035-84-35284	27APR2006	NO	INFECTION	ENTEROCOCCUS FAECIUM SEPSIS
	CA180035-84-35327	19JAN2006	YES	DISEASE	ALL
	CA180035-92-35486	18JUN2006	NO	UNKNOWN	
	CA180035-93-35493	12MAR2006	YES	CARDIOVASCULAR DISEASE	CARDIOPULMONARY ARREST
	CA180035-96-35019	05JUL2006	NO	DISEASE	CML PROGRESSION
	CA180035-96-35066	13MAR2006	NO	DISEASE	CML PROGRESSION

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Disease Group	Subject	Date of Death	Within 30 Days of Last Dosing?	Cause of Death	Cause of Death Specify
Lymphoid Blast/ALL	CA180035-96-35558	23OCT2006	YES	DISEASE	CML (LYMPHOID BLAST PHASE) PROGRESSION
	CA180035-101-35384	05FEB2006	YES	INFECTION	SUSPECTED SEPTICEMIA
	CA180035-103-35092	27JUL2006	NO	INFECTION	SEPSIS
	CA180035-103-35230	25FEB2006	NO	DISEASE	PROGRESSION OF ALL
	CA180035-106-35462	09DEC2006	NO	CARDIOVASCULAR DISEASE	POSSIBLE STROKE
	CA180035-118-35309	14JAN2007	NO	DISEASE	CML PROGRESSION
	CA180035-120-35378	30JAN2006	YES	DISEASE	CML PROGRESSION
	CA180035-124-35226	26AUG2006	NO	DISEASE	WORSENING OF DISEASE
	CA180035-140-35015	27DEC2005	NO	OTHER	PULMONARY INFILTRATE AND SEPSIS
	CA180035-140-35099	02NOV2005	YES	DISEASE	LYMPHOID BLASTS CRISIS WITH CNS INVOLVED
	CA180035-143-35172	08JUN2006	YES	DISEASE	PROGRESSION OF CML
	CA180035-144-35372	25OCT2006	NO	INFECTION	SEPSIS
	CA180035-144-35447	16MAR2006	YES	DISEASE	PROGRESSIVE DISESASE WITH RISING % BLOOD IN BM
	CA180035-150-35616	26MAY2006	YES	FATAL BLEEDING	PULMONARY HEMORRHAGE
	CA180035-174-35398	07NOV2006	NO	DISEASE	PDLMC BLASTIC MENINGITIS
	CA180035-187-35238	23APR2006	NO	DISEASE	PROGRESSION OF CML
	CA180035-188-35269	05OCT2006	YES	INFECTION	SEPTIC SHOCK
	CA180035-188-35292	21NOV2006	YES	INFECTION	PNEUMONIA
	CA180035-196-35271	28MAR2006	YES	DISEASE	LYMPHOBLASTIC DISEASE PROGRESSION
	CA180035-209-35506	05MAY2006	YES	DISEASE	PROGRESSION OF DISEASE
	CA180035-214-35468	19APR2006	YES	DISEASE	BLAST CRISIS OF CML

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Appendix 4: Expected Adverse Events (including Serious Adverse Events)

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Appendix 4: Expected Adverse Events (including Serious Adverse Events)

System Organ Class	Preferred Term or Lower Level Term
Blood and lymphatic system disorders	Pancytopenia (fatal), leukopenia, febrile neutropenia (fatal), aplasia pure red cell, anemia (life-threatening), thrombocytopenia (life-threatening), coagulopathy, disseminated intravescular coagulopathy (fatal), bone marrow depression/failure (fatal)
Cardiac disorders	Congestive heart failure (fatal), cardiac failure/insufficiency (fatal), congestive cardiomyopathy (fatal), cardiac dysfunction, ventricular dysfunction, diastolic dysfunction, ventricular hypokinesia, dyspnoea exertional, cardiomegaly, cardiomyopathy, cardiac arrest (fatal), cardiopulmonary arrest, myocarditis, pericarditis, constrictive pericarditis (fatal), pericardial effusion (fatal), cardiac tamponade (fatal), arrhythmia, tachycardia, nodal rhythm, supraventricular /ventricular arrhythmia, ventricular tachycardia, atrial fibrillation, atrial flutter, palpitations, myocardial infarction, angina pectoris, angina unstable, acute coronary syndrome, chest discomfort/heaviness, cardiogenic shock (fatal), cor pulmonale
Ear and labyrinth disorders	Tinnitus, vertigo
Eye disorders	Dry eye, conjunctivitis, keratoconjunctivitis sicca, visual disorder (including blurred vision, visual acuity reduced)
Endocrine disorders	Diabetes insipidus
Gastrointestinal disorders	Diarrhoea, nausea, vomiting (life-threatening), abdominal pain, abdominal discomfort/distention, flatulence, mucosal inflammation (including mucositis/aphthous stomatitis), mouth/tongue ulceration, diverticulitis, colitis (including neutropenic colitis [fatal], colitis ulcerative), large intestinal ulcer, rectal haemorrhage, rectal ulcer, proctitis, anal fissure, anal ulcer, upper gastrointestinal ulcer, duodenitis, duodenal ulcer, duodenal ulcer haemorrhage (life-threatening), gastritis, gastritis erosive, caecitis/typhlitis, gastric disorder, gastritis haemorrhagic, gastric haemorrhage, gastrointestinal haemorrhage (fatal), dyspepsia, esophagitis, dysphagia, constipation, hemorrhoids, pancreatitis, oral soft tissue disorder, gingivitis, gingival haemorrhage, ascites, ileus, gastroesophageal reflux disease, GI perforation (fatal), intestinal necrosis (fatal)
General disorders and administration site conditions	Superficial oedema, peripheral oedema, generalized/localized oedema, pyrexia, temperature intolerance, chills, fatigue, asthenia, malaise, pain, chest pain, influenza like illness, serositis
Hepatobiliary disorders	Hepatitis, cholecystitis, cholestasis, jaundice
Immune system disorders	Hypersensitivity (including erythema nodosum), anaphylactic shock (life threatening)

Infections and infestations	Opportunistic infections (fatal) (including bacterial, viral, fungal, non-specified), upper respiratory tract infection/inflammation, pneumonia (fatal) (including bacterial, viral and fungal), bronchopneumonia, crytogenic organizing pneumonia, bronchiolitis obliterans with organizing pneumonia, infectious pneumonitis, infective myositis, cytomegalovirus colitis, enterocolitis infection, cystitis, meningoencephalitis/encephalitis (fatal), pharyngolaryngeal abscess, liver abscess (fatal), herpes virus infection, herpes zoster infection neurological, gastroenteritis cryptosporidial, pyoderma gangrenosum, cellulitis, sepsis/septic shock (fatal), ascites infection, endocarditis infective (fatal), infectious colitis/enterocolitis (fatal), colitis pseudomembranous
Injury, poisoning, and procedural complications	Contusion
Investigations	Weight decreased, weight increased, ejection fraction (EF) decreased (fatal), cardiac enzymes increased, troponin I and T increased, blood creatine phosphokinase (CPK) increased, QT prolongation, liver function test abnormal, blood creatinine increased, elevated SGPT (ALT), elevated SGOT (AST), elevated bilirubin, platelet aggregation abnormal, hypocalcaemia, hypophosphataemia, hypothyroidism, hypokalemia, hypomagnesemia, hyponatremia, lipase increased
Metabolism and nutrition disorders	Anorexia, appetite disturbances (decreased or increased appetite), fluid retention, fluid overload, hypoalbuminaemia, hyperuricaemia, dehydration
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, neck pain, back pain, musculoskeletal chest pain, arthralgia, joint effusion, myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle inflammation, myopathy, myositis, rhabdomyolysis, tendonitis, tenosynovitis, avascular necrosis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Tumor lysis syndrome (fatal), lymphoma, anal cancer
Nervous system disorders	Headache, dizziness, syncope, neuropathy (including peripheral), dysgeusia, ageusia, amnesia, somnolence, lethargy, cerebrovascular accident, transient ischaemic attack, extrapyramidal symptoms, CNS haemorrhage (fatal) (including intracranial, cerebral/brain, cerebellar haemorrhages), subdural haematoma, extradural/epidural haematoma, cerebral ischaemia, reversible posterior leukoencephalopathy syndrome, convulsion, seizure, tremor, paresthesia, hypoaesthesia, arachnoiditis, demyelinating polyneuropathy, dysphasia
Psychiatric disorders	Depression, depression suicidal, insomnia, affect lability, anxiety, agitation, irritability, confusional state, mental status changes, libido decreased, suicide attempt

Renal and urinary disorders	Renal failure (fatal), urinary frequency, proteinuria, interstitial nephritis
Reproductive system and breast disorders	Menstruation irregular, polymenorrhoea, gynaecomastia, uterine bleeding, spontaneous abortion
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, pleural effusion (fatal), chylothorax, pulmonary oedema (life-threatening), pulmonary hypertension (fatal), hypoxia (fatal), respiratory failure (fatal), acute respiratory distress syndrome (ARDS) (fatal), pneumonitis (fatal), interstitial lung disease (fatal), pulmonary infiltration (fatal), pneumopathy (fatal), bronchitis, bronchospasm, asthma, pulmonary tuberculosis reactivated, pulmonary/respiratory tract haemorrhage (fatal), atelectasis, tachypnea, embolus pulmonary (fatal), pulmonary fibrosis
Skin and subcutaneous tissue disorders	Skin rash, urticaria, urticaria vesiculosa, acne, dermatitis acneiform, dermatitis, eczema, erythema, bullous conditions (including erythema multiforme), skin exfoliation, blister, skin ulcer, skin lesion/nodule, acute febrile neutrophilic dermatosis (sweet syndrome), palmar-plantar erythrodysaesthesia syndrome, photosensitivity reaction, pigmentation disorder, nail disorder, pruritus, dry skin, alopecia, hyperhidrosis, leukocytoclastic vasculitis
Vascular disorders	Haemorrhages (fatal), purpura, gastric ulcer haemorrhage, rectal haemorrhage, haematochezia, haemarthrosis, scleral haemorrhage, shock (fatal), shock haemorrhagic, intra-abdominal haemorrhage, haemarthrosis, flushing, hypotension, hypertension, livedo reticularis, thrombophlebitis, vasculitis, phlebitis