Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dasatinib

Proprietary Product Name: Sprycel

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

July 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major Variation (Extension of Indications)
Decision:	Approved
Date of Decision:	28 April 2011
Active ingredient(s):	Dasatinib
Product Name(s):	Sprycel
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd 556 Princes Hwy, Noble Park North, VIC 3174
Dose form(s):	Tablet
Strength(s):	20, 50, 70 and 100 mg
Container(s):	Bottle, blister pack
Pack size(s):	30s and 60s
Approved Therapeutic use:	For the treatment of adults aged 18 years and over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase.
Route(s) of administration:	Oral (PO)
Dosage:	The starting dose is 100 mg once daily.
ARTG Number (s)	125557, 125558, 125559, 125560, 125561, 125562, 157352 and 157356.

Product Background

Dasatinib is a tyrosine kinase inhibitor (TKI) which inhibits the activity of BCR-ABL, a tyrosine kinase produced by the gene translocation [t(9,22); the Philadelphia (Ph) chromosome] associated with Chronic Myeloid Leukemia (CML) and Ph positive (+) acute lymphoblastic leukaemia (ALL). It is currently registered as a second line agent for these conditions (after failure of prior therapy, including imatinib in CML and failure of 'prior therapy' in Ph+ ALL). The drug was initially approved in 2007 following consideration by the Australian Drug Evaluation committee (ADEC; now called the Advisory Committee for Prescription Medicines (ACPM)) at its December 2006 meeting.

The current application seeks approval for use of the drug in newly diagnosed patients with CML (as first-line therapy). The proposed starting dose is 100 mg once daily, which is the currently approved second line dose for chronic phase CML. The current standard first line treatment for CML is another kinase inhibitor, imatinib (Glivec).

Regulatory Status

The following table (Table 1) provides a summary of the International regulatory status of this product:

Table 1: Sprycel (dasatinib): Treatment of adults with chronic phase (CP) CML, advanced phase (AP) CML, Ph+ ALL resistant or intolerant to imatinib and newly diagnosed CML.

COUNTRY	Status of original submission (second line CML)	Status of supplementary information: Newly Diagnosed CML in chronic phase
US	Approved	Approved 28 Oct 2010 (priority review granted 7 June 2010)
Japan	Approved	Submitted 29 July 2010, still under review
Germany, Italy, UK, Greece, Austria, Spain, Sweden, Ireland, Netherlands, Belgium, Denmark, Finland, Portugal, Luxemburg, Hungary, Poland, Czech Republic, Romania, Bulgaria, Cyprus, Estonia, Lithuania, Latvia, Malta, Slovakia, Slovenia)	Approved	Approved 6 Dec 2010
Switzerland	Approved	Approved 15 Apr 2011
New Zealand	Approved	Approved 10 Mar 2011*
Canada	Approved	Submitted – under review

*Approved indication in New Zealand is for Newly Diagnosed CML.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There were no quality data submitted with this application.

III. Nonclinical Findings

There were no nonclinical data submitted with this application.

IV. Clinical Findings

Introduction

The current Australian application by Bristol-Myers Squibb Pharmaceuticals (BMS; the sponsor) proposes to extend the indications of Sprycel (dasatinib) film coated tablets 20 mg, 50 mg, 70 mg and 100 mg to include "the treatment of adults aged 18 years or over with newly diagnosed chronic myeloid leukaemia (CML)".

Sprycel is currently approved for the treatment of "adults aged 18 years or over with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib", and "the treatment of adults

aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy".

The current Australian submission included one, pivotal, Phase III, multi-national, multi-centred, randomized, open-label, efficacy and safety study [CA180056] in 519 randomized patients with newly diagnosed Philadelphia chromosome (Ph+) chronic myeloid leukemia in the chronic phase (CML-CP). This study compared the effects of dasatinib 100 mg once a day (QD) (n=259) with imatinib 400 mg QD (n=260) on a number of cytogenetic, molecular, haematological and clinical outcomes. The primary efficacy endpoint in this study was the best confirmed complete cytogenic response (cCCyR) rates within 12 months in the dasatinib and imatinib treatment groups. The cCCyR is a surrogate endpoint for long-term clinical benefit and the study included a justification for the use of this endpoint. The study reported results in subjects with a minimum of 12 months of follow-up data. The study is on-going and plans to follow-up subjects for at least 5 years.

The current Australian submission also included one population pharmacokinetic (PK) study with data from 1216 CML and Ph+ ALL subjects from eight studies. Of these subjects, 235 were newly diagnosed CP-CML imatinib naive subjects enrolled in Study CA180056, while the remaining subjects were imatinib experienced. The study compared the PKs of dasatinib in newly diagnosed imatinib naive subjects with CML-CP and imatinib experienced subjects with CML-CP. It also explored the exposure-response relationships between dasatinib and cCCyR (efficacy) and dasatinib and pleural effusion (safety). The relevant data from this study have been evaluated.

The sponsor proposes to investigate the long-term clinical benefit of dasatinib for the treatment of newly diagnosed CML-CP in a prospectively designed meta-analysis pooling the results from more than 1500 adult subjects from three studies. The three studies are the BMS sponsored on-going pivotal Study CA180056 and two ongoing non-BMS sponsored studies from co-operative groups (SPIRIT2 in the United Kingdom (UK) and SWOG 0325 in the USA/Canada). The three studies are Phase III or IIb, multi-national, multi-centred, randomized and open-label in design and compare dasatinib 100 mg QD with imatinib 400 mg QD in adult patients with newly diagnosed CML-CP. The three studies share various endpoints, although the primary endpoints differ. The meta-analysis will be conducted when all three studies have a minimum of 5 years of follow-up data. The pivotal study design and the prospective long-term meta-analysis are stated to have been endorsed by the European Medicines Agency/Committee for Medicinal Products for Human Use (EMEA/CHMP).

At the date of application to the TGA, dasatinib had not been approved for the treatment of newly diagnosed CML-CP in any country. However, submissions had been made to the European Union (EU) (centralized procedure, 16 April 2010) and the USA (28 April 2010) for the same extension of indication. Subsequent to the application to the TGA, extensions of indication of Sprycel to include the treatment of adult patients with Ph+ CML-CP leukaemia were approved by the FDA (28 October 2010) and recommended for approval by the EMEA/CHMP (meeting of 18-21 October 2010).

Good Clinical Practice Aspects

The BMS sponsored studies were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP)[1], the European Union Directive 2001/20/EC[2] and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50)[3], and in accordance with relevant national regulatory and legislative requirements relating to clinical trials. In addition, initial study protocols and subsequent protocol amendments were approved by the relevant Institutional Ethics Committees (IECs) and/or Institutional Review Boards (IRBs) at all participating centres. Written informed consent was obtained from all subjects or, in those situations where consent could not be given by the subject their legally acceptable representatives, prior to study participation.

Orphan Medical Products

Dasatinib has previously been granted orphan drug status by the TGA for the treatment of chronic myeloid leukaemia in patients who are resistant to, or intolerant of imatinib (12 October 2005), and the treatment of Philadelphia-positive acute lymphoblastic leukaemia (Ph+ ALL) (18 January 2006).

Pharmacokinetics

Population Pharmacokinetic Study

Objectives

The submission included one population pharmacokinetic (PPK) and exposure-response (E-R) study provided to support dasatinib for the treatment of patients with newly diagnosed CML-CP. The objectives of this study were: to characterise the PKs of dasatinib in newly diagnosed CML-CP and in imatinib treatment experienced CML patients; to characterise the relationship between dasatinib exposure and confirmed complete cytogenetic response (cCCyR) in newly diagnosed CML-CP patients; and to characterise the relationship between dasatinib exposure and pleural effusion in newly diagnosed and imatinib treatment experienced CML-CP patients

Data

The PPK analysis was performed using data from 8 clinical studies in subjects with all phases of CML or Ph+ ALL. These eight studies included seven with data from subjects resistant to, or intolerant of imatinib, and one in subjects with newly diagnosed CML-CP

[1] ICH Topic E6 (R1). Guideline for Good Clinical Practice: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

[2] www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf

[3] http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?sid=5aeedc221664e582064ded32ce1b3deb&c=ecfr&tpl=/ecfrbrowse/Title21/21tab_02.tpl. Title 21 is the portion of the Code of Federal Regulations that governs food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP). It is divided into three chapters: Chapter I — Food and Drug Administration Chapter II — Drug Enforcement Administration Chapter III — Office of National Drug Control Policy

[CA180056]. The E-R analysis on cCCyR was performed with data from Study CA180056, and the E-R analysis on pleural effusion was performed on combined data from Studies CA180034 and CA180056.

The *PPK analysis* included data on 1216 subjects (51.0% male, 49.0% female) of mean (standard deviation (SD)) age 52.4 (14.5) years who were predominantly Caucasian (76.2%) and had been treated with dasatinib for first line treatment of newly diagnosed CML-CP (19.3% [n=253]) or were imatinib experienced (80.7% [n=981]). The *E-R analysis on cCCyR* included 235 subjects of mean (SD) age 46.2 (14.6) years from Study CA180056 with newly diagnosed CML-CP treated with dasatinib. The majority of subjects received dasatinib 100 mg QD, while the average daily dose varied from 61 mg to 124 mg due to dose reductions or escalations base on tolerability and response. Of the 235 dasatinib-treated subjects with available PK data from CA180056, 78% (n=184) achieved cCCyR during the treatment and 45% (n=106) had dose modifications or interruptions. The *E-R analysis on pleural effusion* included a total of 802 subjects of mean age: 51.4, SD=14.7 from studies CA180034 and CA180056. Of the 802 subjects, 15% (n=117) had reported pleural effusion and 85% (n=685) had no reported pleural effusion.

Methods

The *PPK model* was developed in three stages. First, a base model without covariate effects was developed by re-estimating a previously reported base model supplemented with additional data from CA180056. Second, a full model was developed by incorporating the estimated covariate effect of treatment status (first line imatinib naive and second line imatinib experienced) on the parameters of interest (apparent clearance [CL/F) and apparent distribution volume of the central compartment [VC/F]). Third, the final model was obtained by eliminating those covariate effects in the full model that were not statistically significant or potentially clinically relevant. The differences in dasatinib PKs between imatinib naive and imatinib experienced CML-CP patients were tested in the full model. The models were specified in terms of fixed and random effect parameters estimated by nonlinear regression using the NONMEM® program. The model parameters were estimated using the first-order conditional estimation (FOCE) with interaction method, and model evaluation was conducted by visual and quantitative predictive performance checks.

The *E-R analysis* on cCCyR was characterised by a logistic regression model which was developed in three stages. First, a base model was developed to estimate the effect of dasatinib steady state average concentration ($C_{avg.ss}$) on cCCyR. Second, a full model was developed to incorporate the effect of covariates. Third, the final model was developed by eliminating covariates that were not statistically significant. The model was evaluated by comparing the model predicted probability of cCCyR with observed rate of cCCyR.

The *E-R analysis* on pleural effusion was characterised by a Cox proportional-hazards (CPH) model of the relationship between exposure and the time-to-occurrence of Grade 1+ pulmonary effusion. The CPH model was developed in three stages. First, a base model was developed to estimate the effect of dasatinib steady-state trough concentration ($C_{min.ss}$) on pleural effusion hazard. Second, a full model was developed to incorporate the effect of covariates. Third, the final model was developed by eliminating covariates that were not statistically significant. The CPH model was evaluated by comparing the model

predicted cumulative probability of pleural effusion versus time with that obtained by Kaplan-Meier (KM) analyses.

PPK Analysis - Results

The PPK model of dasatinib was a linear, two-compartment model with first-order absorption. The results showed that the PKs of dasatinib (VC/F and CL/F) were similar in imatinib experienced CML subjects and in newly diagnosed imatinib naive CML-CP subjects. The estimated CL/F was 283 L/h and VC/F was 882 L and the estimated terminal half life was 5.9 hours [range: 5.3, 9.0 hours].

The steady-state exposure parameters ($C_{min.ss}$, steady-state maximal concentration ($C_{max.ss}$), $C_{avg.ss}$, and area under the plasma concentration time curve at steady state (AUC_{ss})) for all subjects in Study CA180056 in the PPK analysis were simulated from the final PPK model (see Table 2, below). The simulation was based on the final PPK model and the nominal dosing regimens for all the 235 dasatinib treated subjects in Study CA180056. The steady-state exposure parameters were subsequently used in the exposure-response analyses of efficacy and safety.

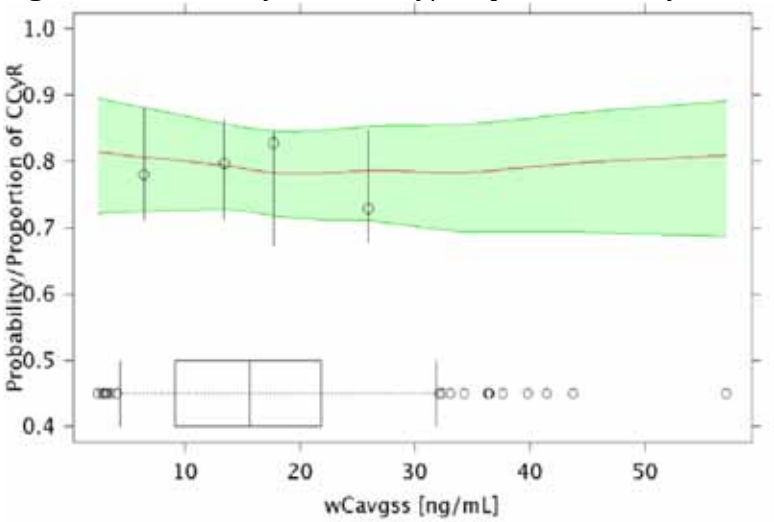
Table 2: PPK Analysis. Mean (CV %) of simulated steady-state exposure parameters for subjects receiving dasatinib 100 mg QD in Study CA180056 (pivotal efficacy and safety study).

	Cmin.ss [ng/mL]	Cmax.ss [ng/mL]	Cavg.ss [ng/mL]	AUCss [ng/mL*hr]
Mean (CV %)	2.00 (70%)	82.2 (69%)	16.5 (55%)	397 (55%)

E-R Analysis CCyR (Efficacy) – Results

The relationship between dasatinib exposure and probability of cCCyR was described by a logistic regression model that included percentage dose interruption duration as a predictor variable. None of the other covariates tested (age, gender and race) were statistically significant predictors of response. Weighted average steady-state concentration ($wC_{avg.ss}$) was the measure of exposure in this analysis. The $wC_{avg.ss}$ of a subject was calculated by averaging the cumulative exposure over the treatment duration (up to the time of cCCyR response, if the subject was a cCCyR responder, or the time of drop-out, if the subject was not a cCCyR responder) in which the subject was taking the active drug. The model showed that the relationship between cCCyR probability and $wC_{avg.ss}$ over the exposure range was not statistically significant (see Figure 1, below).

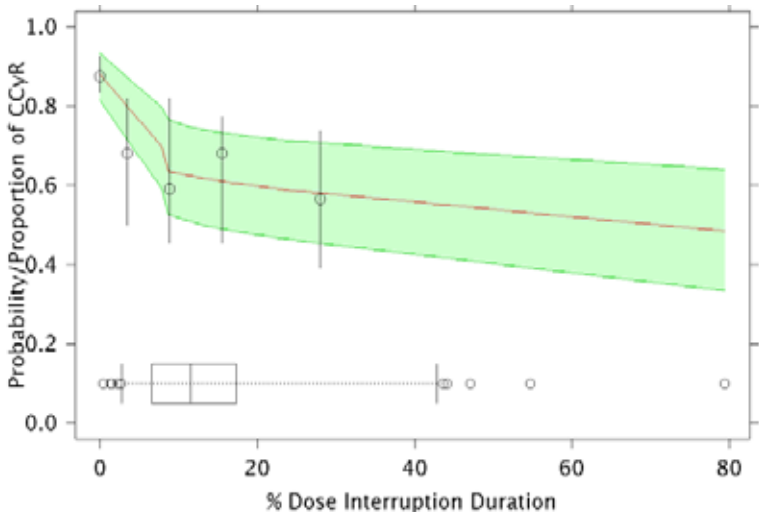
Figure 1: E-R Efficacy. Probability/Proportion of cCCyR versus wCavgss.



Note: Symbols represent the proportion of responders, grouped by quartiles of wCavg.ss and plotted at the median for the groups. Centred curves and shaded area represent median values and 95% confidence interval (CI) of model predicted response probability, respectively. Vertical bars represent 95% model prediction intervals of cCCyR rate grouped by quartiles of wCavg.ss and plotted at the median for the groups. Horizontal box shows the distribution of wCavg.ss: interior bar represents the median, two ends of the box represent the 25th and 75th percentiles, whiskers represent the 5th and 95th percentiles, and points outside the whiskers represent values outlying the 5th and 95th percentiles.

However, the there was a statistically significant relationship between the CCyR and the duration of dose interruption ($p<0.001$). Prolonged dose interruption had a detrimental effect on efficacy, with the probability of cCCyR being lower with increasing duration of dose interruption (see Figure 2, below). The probability of CCyR decreased by 14% for every doubling of dose interruption duration.

Figure 2: E-R Efficacy. Probability/Proportion of cCCyR versus % dose interruption duration.



Note: Symbols in the middle of the plot represent the proportion of responders, grouped by % dose interruption duration (Pintr) of 0 and quartiles of non-zero values of Pintr, plotted at the median Pintr values of the groups. Centred curves and shaded area represent median values and 95% CI of model predicted response probability, respectively. Vertical bars represent 95% model prediction intervals of CCyR rate, grouped by Pintr=0 and quartiles of non-zero values of Pintr, plotted at the median Pintr values of the groups. Horizontal box shows the distribution of Pintr at non-zero values: interior bar represents the median, two ends of the box represent the 25th and 75th percentiles, and whiskers represent the 5th and 95th percentiles, and points outside the whiskers represent values outlying the 5th and 95th percentiles.

E-R Analysis Pleural Effusion (Safety) – Results

The relationship between dasatinib exposure and safety was characterised for the adverse event of pleural effusion, an event of special concern in dasatinib treated subjects. The relationship between dasatinib exposure and the risk of Grade 1+ pleural effusion was characterised by a time to event CPH model. The measure of dasatinib exposure employed in this analysis was steady state trough concentration ($C_{min.ss}$), taking into account changes in $C_{min.ss}$ due to dose modifications and dosing interruptions. Age and $C_{min.ss}$ were identified as statistically significant risk factors for pleural effusion. The $C_{min.ss}$ predictor median [5th to 95th percentiles] was 1.69 [0 to 7.09] ng/mL; the analysis showed that increasing the $C_{min.ss}$ increased the risk of pleural effusion with $C_{min.ss}$ levels of about 7.1 ng/mL (95th percentile) being associated with a 1.7 fold higher risk of pleural effusion compared with median $C_{min.ss}$ levels of about 1.7 ng/mL (p=0.002). The risk of pleural effusion increased 2-fold for each decade increase in age: Hazard Ratio (HR) = 2.01 [95% confidence interval (CI): 1.73, 2.34], p<0.001. The effect of age was not confounded by exposure as the PPK analysis showed that exposure to dasatinib did not depend upon age. None of the other tested predictor variables were found to be associated with an increased risk of pleural effusion (such as, treatment status, gender, race, or history of cardiac disease).

Evaluator's Overall Conclusions

The PPK and E-R study was of good quality. The PPK analysis was comprehensively described and met the TGA adopted guidelines for reporting the results of these studies (CHMP/EWP/185990/06[4]). The methodologies of the E-R analyses were also well described. The PPK analysis showed that the PKs of dasatinib were similar in patients with newly diagnosed CML-CP not previously treated with imatinib and in patients who had been previously treated with imatinib but were resistant to or intolerant of treatment with this drug. Consequently, the description of the PKs of dasatinib included in the currently approved Sprycel Product Information (PI) can be considered to be applicable to dasatinib for the treatment of patients with newly diagnosed CML-CP.

The E-R (efficacy) analysis showed that the probability of achieving cCCyR significantly decreased with increased dose interruption duration in patients with newly diagnosed CML-CP treated with dasatinib. This finding indicates that the duration of dose interruptions in patients with newly diagnosed CML-CP needs to be minimised in order to maximise the probability of achieving cCCyR (efficacy). The probability of achieving cCCyR was not related to the $wC_{avg.ss}$ concentration or to other tested covariates of age, gender, or race.

The E-R (safety) analysis showed that both age and $C_{min.ss}$ concentrations significantly increased the risk of pleural effusion in patients with newly diagnosed CML-CP treated with dasatinib. The risk of experiencing a pleural effusion increased 2-fold for each decade increase in age, while increasing the $C_{min.ss}$ from 1.7 ng/mL to 7.1 ng/mL increased the risk of experiencing a pleural effusion by 1.7-fold. None of the other tested predictor variables

[4] Guideline on Reporting the Results of Population Pharmacokinetic Analyses. http://www.tga.gov.au/docs/pdf/euguide/ewp/18599006en.pdf

were found to be associated with an increased risk of pleural effusion (treatment status, gender, race, or history of cardiac disease).

Drug Interactions

No new data were submitted under this heading.

Pharmacodynamics

No new data were submitted under this heading.

Efficacy

Introduction

The submission included one, pivotal, Phase III, randomized, open-label efficacy and safety study comparing dasatinib 100 mg QD with imatinib 400 mg QD for the treatment of adult patients aged at least 18 years with newly diagnosed CML-CP [CA180056]. This study has been fully evaluated and the findings presented below.

Main (Pivotal) Study [CA180056]

Introduction

The pivotal Phase III study was undertaken in 26 countries at 108 sites: Argentina, Austria, Australia, Belgium, Brazil, Chile, China, Colombia, Czech Republic, Denmark, France, Germany, Greece, Hungary, India, Italy, Japan, Korea, Mexico, Netherlands, Peru, Poland, Russia, Singapore, Spain, and Turkey. The results have been recently published in the New England Journal of Medicine [Kantarjian *et al*, 2010[5]]. The study is also referred to in the literature as the Dasatinib versus Imatinib Study in Treatment Naive CML Patients [DASISION]. The study was initiated on 24 September 2007 and is ongoing. In the submitted Clinical Study Report (CSR) the last observation on the last subject took place on 1 December 2009, the database lock was 11 January 2010 and the date of the CSR was 24 March 2010.

Comment: *The study did not include subjects from the USA, Canada or the United Kingdom (UK). The CSR states that subjects from North American (except for Mexico) were excluded as these subjects were eligible for an ongoing non BMS sponsored study by the Southwest Oncology Group (SWOG 0325), which is included in the long-term dasatinib clinical development plan for newly diagnosed CML-CP.*

Objectives

The *primary objective* was to compare the best confirmed complete cytogenetic response (cCCyR) rates within 12 months in subjects with newly diagnosed CML-CP treated with dasatinib 100 mg QD or imatinib 400 mg QD. The *secondary objectives* in rank order were to assess: time in cCCyR overall; major molecular response (MMR) rate at any time; time to cCCyR overall; time to MMR overall; progression-free survival (PFS); and overall survival (OS). The *tertiary objectives* included a number of cytogenetic, molecular and

[5] Kantarjian H et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia. *N Engl J Med* 2010; 362:2260-70.

clinical efficacy parameters, pharmacokinetic assessments of dasatinib in relation to efficacy and safety variables, and exploration of the development of BCR-ABL point mutations in both treatment groups.

Design

The pivotal Phase III study is an ongoing, multi-national, multi-centred, randomized, open-label study in patients with newly diagnosed CML-CP. Subjects were randomized to a starting dose of dasatinib 100 mg QD or imatinib 400 mg QD in a 1:1 ratio. Randomization used an interactive voice response system (IVRS) accessed centrally by participating investigative sites. Randomized subjects were stratified by Hasford risk score into low (<780), intermediate (≥780 to ≤ 1480), and high (>1480) risk groups [Hasford *et al*, 1998[6]]. The Hasford score stratifies risk based on prognostic factors for survival of age, spleen size, peripheral blood blasts (%), peripheral blood eosinophils (%), peripheral blood basophils (%), and platelet count. The Hasford score was calculated at the time of the original diagnosis of CML and prior to the subject receiving any treatment for CML (including hydroxyurea or anagrelide). Enrolment in the study continued until 519 subjects had been randomized. The results presented in the submitted CSR reflected a minimum of 12 months of treatment.

Bone marrow (BM) cytogenetic responses were evaluated within 6 weeks prior to randomization and then every 3 months for 18 months. However, if a cCyR (0% Ph+ metaphases is achieved at > 12 months, BM cytogenetics are to be performed once per year. After the first 18 months of treatment in subjects without CCyR, BM biopsy or aspirate is to be obtained every 6 months until Month 24. Following Month 24, BM biopsy or aspirate is to be obtained every 12 months. All subjects are to be followed for a minimum of 30 days after the last dose of study therapy or until recovery from all toxic effects, whichever is the longer. Subsequent follow-up visits are to occur at least every four weeks until all study related toxicities return to baseline or ≤ National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI CTCAE[7]) Grade 1, stabilize, or are deemed irreversible. Additionally, subjects who discontinued study therapy and had not died are to be followed yearly for survival. Part of the yearly follow-up for survival includes recording post-Study CML therapy of any kind, including tyrosine kinase inhibitors.

Comment: *This was an open-label study and, consequently, is subject to the well known potential biases of studies of this type compared with double-blind studies. However, in this study the potential biases are mitigated by the use of robust objective primary and secondary efficacy endpoints. Nevertheless, there appears to be no reason why a double-blind study could not have been undertaken, at least for the first 12 months of the study. The use of*

[6] Hasford J *et al*, JNTL Cancer Inst 1998; 90: 850-858

[7] Common Terminology Criteria (CTC) is a standardised classification of side effects used in assessing drugs for cancer therapy, in particular. Specific conditions and symptoms may have values or descriptive comment for each level, but the general guideline is 1 – Mild, 2 – Moderate, 3 – Severe, 4 - Life threatening, 5 - Death.

imatinib as the active comparator is acceptable. Imatinib is the generally accepted standard treatment for newly diagnosed patients with CML-CP and is approved in Australia for the treatment of patients with CML. It is considered that it would be unethical to use a placebo control for the targeted indication. The centralized IVRS randomization method is satisfactory. The use of stratified randomization based on well accepted prognostic factors in CML-CP minimises the potential risk of bias that might arise from non-stratified randomization in this condition. Stratification was based on Hasford prognostic criteria rather than the other well known Sokal prognostic criteria. In the CSR it was stated that the "Sokal score was not chosen as this was described in 1984 in subjects treated primarily with busulfan and includes only 4 of the [Hasford] components for prognostication". However, the Sokal prognostic criteria are well accepted and have been shown to reproducibly separate chemotherapy treated patients into high and low risk groups [Schiffer et al, 2003[8]]. Nevertheless, the use of the Hasford prognostic criteria is considered to be an acceptable stratification method. Planned follow-up procedures and time intervals for assessment are acceptable.

Patient Population

The target population included men and women aged ≥ 18 years with newly diagnosed CML-CP in the 3 months before study entry and based on bone marrow cytogenetics demonstrating the presence of the t(9;22) chromosomal translocation (Philadelphia chromosome positive [Ph+]). All subjects were required to have Ph+ CML-CP, which was defined by the presence of the following criteria: < 15% blasts in peripheral blood and bone marrow; < 30% blasts plus promyelocytes in peripheral blood and bone marrow; < 20% basophils in the peripheral blood; ≥ 100 x 10^9/L platelets; no evidence of extramedullary leukaemic involvement, with the exception of hepato-splenomegaly; and Ph+ or variants must have been demonstrated by bone marrow cytogenetics. In addition, subjects were required to have previously untreated CML-CP, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)[9] Score 0 – 2, and adequate hepatic and renal function. The ECOG inclusion criteria indicate that patients were required to be at least ambulatory and capable of all self care, but unable to carry out work activities and to be up and about more than 50% of waking hours (ECOG Grade 2). The ECOG grades performance from 0 to 5 with a higher score indicating more severe disease (see footnote [9] below).

[8] Schiffer *et al*. (2003) Perspectives on the treatment of chronic phase and advanced phase CML and Philadelphia chromosome positive ALL*. Leukemia* 17:691-699.

[9] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis*.* The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction, 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example light house work, office work, 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair, 5 – Dead

The discontinuation criteria were: withdrawal of informed consent; any clinical AE, laboratory abnormality, or intercurrent illness, which in the opinion of the investigator indicated that continued participation was not in the best interest of the subject; pregnancy; termination of the study by BMS; loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either psychiatric or physical illness; in the opinion of the investigator, continued participation in the study was not in the best interest of the subject; QTcF[10] value > 530 ms ; disease progression despite dose escalation; or subject eligible and willing to undergo stem cell transplant

Comment: *The inclusion criteria are satisfactory and adequately define the target population. The exclusion criteria were extensive and excluded subjects with significant medical histories and concurrent medical conditions. The extensive exclusion criteria have the potential to limit the generalisability of the results of the study to all patients in the community with CML-CP. The initial protocol allowed prior treatment with 28 days of imatinib to improve subject recruitment. This allowance was removed in an early protocol amendment after advice from the United States (US) Food and Drug Administration (FDA). Before implementation of this restrictive amendment at all sites, 7 subjects were randomized with prior imatinib use of less than 28 days. These 7 subjects were included in efficacy and safety analyses. The discontinuation criteria were acceptable and standard for studies of this type. There were only two clinically relevant protocol deviations, one occurring in each treatment group and both due to lack of specified Ph+ criteria.*

Treatments

Dasatinib and Imatinib

Dasatinib 100 mg was administered QD (2 x 50 mg film coated tablets), while imatinib 400 mg (1 x 400 mg film-coated tablet) was administered QD with a meal and a large glass of water. Subjects were permitted to adjust the time of administration of the drugs as long as doses were taken approximately every 24 hours. Dasatinib film coated tablets (20 mg and 50 mg) were provided by the sponsor, and commercially available imatinib film coated tablets (100 mg and 400 mg) were generally sourced through the sponsor.

Permitted dose modifications (escalation or reduction) are summarised below in Table 3. In subjects with a suboptimal response dasatinib could be increased from the initial dose of 100 mg QD to 140 mg QD and imatinib could be increased from the initial dose of 400 mg QD to 600 to 800 mg daily in QD or divided doses. Subjects with a suboptimal response were defined as subjects without a complete haematologic response [CHR] within 3 months, partial cytogenetic response (PCyR) within 6 months**,** CCyR within 12 months**,** or MMR within 18 months. Dose escalation could occur provided that there were: no Grade 3 to 4 haematologic toxicities; no recurrence of the toxicity that led to the dose reduction;

[10] The time between the start of the Q wave and the end of the T wave in the heart's electrical cycle is called the QT interval. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

and no additional ≥ Grade 2 non-haematologic toxicities. Dosing with dasatinib > 180 mg per day or imatinib > 800 mg per day was prohibited.
In general, no dose interruptions/reductions were required for Grade 1 to 2 haematologic events. For Grade 3 to 4 haematologic events, the study drug was interrupted and resumed at one level dose reduction after recovery to Grade ≤ 1. For Grade 2 non-haematologic events, the study drug was interrupted and resumed at the same dose after recovery to Grade ≤ 1. For Grade 3 to 4 non-haematologic events, the study drug was interrupted and resumed at one level dose reduction after recovery to Grade ≤ 1. Dose interruptions, reductions, and treatment discontinuation could be more or less conservative for an individual patient than specified by the guidelines, based on the clinical judgement of the investigator.

For subjects with a dose reduction to 80 mg QD for dasatinib and 300 mg QD for imatinib due to haematologic or non-hematologic toxicities, dose re-escalation was permitted to the starting dose if at least one month after the dose reduction there were: no Grade 3 to 4 haematologic toxicities; no recurrence of the toxicity that led to the dose reduction; and no additional ≥ Grade 2 non-haematologic toxicities. If an AE requiring dose interruption occurred at dasatinib 50 mg QD or imatinib 200 mg QD, the AE must have resolved to Grade ≤ 1 before resumption of study drug at the same dose.

Table 3: Dose modification levels.

Dose Level	Dasatinib (mg)	Imatinib (mg)
Escalation (+1)	140	600-800
Starting dose	**100**	**400**
Reduction (-1)	80	300
Reduction (-2)	50	200

Comment: *The chosen starting dose of dasatinib 100 mg QD is satisfactory. This dose is the currently approved dose for initiating treatment of Ph+ CML-CP resistant to, or intolerant of imatinib. Similarly, the chosen starting dose of imatinib of 400 mg QD is satisfactory. This is the currently approved dose for initiating treatment of CML-CP. The dosing modification guidelines are acceptable.*

Prohibited and Restricted Therapies

The use of hydroxyurea to control the white blood cell count and anagrelide to control the platelet count were permitted at the investigator's discretion. No other anti-cancer agents including chemotherapy, radiation therapy, and anti-cancer biologic agents were permitted. Use of allopurinol was allowed in subjects with white blood cell counts (WBC) ≥ $50x10^3/mm^3$. Use of granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), erythropoietin, or darbepoetin was allowed. Subjects were not permitted to take medications associated with QT prolongation. Antiplatelet agents or anticoagulants were restricted due to possible combined effects with dasatinib, but were allowed if medically indicated. Avoidance was advised for cytochrome P450 (CYP) 3A4 substrates, inhibitors, and inducers. Caution was advised when co-administering dasatinib with drugs with a narrow therapeutic index

highly dependent on CYP3A4 metabolism. Avoidance was advised for proton pump inhibitors and histamine receptor type 2 (H2) antagonists. Short-acting antacids were permitted, but not within 2 hours of dasatinib dose.

Primary Efficacy Endpoint (cCCyR)

The *primary efficacy endpoint was confirmed CCyR rates within 12 months* (confirmed by BM cytogenetics on two separate occasions at least 28 days apart). A cytogenetic response was based on the prevalence of Ph+ cells in metaphase from a BM sample. Bone marrow cytogenetic assessments were undertaken at the laboratory for each investigational site. Twenty-five (25) metaphases, but at least 20 metaphases, from a BM sample were considered ideal for evaluation. Evaluation of the cytogenetic response using only peripheral blood fluorescence-in situ hybridization (FISH) was not acceptable.

Comment: *The primary efficacy endpoint of cCCyR within 12 months is a surrogate measure of long-term clinical benefit. The TGA approved guidelines for the evaluation of anti-cancer medicines indicate that confirmatory Phase III trials should demonstrate that the investigational product provides clinical benefit [CPMP/EWP/205/95/Rev.3/Corr[11]]. The guidelines state that acceptable primary endpoints include overall survival (OS) and* progression free survival *(PFS)/disease free survival (DFS), and that if PFS/DFS is the selected primary endpoint then OS should be reported as the secondary endpoint and vice versa. The guidelines also state that tumour markers "convincingly demonstrated to reflect tumour burden can be used, in combination with other measures of tumour burden, to define tumour response and progression". The guidelines further state that a "justification is expected in the study protocol why endpoints such as survival benefit or symptom control cannot be used as a primary measure of patient benefit".*

*The protocol for Study CA180056 included a discussion of the clinical data supporting the choice of cCCyR within 12 months as the primary efficacy endpoint. The protocol refers to a "landmark" analysis from the IRIS[12] trial of the 5 year follow-up data for patients with CML treated with imatinib that demonstrated that of the 350 patients with a CCyR after 12 months treatment, 97% [95% CI: 94, 99] had not progressed to the accelerated phase or blast crisis after 60 months [*Druker *et al, 2006[13]]. This figure compared with 81% [95% CI: 70, 92] for the 73 patients who did not have a CCyR within 12 months. The difference between the rates at 60 months was statistically significant (p<0.001). No patients who had a CCyR and a major molecular response at 12 months had progressed to the accelerated phase or blast crisis at 60 months. At 60 months, in imatinib treated patients the estimated rate of event-free survival was 83% [95% CI: 79, 87], and 93% [95% CI: 90, 96] had not progressed to the accelerated phase or blast crisis. The estimated overall survival rate at 60 months was 89% [95% CI: 86, 92] in imatinib treated patients. The previous figures have been obtained directly from the* Druker *et al, 2006 publication and are consistent with those provided in the protocol for Study CA180056.*

11 Guideline On The Evaluation Of Anticancer Medicinal Products In Man. www.ema.europa.eu/pdfs/human/ewp/020595en.pdf

12 The Insulin Resistance Intervention after Stroke (IRIS) trial.

13 Druker BJ, Guilhot F, O'Brien SG, *et al.* (2006). Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355:2408-17.

The CSR [CA180056] also included a rationale for the use of the cCCyR as the primary endpoint. In addition to Druker *et al, 2006, the CSR referred to four additional studies which showed a significant correlation between CCyR and long-term clinical benefit [Benelux CML Study Group, 1998[14]; Italian Cooperative Study Group, 1994[15]; de Lavallade et al, 2008[16]; Kantarjian et al, 2008[17]]. These four additional studies have been examined. The Italian CML and Benelux CML Group studies were undertaken in 1994 and 1998, respectively, and showed that in patients treated with INF (with or without hydroxyurea) that cytogenic response in the first 24 months of treatment was predictive of subsequent survival. In de Lavallade et al (2008), 121 (62.6%) patients treated with imatinib had achieved CCyR at 12 months compared with 72 (37.4%) patients treated with imatinib who had not achieved CCyR at 12 months. The patients who had achieved CCyR had a better 5 year PFS than those who had not achieved CCyR (96% versus 74%; p=0.007), and better overall survival (98% versus 74%; p=0.03). The study found no additional PFS or OS benefit in patients with who achieved MMR at 1 year or 18 months for those patients in CCyR. In Kantarjian et al (2008), a strong association was demonstrated between a major cytogenetic response at 6 or 12 months and subsequent PFS to 72 months, and complete cytogenetic response at 18 to 24 months was also associated with subsequent PFS. Furthermore, it is stated in the TGA approved Glivec Product Information (PI) that "the degree of cytogenetic response had a clear effect on long-term outcomes in patients on Glivec".*

Overall, it is considered that the available data indicate that cCCyR within 12 months is an acceptable surrogate for long-term clinical benefit, given that dasatinib is not a new chemical entity and is approved for second-line treatment of CML-CP in patients with resistance or intolerance to prior therapy including imatinib.

Secondary and Tertiary Efficacy Endpoints

Secondary efficacy endpoints, in rank order, included: (i) time in cCCyR at any time; (ii) MMR rate at any time; (iii) time to cCCyR at any time; (iv) time to MMR at any time; (v) PFS; and (vi) OS.

Tertiary efficacy endpoints included: rate of cCHR, confirmed major cytogenetic response (cMCyR), and major molecular response (MMR) within 12 months; time in and time to cCCyR within 12 months; best overall response at any time for cCCyR, cMCyR, and cCHR; time to cMCyR and cCHR; Time to Treatment Failure (TTF); Time to Maximum Clinical Benefit (TMCB); duration of cCCyR within 12 months; duration overall for cCCyR, cMCyR, MMR; and confirmed complete haematologic response (cCHR) for each treatment group.

[14] The Benelux CML Study Group. (1998). Randomized study on hydroxyurea alone versus hydroxyurea combined with low-dose interferon-α2b for chronic myeloid leukemia. *Blood* 191:2713-21.

[15] Kantarjian H et al. Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia: need for new response definitions? *Cancer 2008*;112:837-45.

[16] De Lavallade H, Apperley JF, Khorashad JS, *et al.* (2008). Imatinib for newly diagnosed patients with chronic myeloid leukemia: Incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol* 26:3358-3363.

[17] Kantarjian H *et al.* (2008). Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia: need for new response definitions? *Cancer* 112:837-45.

Definitions of Cytogenetic, Haematologic, Molecular and Other Efficacy Endpoints

Cytogenetic Response

The cytogenetic response criteria are summarised below in Table 4. Best on-study cytogenetic response was assessed based on the percentages of metaphases in the BM that were Ph+. Major Cytogenetic Response (MCyR) was defined as CCyR plus PCyR. A confirmed complete cytogenetic response (cCCyR) was defined as a response noted on two consecutive occasions (at least 28 days apart). If a subject achieved the first CCyR within 12 months but the assessment confirming the CCyR occurred beyond 12 months, this was still counted toward the primary endpoint. The same applied to confirmed MCyR, CHR and MMR within 12 months.

Table 4: Cytogenetic response definitions.

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

Haematologic Response

A complete haematological response (CHR) was obtained when all the listed criteria in Table 5 (below) were met in the peripheral blood. A confirmed CHR (cCHR) was obtained if the listed criteria were met at least 28 days apart.

Table 5: Complete Haematologic Response (CHR) criteria.

- WBC ≤ 10,000/mm^3.
- Platelets < 450,000/mm^3.
- Peripheral blood basophils < 5%.
- No blasts or promyelocytes in peripheral blood.
- < 5% myelocytes plus metamyelocytes in peripheral blood.
- No extramedullary involvement (including no hepatomegaly or splenomegaly.

Molecular Response

Molecular response was assessed using BCR-ABL transcript levels measured by quantitative real-time polymerase chain reaction (QRT-PCR). The standardized baseline, as established in the IRIS trial, was taken to represent 100% on the International Scale (IS), and a 3-log reduction in BCR-ABL transcripts from the standardized baseline was fixed at 0.1%. In this study, a ratio of BCR-ABL/ABL ≤ 0.1% on the IS was considered to be a MMR (that is, at least a 3-log reduction from a standardized baseline value). In this study, a confirmed major molecular response (cMMR) and complete molecular response (CMR) were also examined. A MMR was confirmed if all measurements up to at least 28 days after the initial MMR showed at least a MMR. A CMR was defined as a ratio BCR-ABL/ABL ≤ $10^{-2.5}$ % = 0.00316% on the IS (that is, at least 4.5 log reduction from a standardized baseline value).

Other Secondary and Tertiary Efficacy Definitions

Other secondary efficacy endpoints (including overall survival and progression free survival) and tertiary efficacy endpoint were also assessed.

Statistical Methods

The research hypothesis in this study was that treatment with dasatinib 100 mg QD results in a greater cCCyR rate within 12 months compared with imatinib 400 mg QD in subjects with newly diagnosed CML-CP. The Statistical Analysis Plan specified two interim efficacy and safety analyses when 150 and 260 subjects had been followed for a minimum of 2 and 6 months, respectively. The final analysis of the primary endpoint took place after all subjects had been followed for 12 months or had been lost to follow-up before 12 months. At that time, the primary endpoint was analysed and interim analyses of the secondary endpoints were also conducted. The final analyses of the secondary endpoints will take place when these are mature (after a minimum of 5 years of follow-up).

The primary endpoint of cCCyR rate within 12 months in all randomized subjects was calculated for each of the two treatment groups along with the associated two-sided, exact 95% confidence interval (CI) measured by the Clopper Pearson method. The test for differences in response rates was carried out using a two-sided Chi-square test stratified by Hasford score using the Cochran-Mantel-Haenszel (CMH) method. Superiority of dasatinib compared with imatinib as regards the cCCyR within 12 months was concluded if the p-value using CMH method was less than 0.05. The rate of cCCyR within 12 months was defined as the proportion of subjects who achieved a CCyR within 12 months from the date of randomization, provided that it was confirmed on two consecutive occasions at least 28 days apart. If the first CCyR occurred within 12 months and the assessment confirming the CCyR occurred beyond 12 months, this cCCyR was still counted toward the primary endpoint.

Interim analyses of the secondary efficacy endpoints of time in cCCyR at any time, MMR rate at any time, time to cCCyR at any time, and time to MMR at any time were all tested at a two-sided significance level of 0.0001. Final testing of all secondary efficacy endpoints will be conducted after a minimum of 5 years of follow-up irrespective of significance at the interim 12 month analysis. The secondary efficacy endpoints will be tested at the time of maturity in a sequential fashion at a significance level of 0.05 which preserves the study wide type 1 error. These analyses will be undertaken only if comparison of the primary endpoint and all other comparisons with a smaller rank are statistically significant.

Time to events by treatment groups were estimated by the Kaplan-Meier product-limit method (time in, duration of, time to cCCyR and cCCyR within 12 months; time to and duration of cMCyR, cCHR, and MMR; PFS; OS; TTF; TMCB). A two-sided, 95% CI for the median was computed using the method of Brookmeyer and Crowley. In addition, a Cox proportional hazards model stratified by Hasford scores and treatment group as a single covariate was fitted to the data to produce an estimate of the hazard ratio (HR: dasatinib/imatinib) with associated 95% CI using normal approximation. Comparisons of time-to events were conducted via a two-sided stratified log-rank test. Response rates for

other relevant secondary and tertiary endpoints were estimated along with their exact 95% CIs.

The study included five data sets which were: *all enrolled subjects* included all subjects who signed an informed consent form and were registered into the IVRS; *all randomized subjects*; *all treated subjects* included all randomized subjects who received at least one dose of treatment; *all evaluable subjects* included all treated subjects who were Ph+ according to baseline or on-study BM sample and who had either at least one adequate on-study cytogenetic assessment or discontinued for any reason before a valid on-study cytogenetic assessment was available; and *per-protocol subjects* included all evaluable subjects who were not relevant protocol deviators. The analyses of efficacy were primarily conducted using the "all randomized subjects" dataset (the intention-to-treat principle). The "all evaluable subjects" and "per-protocol subjects" datasets were used to analyse primary efficacy endpoint for the purposes of sensitivity analysis. All analyses were performed by treatment group as randomized, except analyses of dosing and safety, which were analysed by treatment group as received.

Comment: *In the submitted CSR, the primary endpoint (cCCyR rate within 12 months) was analysed using a two-sided significance level of 0.05. Comparisons of the secondary endpoints which were not mature at the time of the primary efficacy endpoint analysis were performed at a significance level of 0.0001. This significance level allowed interim testing of these endpoints without affecting the overall Type I error at maturity (after a minimum of 5 years of follow-up). At the time of the maturity of the secondary endpoints, testing will be undertaken sequentially at a level of 0.05. The sequential testing order of the secondary efficacy endpoints will be: time-in-confirmed CCyR overall; MMR at any time; time-to-confirmed CCyR overall; time-to MMR overall; PFS, and OS. The analysis of the mature protocol specified primary efficacy endpoint and the interim analyses of the protocol specified secondary endpoints which had not yet reached maturity are considered to be the key efficacy analyses in this study report. There were numerous tertiary efficacy endpoint analyses which are considered to be exploratory. Overall, the statistical methods are considered to be satisfactory. The study was designed as a superiority study aimed at demonstrating the superiority of dasatinib compared with imatinib rather than a non-inferiority study aimed at demonstrating the non-inferiority of dasatinib compared with imatinib. No formal null or alternative hypotheses could be identified in the CSR, protocol, or Statistical Analysis Plan, but the study did include a "research hypothesis".*

There were two interim efficacy and safety analyses reviewed by a Data Monitoring Committee (DMC), one at 2 months follow-up with the first 150 randomized subjects and one at 6 months follow-up with the first 260 randomized subjects. The primary endpoint of cCCyR rates within 12 months was evaluated at a nominal significance level of 0.0001. The use of this stopping boundary maintained a two-sided significance level of 0.05 for the main analysis. Following both DMC meetings, the committee recommended continuation of the study without modification.

Sample Size

The sample size calculation was based on an estimated cCCyR rate within 12 months for dasatinib treatment of 81%. The estimated rate appears to have been based on the results from a small pilot study of dasatinib for first line treatment of CML, and data from second

line dasatinib treatment of CML in patients with the least exposure to first line imatinib treatment. With a two-sided α = 0.05 and power of 90%, a total of 518 subjects were needed to show a statistically significant difference in 12 month cCCyR rates between the two treatment groups when the 12 month cCCyR rates in the imatinib 400 mg QD group and the dasatinib 100 mg QD group were assumed to be 69% [Druker *et al*, 2006] and 81%, respectively. A total of 519 subjects were randomized in a 1:1 ratio, indicating that the power of the study was satisfactory.

Disposition of Subjects

A total of 547 subjects were enrolled, 519 were randomized, and 516 were treated (258 with dasatinib and 258 with imatinib). Of the 547 enrolled subjects, 28 were not randomized for the following reasons: study criteria no longer met (n=20); consent withdrawn (n=3); lost to follow-up (n=1); and other (n=4). The disposition of the 519 all randomized subjects is summarised below in Table 6.

Table 6: Subject disposition; all randomized subjects.

	Dasatinib	**Imatinib**
All Randomized	259	260
Treated	258 (100.0%)	258 (100.0%)
On Treatment	218 (84.5%)	210 (81.4%)
Off Treatment (Discontinued)	40 (15.5%)	48 (18.6%)
Death	4 (1.6%)	1 (0.4%)
Disease Progression	7 (2.7%)	13 (5.0%)
Intolerance *	13 (5.0%)	11 (4.3%)
Treatment Failure **	6 (2.3%)	10 (3.9%)
Adverse Event Unrelated to Study Drug	3 (1.2%)	1 (0.4%)
Subject Withdrew Consent	2 (0.8%)	3 (1.2%)
Pregnancy	2 (0.8%)	0
Lost to Follow-Up	0	3 (1.2%)
Poor / Non-Compliance	0	2 (0.8%)
Subject Withdrew Consent	2 (0.8%)	1 (0.8%)
Other	1 (0.4%)	3 (1.2%)

* Intolerance defined as recurrent≥ Grade 3 haematologic toxicity or≥ Grade 2 non hematologic toxicity despite dose reduction necessitating discontinuation of protocol therapy.
** Treatment failure defined according to 2006 ELN guidelines and included a lack of a haematologic response (stable disease, no decrease in WBC, or platelet count below baseline) at 3 months, CHR or cytogenetic response at 6 months, PCyR at 12 months, or CCyR at 18 months.

Subjects started dasatinib at 100 mg QD and imatinib at 400 mg QD with subsequent dose modifications depending on response and tolerability. The median of the average daily dasatinib dose was 99 mg [range 21-136 mg] and the median of the average daily imatinib dose was 400 mg [range 125-657 mg]. The median duration of both dasatinib and imatinib therapy was 14 months, and the range was 0.03 to 24.08 months in the dasatinib group and 0.26 to 25.79 months in the imatinib group.

Comment: *Overall, subject disposition in the two treatment groups was similar. The incidence of discontinuation was greater in the imatinib group than in the dasatinib group:*

48 (18.6%) versus 40 (15.5%), respectively. In each treatment group, disease progression and intolerance (study drug toxicity) were the most common reasons for being off-treatment. The incidence of discontinuation due to disease progression was lower in the dasatinib group than in the imatinib group (7 [2.7%] versus 13 [5.0%], respectively), as was discontinuation due to treatment failure (6 [2.3%] versus 10 [3.9%]). Discontinuation due to intolerance (study drug toxicity) was marginally higher in the dasatinib group compared with the imatinib group: 13 (5.0%) versus 11 (4.3%), respectively.

Baseline Characteristics

The two treatment groups were well balanced as regards baseline characteristics. The mean age [range] of the subjects was 46.4 years [18-64] in the dasatinib group (n=259) and 47.1 years [18-78] in the imatinib group (n=260), with the majority of subjects in both groups being aged between 21 and 65 years old (90.4% and 87.3%, respectively). Both treatment groups had more male than female subjects and most subjects were either "White" or "Asian". The median time from initial CML diagnosis was one month in both treatment groups, and ECOG performance (mostly Score 0), baseline haematology (WBC and platelets), and distribution of Hasford scores (mostly low or intermediate risk) were similar for the two treatment groups. The baseline haematological characteristics of both treatment groups were generally similar, apart from a higher incidence of liver involvement in the dasatinib group (14.3%) than in the imatinib group (6.9%), and a higher platelet count in the dasatinib group (448 x 10^3/mm^3 [range: 58 – 1880]) than in the imatinib group (390 x 10^3/mm^3 [range: 29 - 2930]). In the dasatinib and imatinib groups, baseline Grade 3 or 4 neutropaenia was present in 0% (n=0) and 1.2% (n=3) of subjects, respectively, and the corresponding results for leucopaenia were 0% (n=0) and 0.4% (n=1), platelets 0% (n=0) and 0.8% (n=2), and anaemia 1.9% (n=5) and 0.8% (n=6), respectively. Most subjects had no baseline laboratory haematological and/or biochemical toxicities.

The majority of subjects in both the dasatinib and imatinib groups were treated with hydroxyurea on diagnosis and before entering the study (73.0% [189/259] and 73.1% [190/260], respectively). Prior therapy with anagrelide had been received by 3.1% (n=8) of subjects in the dasatinib group and 1.2% (n=2) in the imatinib group. Imatinib treatment had been received by 1.2% (n=3) of subjects in the dasatinib group and 1.5% (n=4) in the imatinib group before an early protocol amendment excluded all prior imatinib therapy; the original protocol allowed up to 28 days prior treatment with imatinib.

Pre-existing medical conditions were reported in 84.6% of subjects in both treatment groups (all randomized subjects).The most commonly affected body systems were (dasatinib versus imatinib): gastro-intestinal (35.1% versus 32.7%); musculoskeletal (26.6% versus 31.2%); cardiovascular (21.2% versus 21.9%); endocrine-metabolic (21.2% versus 16.5%); head, eyes, ear, nose, throat (21.2% versus 18.5%); genitourinary (20.8% versus 19.2%; and allergies (19.7% versus 25.8%). Alcohol use was reported in 19.7% of dasatinib treated subjects and 25.8% of imatinib treated subjects and the

corresponding figures for tobacco use were 20.8% and 28.1%. Overall, pre-existing medical conditions did not notably differ between the two treatment groups.

Treatment Compliance, Concomitant Therapy, and Post Study CML Treatments.
Treatment compliance was monitored by drug accountability as well as recording study drug administration in the subject's medical record and CRF. No treatment compliance figures could be identified in the CSR.
During the study, concomitant medications were used by 84.9% (219/258) and 82.2% (212/258) of subjects in the dasatinib and imatinib groups, respectively. The most common concomitant medications used by ≥ 10 % of subjects in both treatment groups (dasatinib versus imatinib) were: paracetamol (61% versus 43%); allopurinol (43% versus 48%); omeprazole (29% versus 28%); levofloxacin (26% versus 26%); amoxycillin (26% versus 18%); ibuprofen (23% versus 33%); furosemide (20% versus 20%); lidocaine (23% versus 21%); ciprofloxacin (19% versus 23%); amoxycillin / clavulinic acid (19% versus 14%); diclofenac (18% versus 16%); influenza vaccine (16% versus 15%); tramadol (16% versus 14%); folic acid (16% versus 15%); loxoprem (15% versus 13%); loperamide (12% versus 15%); cetrizine (12% versus 13%); filgrastim (12% versus 13%); potassium (11% versus 14%); pantoprazole (11% versus 12%); and chlorphenamine (10% versus 12%). Apart from filgrastim, the use of antineoplastic and immunomodulating agents was infrequent (≤ 2%) in both treatment groups and was not notably different between the groups.

After discontinuation of randomized treatment, among subjects randomized to dasatinib, the most common subsequent CML treatments included: imatinib (8%), nilotinib (0.8%), cytarabine (0.8%) and dasatinib (0.8%). Among subjects randomized to imatinib, the most common subsequent CML treatments included: dasatinib (8%), imatinib (5%), nilotinib (3%), and cytarabine (1%).

Primary Efficacy Endpoint Results
The cCCyR rate within 12 months was statistically significantly greater in the dasatinib group than in the imatinib group in randomized subjects (see Table 7, below). The analysis includes any number of metaphases.

Table 7: Rate of cCCyR within 12 months; randomized subjects**.**

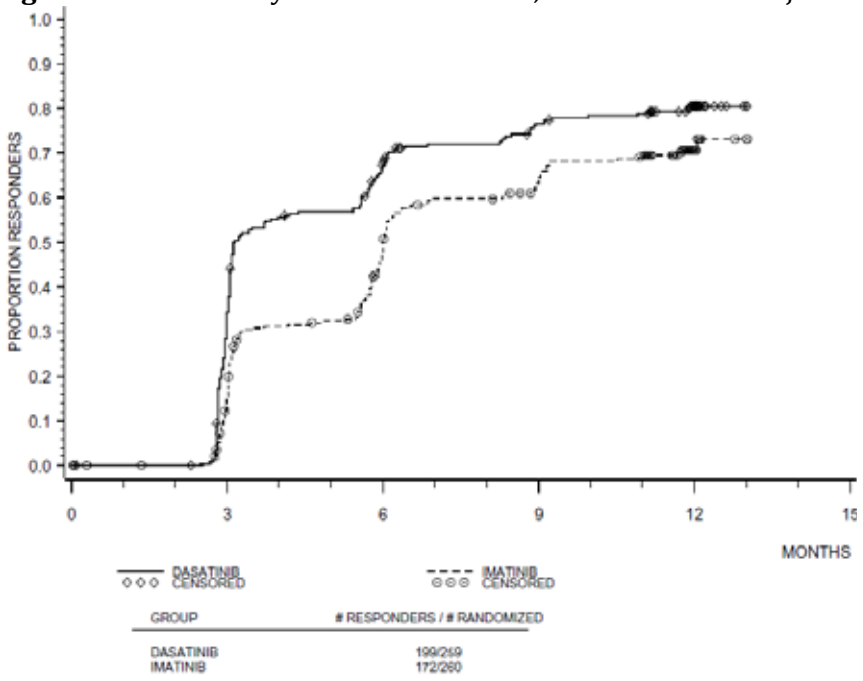
	Dasatinib (n=259)	Imatinib (n=260)
cCCyR within 12 months	76.8% (n=199)	66.2% (n=172)
95% CI (exact)	[71.2% - 81.8%]	[60.1% - 71.9%]
CMH test stratified by Hasford score	p = 0.0067	

In randomized subjects with assessments in ≥ 20 metaphases, the cCCyR rate within 12 months was 76.1% (197/259) in the dasatinib group and 64.2% (167/260) in the imatinib group; p=0.003. In this study, 98% of subjects with a cCCyR had conventional BM assessments with ≥ 20 metaphases. To rule out an effect of the timing of the database lock on the primary endpoint, a sensitivity analysis was conducted for the hypothetical

situation where subjects with a CCyR on one assessment are without the opportunity for a confirmatory cytogenetic assessment. This analysis accounts for all subjects with an unconfirmed CCyR who continue on study treatment at the time of the database lock (7 dasatinib and 5 imatinib). This analysis hypothetically assumes that all five imatinib treated subjects would have confirmed their CCyR in the future and assumes that none of the seven dasatinib treated subjects would have a confirmation. This is analysis is considered to be the most conservative scenario and is biased against dasatinib. In this analysis, the cCCyR within 12 months was 76.8% (199/259) in dasatinib treated subjects and 68.1% (177/260) in imatinib treated subjects; p=0.0247. Sensitivity analyses were also undertaken on the cCCyR rate within 12 months in "all treated subjects", "all evaluable subjects", and "per-protocol subjects". In each of these three populations, the cCCyR rates in the dasatinib and imatinib groups were similar to those in "randomized subjects" and all pairwise comparisons were statistically significant (p<0.05).

The time to cCCyR within 12 months occurred more rapidly in the dasatinib group than in the imatinib group (see Figure 3, below). The median time to cCCyR in subjects with cCCyR within 12 months was 3.1 months [95% CI: 3.0, 3.1] in the dasatinib group and 5.5 months [95% CI: 3.3, 5.7] in the imatinib group. The respective best cCCyR rate by time for dasatinib versus imatinib at the following time points in all randomized subjects were: within 3 months 54.4% versus 30.0%; within 6 months 69.9% versus 56.2%; within 9 months 75.3% versus 63.5%; and within 12 months 76.8% versus 66.2%. Only four subjects with a cCCyR reported disease progression (1/199 dasatinib and 3/177 imatinib).

Figure 3: Time to cCCyR within 12 months; all randomized subjects.



Comment: *The study satisfactorily demonstrated that the cCCyR rate within 12 months was statistically significantly higher in the dasatinib group than in the imatinib group. This suggests that the long-term clinical benefit of progression free survival and overall survival is*

likely to be superior in dasatinib treated patients compared with imatinib treated patients. The primary efficacy analysis was supported by the sensitivity analyses. The sponsor was requested to undertake a post-hoc analysis of the 95% CI for the difference between the cCCyR rates. This post-hoc analysis showed that the absolute difference [95% CI] between the two treatments in the cCCyR rate in randomized subjects was 10.7% [95% CI: 3.0%, 18.4%]. This post hoc analysis supports the primary CMH analysis of the difference cCCyR rates in the two treatment groups. The median time to cCCyR analysis supports the superiority of dasatinib compared with imatinib. The observed cCCyR rates were lower than those estimated for the sample size and power calculations for both dasatinib (estimated 81% and observed 76.8%) and imatinib (estimated 69% and observed 66.2%). The observed cCCyR rates in both the dasatinib and imatinib groups were about 4% and 3% lower than those estimated to calculate the power and sample size. The observed difference in cCCyR rates between the two treatments was 10.7% compared with the estimated difference of 12%. Based on the cCCyR estimates to calculate the sample size and power it is considered that the observed statistically significant difference between the two treatment groups is clinically meaningful.

Secondary Efficacy Endpoint Results

The s*econdary efficacy endpoints,* in rank order, included: (i) time in cCCyR at any time; (ii) MMR rate at any time; (iii) time to cCCyR at any time; (iv) time to MMR at any time; (v) PFS; and (vi) OS. The results of the analyses of these endpoints are summarised below in Table 8.

Median duration of cCCyR at any time or within 12 months for both treatment groups in subjects with cCCyR had not been reached. In subjects who had achieved a cCCyR at any time, the median time to cCCyR was 3.1 [95% CI: 3.0, 3.1] months and 5.6 [95% CI: 3.3, 5.8] months in the dasatinib and imatinib groups, respectively. Based on the Kaplan-Meier estimates in subjects with cCCyR, the estimated rate of remaining in cCCyR at 12 months was 97.4% [CI: 92.5%, 100%] in the dasatinib group and 99.1% [95% CI: 97.2%, 100%] in the imatinib group.

In subjects who achieved a MMR at any time, the median time to MMR was 6.3 [95% CI: 6.0, 8.6] and 9.2 [95% CI: 9.0, 11.7] months in the dasatinib and imatinib groups, respectively. The respective best MMR rates by time for dasatinib versus imatinib at the following time points in all randomized subjects were: within 3 months 8.1% versus 0.4%; within 6 months 27.0% versus 8.1%; within 9 months 39.0% versus 18.5%; and within 12 months 45.9% versus 28.1%. Rates of CMR at any time were 8.5% in the dasatinib group and 4.2% in the imatinib group, with respective rates of CMR within 12 months being 4.6% and 2.3%; CMR was defined as at least 4.5 log reduction from a standardized baseline value BCR-ABL ratio ≤ 0.0032%, or BCR-ABL ratio ≤ 0.0032% on the IS.

Table 8: Secondary efficacy endpoints; all randomized subjects.

Endpoint	Dasatinib (n=259)	Imatinib (n=260)
Time in cCCyR at any time	Hazard ratio = 0.7 [99.99% CI: 0.4 - 1.4] [a] ; p < 0.035	
Time to cCCyR at any time *Median (months) in subjects with cCCyR*	Hazard ratio = 1.55 [99.99% CI: 1.0 - 2.3] [b] ; p < 0.0001 * *3.1 [95% CI: 3.0 - 3.1]*	*5.6 [95% CI: 3.3 - 5.8]*
Time to MMR at any time *Median (months) in subjects with MMR*	Hazard ratio = 2.01 [99.99% CI: 1.2 - 3.4] [c] ; p < 0.0001 * *6.3 [95% CI: 6.0 - 8.6]*	*9.2 [95% CI: 9.0 - 11.7]*
MMR rate at any time	52.1% [95% CI: 45.9 - 58.3]	33.8 % [95% CI: 28.1 - 39.9] p < 0.00003 *
PFS at 12 months	96.4% [95% CI: 94.1 - 98.7]	96.7% [95% CI: 94.4 - 99.0]
OS at 12 months	97.2% [95% CI: 95.2 - 99.3	98.8% [95% CI: 97.4 - 100.0]

* Considered statistically significant as the specified significance level was p = 0.0001; all p values were adjusted for Hasford score.
[a] For time in cCCyR (a measure of durability), a hazard ratio of 0.7 indicates that a subject treated with dasatinib is 30% less likely to have disease progression after achieving a cCCyR or never achieving a cCCyR compared with a subject treated with imatinib; subjects who never achieved a cCCyR were considered to have progressed on Day 1.
[b] For time-to cCCyR, a hazard ratio of 1.55 indicates that a subject treated with dasatinib is 55% more likely to achieve a cCCyR at any time compared with a subject treated with imatinib.
[c] For time-to MMR, a hazard ratio of 2.01 indicates that a subject treated with dasatinib is more than 2 times more likely to achieve a MMR at any time compared with a subject treated with imatinib.
cCCyR - confirmed complete cytogenetic response, CI - confidence interval, MMR - major molecular response, OS - overall survival, PFS - progression-free survival

With a minimum of 12 months of follow-up, similar high rates of PFS were noted in both dasatinib and imatinib groups. Progression occurred in 5% (n=12) of subjects in the dasatinib group and 6% (n=15) in the imatinib group. Transformation to accelerated or blast phase occurred in 1.9% (5/259) of subjects in the dasatinib group and 3.5% (9/260) of subjects in the imatinib group. Based on the Kaplan-Meier estimates, the estimated 12 month PFS rate in all randomized subjects was 96.4% [95% CI: 94.1%, 98.7%] and 96.7% [95% CI: 94.4%, 99.0%] for the dasatinib and imatinib groups, respectively. The estimated one year survival rates for dasatinib and imatinib treated subjects were also similarly high: 97.2% [95% CI: 95.2%, 99.3%] and 98.8% [95% CI: 97.4%, 100%], respectively.

Comment: *The interim analyses of the secondary efficacy endpoint generally support the superiority of dasatinib compared with imatinib in subjects followed-up for a minimum of 12 months. However, these were interim analyses with the final analyses being planned in subjects with a minimum of 5 years of follow-up. The protocol specified that the secondary efficacy endpoints be ranked in order of importance and the interim analysis of the first of the ranked endpoints (time in CCyR at any time) was not statistically significant given that the pre-specified significance level was 0.0001. Overall, the results of the secondary efficacy endpoints in rank order showed that subjects treated with dasatinib compared with imatinib: were 30% less likely to have disease progression after achieving a cCCyR or never achieving a cCCyR (not statistically significant, p > 0.0001); had a greater MMR at any time (52.1% versus 33.8%, statistically significant, p < 0.0001); were 55% more likely to achieve a cCCyR at any time (statistically significant, p < 0.0001); were twice as likely to achieve a*

MMR at any time (statistically significant, p < 0.0001); had a similar rate of progression free survival at 12 months; and had a marginally smaller rate of overall survival at 12 months.

Tertiary Efficacy Endpoint Results

There were numerous tertiary efficacy endpoint analyses, and only the results for selected tertiary endpoint analyses are summarised below.

CCyR Endpoints: Overall, the tertiary endpoints which assessed CCyR outcomes supported the primary efficacy endpoint cCCyR within 12 months analysis. The rate of best unconfirmed CCyR within 12 months based on any number of metaphases was higher in dasatinib treated subjects than in imatinib treated subjects (85.3% [n=221] versus 73.5% [n=191], respectively). Similarly, the rate of best unconfirmed CCyR within 12 months based on≥ 20 metaphases was higher in dasatinib treated subjects than in imatinib treated subjects (83.4% [n=216] versus 71.5% [n=186], respectively. The cCCyR at any time based on any number of metaphases was higher in the dasatinib treated subjects than in imatinib treated subjects: 76.8% versus 68.1%, respectively, difference = 8.8% [95% CI: 1.2%, 16.4%]. The cCCyR at any time based on ≥ 20 metaphases was higher in dasatinib treated subjects than in imatinib treated subjects: 76.1% versus 66.2%, respectively; difference = 9.9% [95% CI: 2.2%, 17.6%].

CHR Endpoints: Confirmed CHR within 12 months in randomized subjects was similar in the dasatinib and imatinib treatment groups: 91.5% (273/259) and 94.6% [246/260]; difference = -3.1% [95% CI: -7.5%, 1.3%]. The median time to confirmed CHR in subjects with confirmed CHR was the same in both treatment groups: 1.0 [95% 0.9, 1.0] month in the dasatinib group and 1.0 [95% CI: 1.0, 1.0] month in the imatinib group. Median duration of cCHR in subjects who achieved cCHR had not yet been reached. In dasatinib and imatinib treated subjects with a cCHR, the estimated rate of remaining in cCHR at 12 months was 98.3% [95% CI: 96.6, 100] and 96.6% [95% CI: 94.3, 98.9], respectively.

Time to Maximum Clinical Benefit: The hazard ratio [dasatinib: imatinib] was 0.85 [95% CI: 0.53, 1.38], indicating a non statistically significant trend to towards fewer subjects with disease progression / treatment failure / drug intolerance in dasatinib treated subjects compared with imatinib treated subjects (31/259 versus 36/260, respectively).

Treatment Failure: Treatment failure according to the ELN Guidelines[18] occurred in 6.9% (n=18) of subjects in the dasatinib group and 9.6% (n=25) of subjects in the imatinib group. The ELN Guidelines published in 2006 define treatment failure as: (a) disease progression; (b) no haematologic response at 3 months; (c) no CHR or cytogenetic response at 6 months; (d) no PCyR at 12 months; or (e) no CCyR at 18 months.

BCR/ABL Mutations: In treated subjects who discontinued study drug, 60% (24/40) in the dasatinib group and 73% (35/48) in the imatinib group had mutation data. Only 17% (4/24) subjects in the dasatinib group and 14% (5/35) subjects in the imatinib group had mutations identified at the end of treatment. All mutations were outside the P-loop or activation loop. Among the four dasatinib treated subjects, the T315I mutation (in 3

[18] European Leukaemia Net. http://www.leukemia-net.org/content/physicians/recommendations/

subjects) or F317L mutation (in 1 subject) were identified. Among the five imatinib treated subjects, the M244V (in 1 subject), E355G (in 2 subjects), and F359V (in 1 subject) mutations were identified, while one subject had two mutations (D276G and F359C).

Comment: *There was no adjustment of the significance levels for multiplicity of testing of the tertiary endpoints and, consequently, the study wide Type 1 error has not been maintained. Therefore, all significance levels for the pairwise comparisons between dasatinib and imatinib for the tertiary efficacy endpoints should be considered to be nominal rather than actual and the results exploratory rather than definitive. Overall, the rates for the CCyR endpoints numerically favoured dasatinib over imatinib, while the numerical results for the CHR endpoints were similar for the two treatments. Time to maximum treatment benefit numerically favoured dasatinib over imatinib, while treatment failure rates were numerically lower in the dasatinib group compared with imatinib group.*

Clinical Studies in Special Populations

The sponsor's Clinical Summary of Efficacy included a summary of the rates of cCCyR within 12 months (primary efficacy endpoint) comparing dasatinib 100 mg QD with imatinib 400 mg QD in sub-populations by age, race, gender, region and Hasford risk score. The cCCyR response rates in both the dasatinib and imatinib treatment groups were higher in subjects aged ≥ 65 years (80% versus 76%, respectively) than in subjects aged < 65 years (76% versus 65%, respectively). However, the number of patients in both treatment groups aged ≥ 65 years was small (total = 54) and preclude meaningful conclusions concerning efficacy in this age group. The majority of patients in both treatment groups were aged from 21 to 65 years and the response rate in the dasatinib group was higher than in the imatinib group (76.5% [179/234] versus 64.3% [146/227], respectively). The two main racial groups were Caucasian and Asian and cCCyR response rates were marginally higher in Caucasian subjects of the dasatinib and imatinib groups (78% versus 69%, respectively) compared with Asian subjects (75% versus 62%, respectively). In both treatment groups, female subjects had marginally higher cCCyR response rates than males (79% versus 75%, respectively, in the dasatinib group and 69% versus 64%, respectively, in the imatinib group).

The cCCyR rates were higher in the Hasford score low risk group for both dasatinib and imatinib (90% versus 69%, respectively) than in both the Hasford score intermediate risk group (70% versus 67%, respectively) and the Hasford score high risk group (71% versus 60%, respectively). The MMR rates at any time were also higher in the Hasford score low risk group for both dasatinib and imatinib (59% versus 43%, respectively) than in both the Hasford score intermediate risk group (51% versus 33%, respectively) and the Hasford score high risk group (43% versus 22%, respectively). The cCCyR rate and the MMR rate at any time were higher in the dasatinib group than in the imatinib group in the Hasford score low, intermediate and high risk groups.

Analysis Performed Across Trials (Pooled Analyses and Meta-Analyses)

No analyses were submitted pooling data across clinical trials. The submission included the integrated statistical analysis plan for the planned meta-analysis of three, multi-national, multi-centred, randomized, open-label studies comparing dasatinib 100 mg QD

with imatinib 400 mg QD for the treatment of patients with newly diagnosed CML [CA180056, SWOG (CA180072) and SPIRIT 2 (CA180216)]. The primary endpoint of this study is progression free survival with a minimum of 5 years of follow-up. Secondary endpoints include; time to CCyR, time to MMR, duration of CCyR, time in CCyR, transformation free survival, and overall survival. Long term safety will also be assessed.

Product Information (PI) with Respect to Efficacy

It is recommended that the approved indication be "the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase". This wording more closely reflects the patient population included in the pivotal study than the wording proposed by the sponsor.

Evaluator's Overall Conclusions on Clinical Efficacy

Overall, it is considered that the pivotal study has satisfactorily established superior efficacy of dasatinib 100 mg QD (n=259) compared with imatinib 400 mg QD (n=260) for the treatment of newly diagnosed CML-CP in adult patients with at least 12 months of follow-up data. The primary efficacy endpoint in the pivotal study was the cCCyR rate within 12 months. This endpoint is considered to be an acceptable surrogate for long-term clinical benefit. The study showed that subjects treated with dasatinib 100 mg QD had a statistically significantly higher cCCyR rate within 12 months than subjects treated with imatinib 400 mg QD (76.8% [n=199] versus 66.2% [n=172], respectively, p=0.0067). A *post hoc* analysis of the 95% CI of the CMH weighted rate difference between treatments for the cCCyR confirmed the results of the primary analysis. In this *post hoc* analysis, the difference between the two treatments in the cCCyR rates was 10.7% [95% CI: 3.0%, 18.4%]. There were a number of sensitivity analyses of the difference in cCCyR rates between treatments and all supported the results of the primary efficacy analysis.

The pivotal study included a number of pre-specified secondary efficacy endpoints and interim analyses were presented for these parameters. As the study is ongoing the definitive analysis of the pre-specified efficacy endpoints will take place when the data are mature (after subjects have been followed-up for at least 5 years). Overall, the secondary efficacy analyses either supported the superiority of dasatinib over imatinib or at least showed that the difference between the two treatments was unlikely to be clinically significant. There were a number of tertiary efficacy endpoints for which the analyses had not been adjusted for multiplicity of testing. Consequently, the study wide significance level of p=0.05 has not been maintained by the tertiary efficacy analyses and the statistical results observed for these analyses are considered to be nominal rather than actual.

Safety

Introduction

The evaluation of safety focuses on the comparison between dasatinib 100 mg QD and imatinib 400 QD mg in the pivotal efficacy and safety study [CA180056]. In this study, safety analyses were performed on subjects who had received at least one dose of study medication (the all treated population). Safety and tolerability assessments included

spontaneously reported AEs, measurement of vital signs, laboratory tests of haematological and biochemical parameters, and diagnostic tests (Chest Radiograph (CXR), electrocardiogram (ECG), echocardiograms [ECHOS]). The severity of on-study AEs was graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3. AE terms used by investigators were coded and grouped by system organ class and preferred term using the MedDRA dictionary (version 11.0). AEs were generally summarised by severity using the following categories "any Grade", "Grade 3 to 4", and "Grade 5" (death). The causal relationship between the AE and the study drug was determined by the study investigator (as certain, probably, possibly, not likely, not related to treatment).

AEs occurring on or after Day 1 of treatment and no later than 30 days following the last day of treatment were considered on-study. Drug related AEs with an onset more than 30 days after the end of treatment were defined as late toxicities. Events with an onset prior to Day 1 for randomized subjects were pre-treatment events. ECG assessments performed no later than the first day of study medication were defined as baseline. On-study ECG assessments were those conducted on or after Day 2 and no later than 30 days following the last day of treatment.

The sponsor's Summary of Clinical Safety states that there are 2,440 dasatinib treated patients across all clinical trials. These subjects include 2,182 patients from eight studies with CML or Ph+ALL resistant to imatinib and exposed to dasatinib for up to 36 months at doses of 50 mg BD and 70 mg BD (n=1383) and 100 mg QD and 140 mg QD (n=799), and 258 patients from the current pivotal study with CML-CP.

Exposure

The safety data (with a minimum of 12 months of follow-up) were collected from 516 treated subjects (258 in both treatment groups). Subjects started dasatinib at 100 mg QD and imatinib at 400 mg QD and, dose was subsequently adjusted based on response and tolerability.

Dose interruption was defined as a complete omission of dosing on two consecutive occasions. Dose interruptions occurred more frequently in dasatinib treated subjects than in imatinib treated subjects (53.3% [135/258] versus 35.3% [91/258], respectively). The proportion of subjects with > 3 dose interruptions was 8.1% (n=21) in the dasatinib group and 3.9% (n=10) in the imatinib group. The median duration of the first dose interruption due to toxicity was 14 days [range: 2-81] in the dasatinib group and 13 days [range: 2-91] in the imatinib group. Overall, first dose interruptions in the dasatinib and imatinib groups due to haematological toxicities were 26.7% (n=69) and 18.6% (n=48), respectively, and 19.0% (n=49) and 11.6% (n=30), respectively, for non-haematological toxicities.

Dose reduction was defined as the administration of a dose that was lower than both the previous dose and the starting dose such that the reduced dose was given on at least two consecutive occasions. Dose reductions occurred more commonly in the dasatinib group than in the imatinib group (23.3% [60/258] and 14.0% [36/258], respectively). The

proportion of subjects with > 3 dose reductions was 0.4% (n=1) in both treatment groups. The median time to first dose interruption or reduction due to toxicity was 44 days in both treatment groups, with the range being 2 to 615 days in dasatinib treated subjects and 3 to 438 days in imatinib treated subjects. Overall, first dose reductions in the dasatinib and imatinib groups due to haematological toxicities were 12.4% (n=32) and 8.1% (n=21), respectively, and 8.5% (n=22) and 4.7% (n=12), respectively, for non-haematological toxicities.

Dose escalation was defined as the administration of a dose that was higher than both the previous dose and the starting dose and such that the escalated dose was given at least two consecutive times. Dose escalations occurred in a smaller proportion of subjects in the dasatinib group compared with the imatinib group (5.4% [14/258] and 14.0% [36/258], respectively). The most common reason for dose escalation in both the dasatinib and imatinib group was PCyR (2.3% [n=6] and 4.7% [n=12], respectively).

Adverse Events

Overview

In the sponsor's Summary of Clinical Safety it was stated that, following clinical review of adverse event MedDRA preferred terms in CA180056, some adverse events terms were remapped into composite categories of special interest or other preferred terms. The purpose of remapping was to comply with regulatory guidance for reporting adverse reactions in the prescribing information required by the FDA and the EU. In the remapping process, some MedDRA preferred terms were grouped into a single unifying term. Other terms were excluded when they were overly general and/or non-specific, when no clear relationship to dasatinib was observed, or when a more encompassing term was present in the same subject. It was stated that remapping avoided exhaustive lists of every reported AE, including those that were minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy. Remapping was performed by physicians in the BMS clinical research and pharmacovigilance departments.

In general, the frequencies of AEs expressly reported in the CSR and remapped AEs were similar, apart from the number of blood and lymphatic system disorders which were negligible in the remapped data due to exclusion of laboratory toxicities. Investigators were specifically instructed not to list laboratory abnormalities (such as blood or lymphatic system disorders) as AEs except if they met the criteria for SAEs, in which case they were to be reported as a SAE and were required to report the actual laboratory results. Therefore, blood or lymphatic system disorders are not meaningfully accounted for in the remapped AE summary tables. In this review of the AE data (both regardless of relationship to treatment and drug related), the original AEs as reported in the CSR rather than the remapped AEs have been described and discussed unless otherwise stated.

Adverse Events

The incidence of on-study AEs (any grade), irrespective of relationship to treatment, was 92.6% (n=239) in both treatment groups, and the majority of AEs in both groups were Grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 36.4% (n=94) of dasatinib treated

subjects and 30.6% (n=79) of imatinib treated subjects, and the corresponding figures for Grade 5 severity AEs (death) were 2.3% (n=5) and 1.6% (n=4). The majority of Grade 3 or 4 AEs were haematological toxicities. However, investigations were specifically requested not to list laboratory abnormalities as AEs. Consequently, haematological toxicities (myelosuppression) have been discussed below. Preferred term AEs by worst CTC Grade occurring on-treatment, irrespective of relationship to treatment, and occurring with an incidence of ≥ 10% (any grade) in either treatment group are summarised below in Table 9. While the total number of AEs (any grade) were identical in the two treatment groups, non-haematological AEs occurred more commonly in the imatinib group than in the dasatinib group and haematological abnormalities (anaemia, thrombocytopaenia, and neutropaenia) occurred more commonly in the dasatinib group than in the imatinib group.

On study drug related AEs (any grade) were reported in 79.8% (n=206) of subjects in the dasatinib group and 85.3% (n=220) in the imatinib group, and respective Grade 3 or 4 AEs were reported in 30.2% (n=78) and 23.6% (n=61) of subjects. With the exception of pleural effusion, all of the most commonly reported drug related non-haematological AEs (≥ 10% any Grade) were either reported less frequently in the dasatinib group than in the imatinib group or with similar frequencies in both treatment groups. Commonly reported drug related non-haematological AEs occurring less frequently with dasatinib than with imatinib included eyelid oedema (0.8% versus 13.2%), nausea (7.8% versus 19.8%), vomiting (4.7% versus 10.1%), muscle spasms (3.9% versus 17.4%), myalgia (5.8% versus 11.6%), and rash (8.9% versus 13.2%). Drug related pleural effusion was more commonly reported with dasatinib than with imatinib (10.1% [n=26] versus 0%). Commonly reported drug related non-haematological AEs occurring with similar frequencies in both treatment groups (dasatinib versus imatinib) included diarrhoea (17.4% in each group) and headache (11.6% versus 10.5%). Drug related common haematological AEs (≥ 10% any grade) occurring more frequently in the dasatinib group (versus imatinib) were thrombocytopaenia (19.0% versus 14.7%) and neutropaenia (18.2% versus 14.3%). There were no reported drug related commonly reported haematological AEs (≥ 10% any grade) occurring more frequently in the imatinib group than in the dasatinib group.

Table 9: Study CA180056. On-study AEs (n [%]) by worst CTC Grade with preferred term incidence rate of ≥ 10 % in either treatment groups; treated subjects.

	Dasatinib (n=258)			Imatinib (n=258)		
	Any Grade	Severe Grade 3-4	Grade 5	Total Any Grade	Severe Grade 3-4	Grade 5
Subjects with Any AE	239 (92.6)	94 (36.4)	6 (2.3)	239 (92.6)	79 (30.6)	4 (1.6)
Diarrhoea	74 (28.7)	3 (1.2)	0	73 (28.3)	4 (1.6)	0
Thrombocytopaenia	55 (21.3)	36 (14.0)	0	47 (18.2)	23 (8.9)	0
Neutropaenia	48 (18.6)	32 (12.4)	0	40 (15.5)	28 (10.9)	0
Headache	47 (18.2)	0	0	39 (15.1)	1 (0.4)	0
Cough	44 (17.1)	0	0	21 (8.1)	0	0
Pyrexia	34 (13.2)	1 (0.4)	0	33 (12.8)	1 (0.4)	0
Rash	31 (12.0)	0	0	39 (15.1)	2 (0.8)	0
Anaemia	31 (12.0)	5 (1.9)	0	24 (9.3)	5 (1.9)	0
Haemoglobin decreased	30 (11.6)	9 (3.5)	0	13 (5.0)	5 (1.9)	0
Nausea	30 (11.6)	0	0	56 (21.7)	0	0
Vomiting	28 (10.9)	1 (0.4)	0	43 (16.7)	1 (0.4)	0
Fatigue	28 (10.9)	1 (0.4)	0	30 (11.6)	0	0
Pleural Effusion	26 (10.1)	0	0	1 (0.4)	0	0
Myalgia	26 (10.1)	1 (0.4)	0	34 (13.2)	0	0
Asthenia	24 (9.3)	0	0	29 (11.2)	2 (0.8)	0
Weight Increased	20 (7.8)	3 (1.2)	0	28 (10.9)	5 (1.9)	0
Back Pain	19 (7.4)	0	0	27 (10.5)	0	0
Arthralgia	18 (7.0)	0	0	37 (14.3)	2 (0.8)	0
Nasopharyngitis	18 (7.0)	0	0	29 (11.2)	0	0
Pain in extremity	15 (5.8)	0	0	32 (12.4)	0	0
Peripheral Oedema	14 (5.4)	0	0	29 (11.2)	1 (0.4)	0
Muscle Spasms	10 (3.9)	0	0	51 (19.8)	1 (0.4)	0
Eyelid Oedema	2 (0.8)	0	0	35 (13.6)	0	0

Note: Subjects may have more than one event within a class.

Deaths and Serious Adverse Events

Deaths

At the database lock date of 10 January 2010, there had been 16 deaths from any cause: ten (3.9%) in the dasatinib group and six (2.3%) in the imatinib group. Deaths within 30 days of last treatment had been reported in ten subjects: six (2.3%) in the dasatinib group and four (1.6%) in the imatinib group. *Of the ten deaths in the dasatinib group*: four were due to disease progression; four were due to infection; and two were due to myocardial infarction. None of the four deaths due to infection in the dasatinib group appeared to have been associated with significant leucopaenia or neutropaenia at the time of the infection and all subjects were receiving multiple antibiotics. The deaths due to infection

in the dasatinib group were reported as 1 x Klebsiella meningoencephalitis, 1 x unknown cause of infection, 1 x sepsis and 1 x pneumonia, occurring at 1, 3, 5 and 68 days after discontinuing dasatinib, respectively. *Of the six deaths in the imatinib group*: four were due to disease progression; one was due to a myocardial infarction; and one was due to an "unknown cause / clinical deterioration and decrease in performance status" and was classified as "other". Of the 16 deaths in the two treatment groups, two were considered to be drug related (one of the myocardial infarctions in each treatment group).

Other Serious Adverse Events (SAEs)

On-study SAEs, regardless of relationship to study drug, were reported in 17.4% (n=45) of subjects in the dasatinib group and 13.2% (n=34) of subjects in the imatinib group. The majority of SAEs in both treatment groups were Grade 3 or 4 toxicities: 10.5% (n=27) in the dasatinib group and 8.1% (n=21) in the imatinib group. In both treatment groups, the most commonly reported SAEs (any grade) occurred in the gastrointestinal system (3.9% [n=10] dasatinib versus 2.7% [n=7] imatinib), followed by infections and infestations (3.9% [n=10] dasatinib versus 2.3% [n=6] imatinib). SAEs reported in 2 or more subjects in either treatment group are summarised below in Table 10.

Severe (Grade 3 or 4) SAEs (regardless of relationship to treatment) were reported in 10.5% (n=27) of dasatinib treated subjects and 8.1% (n=21) of imatinib treated subjects. Severe SAEs reported by two or more subjects in the dasatinib group included thrombocytopaenia (4 [1.6%]), abdominal pain (3 [1.2%]), anaemia (2 [0.8%]), and disease progression (2 [0.8%]). Severe (Grade 3 or 4) SAEs reported by two or more subjects in the imatinib treated group included diarrhoea (3 [1.2%]), vomiting (3 [1.2%]), thrombocytopaenia (2 [0.8%]), pneumonia (2 [0.8%]), and febrile neutropaenia (2 [0.8%]).

Drug related SAEs were reported by 7.8% (n=20) and 5.0% (n=13) of subjects in the dasatinib and imatinib groups, respectively. Drug related SAEs reported by 2 or more subjects in the dasatinib group were pleural effusion (4 subjects, 1.6%), thrombocytopaenia (3 subjects, 1.2%), and pyrexia (2 subjects, 0.8%). Drug related SAEs reported by two or more subjects in the imatinib group were febrile neutropaenia (2 subjects, 0.8%) and vomiting (2 subjects, 0.8%). All other drug related SAEs each occurred in one subject. Severe (Grade 3 or 4) drug related SAEs were reported by 3.9% (n=10) of subjects in both treatment groups.

Table 10: Study CA180056. Reported on-study SAEs (n [%]) by worst CTC Grade with 2 or more subjects (preferred term) in either treatment group; treated subjects.

	Dasatinib (n=258)			Imatinib (n=258)		
	Total Any Grade	Severe Grade 3-4	Grade 5	Total Any Grade	Severe Grade 3-4	Grade 5
Subjects with Any AE	45 (17.4)	27 (10.5)	6 (2.3)	34 (13.2)	21 (8.2)	4 (1.6)
Pleural Effusion	4 (1.6)	0	0	0	0	0
Thrombocytopaenia	4 (1.6)	4 (1.6)	0	3 (1.2)	2 (0.8)	0
Abdominal Pain	3 (1.2)	3 (1.2)	0	1 (0.4)	0	0
Pneumonia	3 (1.2)	1 (0.4)	1 (0.4)	2 (0.8)	2 (0.8)	0
Disease Progression	3 (1.2)	2 (0.8)	1 (0.4)	3 (1.2)	1 (0.4)	2 (0.8)
Diarrhoea	2 (0.8)	1 (0.4)	0	3 (1.2)	1 (0.4)	0
Vomiting	2 (0.8)	1 (0.4)	0	3 (1.2)	1 (0.4)	0
Anaemia	2 (0.8)	2 (0.8)	0	0	0	0
Fatigue	2 (0.8)	1 (0.4)	0	0	0	0
Pyrexia	2 (0.8)	1 (0.4)	0	1 (0.4)	1 (0.4)	0
Acute MI	2 (0.8)	0	2 (0.8)	0	0	0
MI	2 (0.8)	1 (0.4)	0	1 (0.4)	0	1 (0.4)
Febrile Neutropaenia	0	0	0	2 (0.8)	2 (0.8)	0

Note: Subjects may have more than one event within a class.

Adverse Events of Special Significance

Fluid Retention

Fluid retention is a safety issue of concern in subjects treated with tyrosine kinase inhibitors. Fluid retention occurred more commonly in the imatinib group (46.9% [n=121]) than in the dasatinib group (22.1% [n=57]), but severe (Grade 3 or 4) events occurred infrequently in both the dasatinib (1.2% [n=3]) and the imatinib groups (0.4% [n=1]). AEs characterised by fluid retention are summarised below in Table 11.

Table 11: Fluid retention AEs (n [%]); treated subjects.

	Dasatinib (n=258)			Imatinib (n=258)		
	Any Grade	Severe Grade 3-4	Grade 5	Any Grade	Severe Grade 3-4	Grade 5
Fluid Retention	57 (22.1)	3 (1.2)	0	121 (46.9)	1 (0.4)	1 (0.4)
Superficial Oedema	28 (10.9)	0	0	103 (39.9)	1 (0.4)	0
Pleural Effusion	26 (10.1)	0	0	1 (0.4)	0	0
Other Fluid Related	18 (7.0)	3 (1.2)	0	26 (10.1)	1 (0.4)	1 (0.4)
Ascites	0	0	0	1 (0.4)	0	0
CHF/cardiac dysf.	7 (2.7)	2 (0.8)	0	4 (1.6)	1 (0.4)	0
Generalised Oedema	5 (1.9)	0	0	18 (7.0)	0	1 (0.4)
Pericardial Effusion	5 (1.9)	1 (0.4)	0	3 (1.2)	0	0
Pulmonary Oedema	1 (0.4)	0	0	0	0	0
Pulmonary Hypert.	4 (1.6)	0	0	0	0	0

Note: Subjects may have more than one event within a class. Dys.=dysfunction. CHF=congestive heart failure. Hypert.=hypertension

Pleural effusions were graded using NCI CTCAE (V.3) criteria into the following categories: Grade 1 - asymptomatic; Grade 2 - symptomatic, intervention such as diuretics or up to 2 therapeutic thoracenteses indicated; Grade 3 - symptomatic and supplemental oxygen, > 2 therapeutic thoracenteses, tube drainage, or pleurodesis indicated; and Grade 4 - life-threatening (causing haemodynamic instability or ventilatory support indicated). The protocol specified active monitoring to detect pleural effusions (such as CXR, ECHO). Pleural effusions were reported by 26 (10.1%) subjects in the dasatinib group and one (0.4%) subject in the imatinib group, and all cases in both treatment groups were of Grade 1 or 2 severity.

Of the 26 dasatinib treated subjects with pleural effusions, nine were female and 17 were male. In four dasatinib treated subjects, the pleural effusion was considered serious (3 events resulted in hospitalisation or prolonged hospitalisation, and 1 event was considered to be an important medical event by the investigator). All four dasatinib treated subjects with pleural effusion SAEs (Grade 1 or 2) were able to continue dasatinib without discontinuation for this event; two were continuing therapy at the time of the last available report and two had discontinued due to reasons other than pleural effusion (1x disease progression, 1x treatment failure). Most (84.6%, n=22) of the pleural effusions reported in dasatinib treated subjects occurred more than eight weeks after the start of study drug. The median time to the first pleural effusion in dasatinib treated subjects was 28 weeks [range: 4, 88 weeks], and the median duration of pleural effusion was 50 days

[range: 5, 585 days]. In the 26 dasatinib treated subjects with pleural effusions, five had recurrent effusions (3 had two separate episodes, 1 had three separate episodes and 1 had four separate episodes). Management of the effusion in the 26 subjects was generally by dose interruption (n=19) or dose reduction (n=8). Additionally, seven of the subjects were treated with corticosteroids, twelve with diuretics and one with therapeutic thoracentesis. Of the 26 subjects, three discontinued dasatinib due to pleural effusion and 23 continued on dasatinib despite the pleural effusion. The pleural effusion resolved in eleven of the 23 subjects who continued dasatinib therapy.

Pericardial effusion was reported by five (1.9%) dasatinib treated subjects and three (1.2%) imatinib treated subjects, and none of the eight subjects had the condition on baseline ECHO. Pericardial effusions in all subjects were managed successfully with the exception of one subject in the dasatinib group who discontinued due to pericardial and pleural effusions. *Pulmonary hypertension* occurred in four (1.6%) dasatinib treated subjects and appeared to have been precipitated by pericardial and/or pleural effusions. No pulmonary hypertension events were considered to be serious or resulted in discontinuation.

Bleeding

Bleeding (any grade) was reported in 11.6% (n=30) of dasatinib treated subjects and 11.2% (n=29) of imatinib treated subjects, and the respective frequencies for severe (Grade 3 or 4) bleeding were 1.2% (n=3) and 1.6% (n=4). Of the four subjects with Grade 3 to 4 bleeding events for whom platelet count information was available (1 dasatinib, 3 imatinib), none of these events occurred within three days of severe (Grade 3 or 4) thrombocytopenia. In all subjects with a reported bleeding event, a similar number required transfusions of packed red blood cells in both treatment groups (4 dasatinib and 3 imatinib). Bleeding events were categorised as gastrointestinal (GI), central nervous system (CNS) or Other bleeding (see Table 12, below). "Other" bleeding events were a composite of MedDRA terms including ear haemorrhage, epistaxis, gingival bleeding, haematoma, haematuria, haemoptysis, petechiae, and scleral haemorrhage.

Table 12: Bleeding AEs (n [%]); treated subjects.

	Dasatinib (n=258)			**Imatinib (n=258)**		
	Total Any Grade	Severe Grade 3-4	Grade 5	Total Any Grade	Severe Grade 3-4	Grade 5
GI Bleeding	5 (1.9)	2 (0.8)	0	4 (1.6)	1 (0.4)	0
CNS Bleeding	1 (0.4)	1 (0.4)	0	0	0	0
Other	24 (9.3%)	0	0	25 (9.7)	3 (1.2)	0

Note: Subjects may have more than one event within a class.

In subjects with Grade 3 or 4 thrombocytopaenia (49/256 [19%] dasatinib; 27/257 [11%] imatinib), bleeding events were reported more frequently in the dasatinib group than in the imatinib group (12/49 subjects [25%] versus 4/27 subjects [15%], respectively). Of the twelve subjects in the dasatinib group with bleeding events and Grade 3 or 4

thrombocytopaenia, eleven reported "other" bleeding events which were either Grade 1 (n=9) or Grade 2 (n=3) events, and one reported Grade 1 GI bleeding.

Cardiac Disorders

The incidence of cardiac disorders, regardless of relationship to treatment, was higher in dasatinib treated subjects (10.5% [n=27]) than in imatinib treated subjects (7.4% [n=19]). The majority of cardiac disorders in both groups were Grade 1 or 2 in severity, with Grade 3 or 4 events being reported in 1.6% (n=4) of dasatinib treated subjects and 0.4% (n=1) of imatinib treated subjects. Grade 5 events (death) were reported in 0.4% (n=1) of subjects in both groups. Cardiac disorders reported as SAEs occurred in 1.2% (n=3) of dasatinib treated subjects and 0.8% (n=2) of imatinib treated subjects. Dosage interruptions / reductions due to cardiac disorders occurred more commonly in dasatinib treated subjects than imatinib treated subjects (2.3% [n=6] versus 1.2% [n=3]), as did discontinuations (0.8% [n=2] versus 0% [n=0]). Only palpitations and pericardial effusion occurred in more than one subject in both treatment groups. However, the total number of AEs related to congestive heart failure (CHF)/ cardiac dysfunction occurred more frequently in the dasatinib group than in the imatinib group (2.7% [n=7] versus 1.6 % [n=4]).

Both treatment groups included a significant proportion of randomized subjects with a baseline history of cardiovascular disease (23.6% [n=61] dasatinib; 23.5% [n=61] imatinib). The most frequent baseline cardiovascular diseases in the dasatinib and imatinib treatment groups were, respectively, undergoing treatment for hypertension (13.5% versus 13.1%), hyperlipidaemia (8.5% versus 7.3%) and diabetes mellitus (6.9% versus 5.0%). The high proportion of subjects with a baseline history of cardiovascular disease occurred despite protocol specified exclusions relating to uncontrolled or significant cardiovascular disease. Baseline cardiovascular conditions in the respective treatment groups (dasatinib versus imatinib) included: prior myocardial infarction (1.5% versus 1.9%); percutaneous coronary intervention (1.2% versus 1.2%); documented coronary artery disease (0.8% versus 3.1%); left ventricular (LV) dysfunction with left ventricular ejection fraction (LVEF) < 40% (0.8% versus 0.4%); LV dysfunction with CHF (0.4% versus 1.5%); and unstable angina (0.4% versus 0.8%). Cardiac disorders (any grade) occurring during the study were more than twice as likely to be reported in subjects with a baseline history of cardiovascular disease than in subjects without such a history in both the dasatinib (19.7% [12/61] versus 7.1% [14/197]), and imatinib (11.5% [7/61] versus 4.1% [n=8]) treatment groups.

Other Adverse Events of Special Interest

Diarrhoea (any grade) occurred with similar frequencies in the dasatinib and imatinib groups (28.7% [n=74] and 28.3% [n=73], respectively), as did diarrhoea of Grade 3 or 4 severity (1.2% [n=3] and 1.6% [n=4], respectively). *Nausea / vomiting* (any grade) occurred notably more frequently in the imatinib group (38.4% [n=99]) than in the dasatinib group (22.5% [n=58]), while Grade 3 or 4 severity nausea / vomiting occurred in 0.4% (n=1) of subjects in both groups. *Fatigue* (any grade) occurred with similar frequencies in the dasatinib and imatinib groups (10.9% [n=28] and 11.6% [n=30],

respectively), as did fatigue of Grade 3 or 4 severity (0.4% [n=1] and 0% [n=0], respectively). *Myalgias / arthralgias* (any grade) occurred more frequently in the imatinib group (27.5% [n=71]) than in the dasatinib group (17.1% [n=44]), while Grade 3 or 4 severity myalgias / arthralgias occurred with similar frequencies in the two treatment groups (0.8% [n=2] and 0.4% [n=1], respectively). *Rash* (any grade) occurred notably more frequently in the imatinib group (15.1% [n=39) than in the dasatinib group (12.0% [n=31]), as did rash of Grade 3 or 4 severity (0.8% [n=2] and 0%, respectively).

Laboratory Tests

Haematological (Myelosuppression)

In treated subjects, anaemia, neutropaenia, thrombocytopaenia, and leucopaenia of Grade 1 to 4 severity occurred in the majority of subjects in both treatment groups but with a greater incidence in the dasatinib group compared to the imatinib group (see Table 13, below).

Table 13: Myelosuppression on-treatment, n (%); treated subjects.

	Dasatinib (n=256)			**Imatinib (n=257)**		
	Grade 1-4	Severe Grade 3-4	Grade 5	Grade 1-3	Severe Grade 3-4	Grade 5
Hb (anaemia)	231 (90.2)	26 (10.2)	0	216 (84.0)	17 (6.6)	0
ANC (neutropaenia)	168 (65.6)	53 (20.7)	0	149 (58.0)	52 (20.2)	0
Platelets (thrombocytopaenia)	181 (70.7)	49 (19.1)	0	160 (62.3)	27 (10.5)	0
WBC (leucopaenia)	173 (67.6)	22 (8.6)	0	164 (63.8)	25 (9.7)	0

Hb – Grade 1 < LLN - 10.0 g/dL; Grade 2 < 10.0 – 8.0 g/dL; Grade 3 < 8.0 – 6.5 g/dL; Grade 4 < 6.5 g/dL; Grade 5 Death

ANC – Grade 1 < LLN - 1.5 x 10^9/L; Grade 2 < 1.5 – 1.0 x 10^9/L; Grade 3 < 1.0 – 0.5 x10^9/L; Grade 4 < 0.5 x 10^9/L; Grade 5 Death

Platelets – Grade 1 < LLN – 75.0 x 10^9/L; < 75.0 – 50.0 x 10^9/L; <50.0 – 25.0 x 10^9/L; < 25.0 x 10^9/L; Grade 5 Death

WBC – Grade 1 < LLN - 3.0 x 10^9/L; Grade 2 < 3.0 - 2.0 x 10^9/L; Grade 3 < 2.0 – 1.0 x 10^9/L; Grade 4 < 1.0 x 10^9/L; Grade 5 Death

In the dasatinib and imatinib groups, respectively, rates of Grade 3 or 4 leucopaenia (8.6% versus 9.7%), neutropaenia (20.7% versus 20.2%), and anaemia (10.2% versus 6.6%) were similar in both groups. However, the rates of Grade 3 or 4 thrombocytopenia were notably higher in the dasatinib group than in the imatinib group (19.1% versus 10.5%, respectively). Overall, discontinuations due to myelosuppression were small (7 [1.4%] subjects). Discontinuations due to thrombocytopaenia occurred in five subjects (3 dasatinib versus 2 imatinib), while one subject discontinued due to leucopaenia (dasatinib) and one due to neutropaenia (imatinib).

In subjects with Grade 3 or 4 thrombocytopaenia, onset occurred within 4 to 8 weeks of starting treatment in 59.2% (29/49) of subjects in the dasatinib group and 40.7% (13/27) of subjects in the imatinib group, with the respective figures for onset after 8 weeks being 36.7% (18/49) and 51.9% (14/27). In subjects with Grade 3 or 4 neutropaenia, onset occurred within 4 to 8 weeks of starting treatment in 22.6% (12/53) of subjects in the dasatinib group and 46.2% (24/52) of subjects in the imatinib group, with the respective figures for onset after 8 weeks being 67.9% (36/53) and 50.0% (26/52). In subjects with Grade 3 or 4 leucopaenia, onset occurred in 4 to 8 weeks of starting treatment in 36.4% (8/22) of subjects in the dasatinib group and 56.0% (14/25) of subjects in the imatinib group, with the respective figures for onset after 8 weeks being 63.6% (14/22) and 40.0% (10/25).

At baseline, 94.6% to 96.2% of randomized subjects had Grade 0 leucopaenia, neutropaenia, or thrombocytopaenia, and 37.5% to 43.5% had Grade 0 anaemia. Baseline Grade 3 to 4 haematological AEs were found in ≤ 2.3% of randomized subjects. Most subjects developed haematological AEs on treatment with the majority being Grade 1 or 2 severity. On study, 66.2% (163/246) of subjects in the dasatinib group and 62.9% (156/248) in the imatinib group with no leucopaenia at baseline (Grade 0) had worsening to Grade 1 to 4 during the study, with 8.1% (20/246) of subjects in the dasatinib group and 10.0% (25/248) of subjects in the imatinib group having at least one Grade 3 or 4 event. On study, 64.2% (156/243) of subjects in the dasatinib group and 56.7% (139/245) in the imatinib group with no neutropaenia at baseline (Grade 0) had worsening to Grade 1 to 4 during the study, with 18.9% (46/243) of subjects in the dasatinib group and 20% (48/245) of subjects in the imatinib group having at least one Grade 3 or 4 event. On study, 69.4% (168/242) of subjects in the dasatinib group and 60.6% (148/244) in the imatinib group with no thrombocytopenia at baseline (Grade 0) had worsening to Grade 1 to 4 during the study, with 19.0% (46/242) of subjects in the dasatinib group and 9.8% (24/244) of subjects in the imatinib group having at least one Grade 3 or 4 event. On study, 77.1% (74/96) of subjects in the dasatinib group and 64.6% (73/113) of subjects in the imatinib group with no anaemia at baseline (Grade 0) had worsening to Grade 1 to 4 during the study, with 5.2% (5/96) of subjects in the dasatinib group and 2.7% (3/113) of subjects in the imatinib group having at least one Grade 3 or 4 event.

A similar proportion of subjects in the dasatinib and imatinib groups had recurrent Grade 3 or 4 leucopaenia (1.6% versus 1.9%) or neutropaenia (5.4% versus 5.8%). A higher proportion of subjects in the dasatinib group compared with the imatinib group had recurrent Grade 3 or 4 thrombocytopaenia (6.2% versus 1.6%). A higher proportion of subjects in the dasatinib group compared with the imatinib group had recurrent Grade 3 or 4 anaemia (1.9% versus 0.8%), but subject numbers were small (5 versus 2). In treated subjects, 10.1% (n=26) in the dasatinib group and 5.8% (n=15) in the imatinib group received transfusions. The most common type of transfusion in the dasatinib and imatinib groups (respectively) was packed red blood cells (7.8% [n=20] versus 5.0% [n=13]), followed by platelets (2.7% [n=7] versus 1.9% [n=5]) and fresh frozen plasma (0.4% [n=1] versus 0.4% [n=1]).

Liver Function

The study included only subjects with adequate hepatic function defined as total bilirubin ≤ 2.0 x the institutional upper limit of normal (ULN), and alanine aminotransferase (ALT) and aspartate aminotransferase (AST)≤ 2.5 x the institutional ULN. None of the subjects had Grade 3 or 4 ALT, AST, or total bilirubin abnormalities at baseline. During the study there were four (1.6%) subjects in the dasatinib group with one or more Grade 3 liver function abnormalities (1x Grade 3 ALT; 1x Grade 3 AST; 3x Grade 3 total bilirubin), and three (1.2%) subjects in the imatinib group with one or more Grade 3 or 4 liver function abnormalities (2x Grade 3 ALT; 1x Grade 4 ALT; 1 x Grade 1 AST; 1x Grade 4 ALT). Liver function test abnormalities resulted in study drug discontinuation in two subjects (both in the imatinib group). One of the seven dasatinib treated subjects with Grade 3 ALT and AST on Day 367 had extramedullary CML disease involvement of the liver at baseline. In this subject dasatinib was not interrupted, reduced or discontinued and the transaminitis resolved within approximately five weeks and did not recur.

Renal Function

The study included only subjects with adequate renal function defined as serum creatinine ≤ 3 x the institutional ULN. None of the subjects had Grade 3 or 4 creatinine levels at baseline. During the study, three subjects had Grade 3 creatinine levels (1 [0.4%] dasatinib; 2 [0.8%] imatinib), and no subjects had Grade 4 creatinine levels.

Other Laboratory Chemistry Results

The most commonly occurring "other" laboratory chemistry Grade 3 or 4 events were reported in ≤2 subjects: Grade 3 hypocalcaemia (1 subject in each group); Grade 3 or 4 hypomagnesaemia (0 subjects in each group); Grade 3 hyponatraemia (2 subjects in each group); Grade 4 hyperuricaemia (2 subjects in each group); Grade 3 high alkaline phosphatase levels (1 subject in the dasatinib group versus 0 in the imatinib group).

Vital Signs, ECG and ECHO Results

No tabulated summary of pulse rate or blood pressure changes during the study could be located in the CSR. No obvious significant abnormalities in vital signs in individuals were noted.

ECGs were performed at baseline and after 4 weeks of treatment. QTc(F) intervals and changes from baseline were similar for the two treatment groups. Only two subjects had a QTc(F) > 500 ms , one (0.4%) in each treatment group. QTc(F) increases from baseline of > 60 ms were observed in 4.7% (n=12) of subjects in both treatment groups. The median QTc(F) change from baseline was lower with dasatinib than with imatinib (3.0 ms versus 8.2 ms).

ECHOs were performed and read locally at baseline and after 3 months of treatment. None of the subjects had LVEF < 20% during the study. On-study pericardial effusions were observed in 3.5% (n=9) of subjects in the dasatinib group and 3.9% (n=10) of subjects in the imatinib group. The proportion of subjects with LVEF 20% to 50% was 2.7% (n=7) in the dasatinib group and 1.6 % (n=4) in the imatinib group. Of the eleven subjects with

LVEF 20% to 50% all except one (dasatinib) had mild / moderate cardiac dysfunction at baseline, and seven (4 dasatinib, 3 imatinib) of the eleven had baseline cardiac risk factors including prior myocardial infarction (MI), CHF, hyperlipidaemia, diabetes or hypertension. Of the eleven subjects with LVEF 20% to 50%, eight remain on study treatment (5 dasatinib, 3 imatinib). The proportion of subjects with abnormally elevated pulmonary artery systolic pressure (PASP > 40 mmHg) estimated by Doppler echocardiography was higher in the dasatinib group than in the imatinib group (5.8% [n=15] versus 2.7% [n=5], respectively). In the five subjects with > 20 mmHg increase in PASP from baseline and an on-study PASP > 40 mmHg, one subject in the dasatinib group had symptomatic dyspnoea (Grade 2).

Safety in Special Populations

Age

The data for subjects aged ≥ 65 years should be interpreted cautiously as subject numbers in both the dasatinib and imatinib groups were small (25 and 29, respectively). In subjects aged ≥ 65 years, the proportion with any AE was 96.0% (24/25) in the dasatinib group and 96.6% (28/29) in the imatinib group, and the corresponding figures for subjects aged < 65 years were 92.3% (215/233) and 92.1% (211/229). SAEs occurred more commonly in subjects aged ≥ 65 years than in subjects aged < 65 years in both treatment groups, and in dasatinib treated subjects compared with imatinib treated subjects in both age groups. Similarly, discontinuations due to AEs regardless of relationship to treatment also occurred more commonly in subjects aged ≥ 65 years than in subjects aged < 65 years. Deaths occurred more commonly in subjects aged ≥ 65 years (4.0% [1/25] dasatinib versus 6.9% [2/29] imatinib) compared with subjects aged < 65 years (2.1% [5/233] dasatinib versus 0.9% [2/229] imatinib).

In both treatment groups, the following events were reported at a frequency of at least twice as often in the older subjects than in the younger subjects: dyspnoea; decreased appetite; peripheral oedema; upper abdominal pain; localized oedema; and pruritus. Events that met this threshold but only in the dasatinib group were: pleural effusion (≥ 65 years: 24.0%, < 65 years: 8.6%); nausea (24.0% versus 6.0%); muscle spasms (12.0% versus 3.0%); dizziness (8.0% versus 0%); cough (8.0% versus 0%); and face oedema (8.0% versus 3.9%). No events met this threshold only in the imatinib group. In both treatment groups the following events were reported at a frequency of at least twice as often in younger subjects than in older subjects: pyrexia; arthralgia; and pain in extremity. Events that met this threshold but only in the dasatinib group were: oedema (< 65 years: 1.3%, ≥ 65 years: 0%); periorbital oedema (0.4% versus 0); and eyelid oedema (0.9% versus 0%). No events met this threshold only in the imatinib group.

Sex

In both treatment groups, AEs occurred more frequently in females than in males in both treatment groups: dasatinib (96.5% [110/114] versus 89.6% [129/144]) and imatinib (94.8% [91/96] versus 91.4% [148/162]). However, in both treatment groups SAEs occurred more frequently in males than in females in both treatment groups: dasatinib (20.1% [29/144] versus 14.0% [16/114]) and imatinib (14.2% [23/162] versus 11.5%

[11/96]). Discontinuations due to AEs occurred with similar frequencies in males and females in the dasatinib group (6.3% (9/144) versus 6.1% (7/114, respectively). In contrast, in the imatinib group the frequency was higher in females than in males (8.3% [8/96] versus 4.9% [8/162], respectively). Deaths occurred more commonly in males (2.6% [n=8], four deaths in both the dasatinib and imatinib groups) than in females (1.0% [n=2], both deaths in the dasatinib group).

Race

The majority of treated subjects were Caucasian (53.1% [n=274]), with the next largest group being Asian (39.0% [n=201]). AEs occurred more commonly in Caucasian than in Asian subjects (94.5% [n=259] versus 89.1% [n=179], respectively). However, SAEs and discontinuations due to AEs occurred with similar frequencies in both Caucasian and Asian subjects. The number of Black (n=3) and Other race (n=38) subjects were too small to make meaningful comparisons based on race.

Immunological Adverse Events

Immune system disorders (any grade) were reported in three [1.2%] dasatinib treated subjects (1x allergy to arthropod bite, 1x house dust allergy, 1 x hypersensitivity), and one [0.4%] imatinib treated subject (1x hypersensitivity).

Safety Related to Drug-Drug Interactions

No new data in the submission.

Adverse Events Resulting in Discontinuation

The proportion of treated subjects with at least one AE (any grade), including late toxicities, resulting in treatment discontinuation was 7.4% (n=19) in the dasatinib group and 6.2% (n=16) in the imatinib group. The proportion of Grade 3 or 4 AEs resulting in treatment discontinuation was 4.3% (n=11) in both treatment groups. AEs (any grade) resulting in discontinuation in 2 (0.8%) or more subjects in either of the two treatment groups were (dasatinib versus imatinib): disease progression 2.3% (n=6) versus 0.8% (n=2); pleural effusion 1.2% (n=3) versus 0% (n=0); chest pain 0.8% (n=2) versus 0% (n=0); and thrombocytopaenia 0.8% (n=2) versus 1.2% (n=3). There were a number of other AEs resulting in discontinuation each involving one subject only. There were minor inconsistencies in haematologic AEs reported as leading to discontinuation and haematological laboratory defined AEs resulting in discontinuation. Laboratory haematological AEs resulting in discontinuation were thrombocytopaenia in five subjects (3 dasatinib versus 2 imatinib), leucopaenia in 1 subject (dasatinib) and neutropaenia in one subject (imatinib).

Post-Marketing Experience

Based upon the accumulating clinical and post-marketing experience, four adverse drug reactions were added to the dasatinib Company Core Data Sheet (CCDS) dated [20 November 2009] and include: atrial fibrillation/atrial flutter, thrombosis/embolism (including pulmonary embolism, deep vein thrombosis), interstitial lung disease, and fatal gastrointestinal [haemorrhage]".

Product Information (PI) with Respect to Safety

The PI amendments relating to the current submission have been checked and the additional information is considered to accurately reflect the submitted data. However, there are a number of questions relating to the new safety data. It was noted that the emphasis in the safety sections of the PI relate primarily to adverse drug reaction data rather than to adverse event data regardless of relationship to treatment.

Evaluator's Overall Conclusions on Safety

In both the dasatinib and imatinib treatment groups nearly all subjects experienced at least one or more AEs (any grade) (92.6% [n=239] in each group), while severe Grade 3 or 4 AEs occurred more commonly in the dasatinib group than in the imatinib group (36.4% [n=94] versus 30.6% [n=79], respectively). The high rates of AEs in both treatment groups did not translate into correspondingly high discontinuation rates due to AEs (any grade AEs 7.4% [n=19] dasatinib versus 6.2% [n=18] imatinib, and Grade 3 or 4 AEs 4.3% [n=11] in both groups). The difference between reported AEs and discontinuations due to AEs suggest that most AEs in both treatment groups were manageable by dose reductions and/or dose interruptions and/or symptomatic treatment rather than dose discontinuation. Both dose interruptions and dose reductions occurred more commonly in dasatinib treated subjects compared with imatinib treated subjects. First dose reductions in the dasatinib and imatinib groups due to haematological toxicities were 12.4% and 8.1%, respectively, and to non-haematological toxicities were 8.5% and 4.7%, respectively. First dose interruptions in the dasatinib and imatinib groups due to haematological toxicities were 26.7% and 18.6%, respectively, and to non-haematological toxicities 19.0% and 11.6%, respectively.

Although the overall AE rates (any grade) were identical for the two treatment groups the pattern of AEs differed with non-haematological AEs occurring more commonly in the imatinib group and haematological AEs (myelosuppression) occurring more commonly in the dasatinib group. Non-haematological AEs (any grade) occurring with a frequency of at least 5% in the imatinib group and at least 5% more frequently than in the dasatinib group were the GIT disorders of nausea (21.7% versus 11.6%) and vomiting (16.7% versus 10.9%), the musculoskeletal disorders of arthralgia (14.3% versus 7.0%), pain in extremity (12.4% versus 5.8%), and muscle spasms (19.8 versus 3.8) and the fluid retention disorders of peripheral oedema (19.8% versus 5.4%) and eyelid oedema (13.6% versus 0.8%). Non-haematological AEs (any grade) occurring with a frequency of at least 5% in the dasatinib group and at least 5% more frequently than in the imatinib group were the respiratory, thoracic and mediastinal disorders of cough (17.1% versus 8.1%) and pleural effusion (10.1% versus 0.4%). Grade 3 or 4 non-haematological AEs occurring with a frequency≥ 1% in the imatinib group and more commonly than in the dasatinib group were diarrhoea (1.6% versus 1.2%) and weight increased (1.9% versus 1.2%). There were no Grade 3 or 4 non-haematological AEs occurring with a frequency≥ 1% in the dasatinib group and more commonly than in the imatinib group. Non-haematological AEs (any grade) resulting in discontinuation in two (0.8%) or more subjects in either of the two treatment groups (dasatinib versus imatinib) were disease progression (2.3%

[n=6] versus 0.8% [n=2]), pleural effusion (1.2% [n=3] versus 0% [n=0]) and chest pain (0.8% [n=2] versus 0% [n=0]).

Myelosuppression determined by haematological laboratory abnormalities were more common in the dasatinib group than in the imatinib group. Haematological toxicities (Grade 1-4) of anaemia, neutropaenia, thrombocytopaenia and leucopaenia all occurred more commonly in dasatinib treated subjects than in imatinib treated subjects: anaemia 90.2% (n=231) versus 84.0% (n=216); neutropaenia 65.6% (n=168) versus 58.0% (n=149); thrombocytopaenia 70.7% (n=181) versus 62.3% (n=160); and leucopaenia 67.6% (n=173) versus 63.8% (n=164). Grade 3 or 4 severe anaemia occurred more commonly in the dasatinib group than in the imatinib group (10.2% [n=26] versus 6.6% [n=17]) as did Grade 3 or 4 severe thrombocytopaenia (19.1% [n=49] versus 10.5% [n=27]), while Grade 3 or 4 severe neutropaenia occurred with similar frequencies in both groups (20.7% [n=53] dasatinib versus 20.2% [n=52] imatinib), and Grade 3 or 4 severe leucopaenia occurred marginally more commonly in the imatinib group than in the dasatinib group (9.7% [n=25] versus 8.6% [n=22]). Overall discontinuations due to myelosuppression were small (7 [1.4%] subjects). Discontinuations due to thrombocytopaenia occurred in five subjects (3 dasatinib versus 2 imatinib), while one subject discontinued due to leucopaenia (dasatinib) and one due to neutropaenia (imatinib). Both first dose reductions and interruptions due to haematological toxicities occurred more commonly in the dasatinib group than in the imatinib group. The proportion of subjects receiving transfusions was greater in the dasatinib group (10.1%) than in the imatinib group (5.8%) with most transfusions being packed red blood cells followed by platelets and fresh frozen plasma. There were no deaths due to haematological toxicities in the pivotal study.

SAEs (any grade) occurred more frequently in the dasatinib group (17.4% [n=45]) than in the imatinib group (13.2% [n=34]), as did Grade 3 or 4 SAEs (10.5% [n=27] versus 8.2% [n=21]). The most commonly occurring SAEs (any grade) occurring with a frequency of ≥ 1% in the dasatinib (versus imatinib) group were pleural effusion (1.6% versus 0%), thrombocytopaenia (1.6% versus 1.2%), abdominal pain (1.2% versus 0.4%), pneumonia (1.2% versus 0.8%), and disease progression (1.2% versus 1.2%). The only Grade 3 or 4 SAEs reported with a frequency of ≥ 1% occurred in the dasatinib group (versus imatinib) were thrombocytopaenia (1.6% versus 0.8%) and abdominal pain (1.2% versus 0%). Death was reported in 16 subjects at the date of the database lock: ten (3.9%) in the dasatinib group and six (2.3%) in the imatinib group. The ten deaths in the dasatinib group were considered to be due to disease progression (n=4), infection (n=4), and myocardial infarction (n=2). The six deaths in the imatinib group were considered to be due to disease progression (n=4), myocardial infarction (n=1), and "Other" (n=1).

AEs (any grade) characterised by fluid retention occurred more than twice as commonly in the imatinib group than in the dasatinib group (46.9% [n=121] versus 22.1% [n=55]), but Grade 3 or 4 fluid retention AEs were uncommon in both groups (0.4% [n=1] versus 1.2% [n=3], respectively). Cardiac disorders, occurred more frequently in the dasatinib group than in the imatinib group (10.5% [n=27] versus 7.4% [n=19]), as did Grade 3 or 4

cardiac AEs (1.6% [n=4] versus 0.4% [n=1], respectively). Bleeding events (any grade) occurred with similar frequencies in both the dasatinib and imatinib groups (11.6% [n=30] and 11.2% [n=29], respectively), while Grade 3 or 4 bleeding events were uncommon in both groups (1.3% [n=3] and 1.6% [n=4], respectively). There were no notable differences between the two treatment groups as regards vital sign, ECG or ECHO abnormalities.

Overall, no new safety concerns were observed with dasatinib in the pivotal study in subjects with a minimum of 12 months of follow-up. Haematological toxicities (myelosuppression) were more common in the dasatinib group than in the imatinib group, while the reverse was observed for non-haematological toxicities. Both serious adverse events and deaths occurred more commonly in the dasatinib group than the imatinib group. Treatment discontinuations due to AEs were marginally higher in the dasatinib group than in the imatinib group, but most adverse events appear to have been adequately managed by dose reductions and/or dose interruptions and/or appropriate symptomatic treatment. The overall safety profile of dasatinib for the treatment of patients with newly diagnosed CML is considered to be acceptable. However, the marginally higher rates of treatment discontinuation due to AEs and the higher rates of both first dose interruptions and dose reductions with dasatinib than with imatinib suggests that dasatinib is less well tolerated than imatinib.

Response from Sponsor

While the rates of first dose interruptions and dose reductions were higher with dasatinib compared to imatinib, this did not translate into significant differences in the discontinuation rates due to AEs. The confidence interval for the difference of the rates of discontinuation for AEs includes zero and, thus, does not suggest a statistically significant difference. Importantly, the majority of the most common adverse drug reactions (≥ 10%) were similar or lower with dasatinib compared to imatinib.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

The clinical evaluator posed a series of questions regarding the proposed PI and the sponsor responded to these questions in their Pre-Advisory Committee for Prescription Medicines (ACPM) response.

A summary of the sponsor comments on the clinical evaluation report are presented below:

As a measure to ensure clarity and consistency of the use of AE versus ADR terminology to describe all events regardless of relationship to treatment versus drug-related events, the PI has been amended where appropriate.

Clinical Evaluator Comment:

Exposure

In the fourth paragraph under this section, the following remark is made:

The most common reason for dose escalation in both the dasatinib and imatinib group was PCyR (2.3% [n=6] and 4.7 % [n=12], respectively).

Sponsor Response:

The reason for this dose escalation is defined by suboptimal response, rather than PCyR.

Clinical Evaluator's Summary and Conclusions

Clinical Aspects

The pivotal Phase III study [CA180056] is an ongoing, multi-national, multi-centred, randomized, open-label study in adult patients with newly diagnosed Ph+ CML-CP. Subjects were randomized 1:1 to a starting dose of dasatinib 100 mg QD (n=259) or imatinib 400 mg QD (n=260). The dose could be subsequently escalated, reduced, temporarily interrupted of permanently discontinued, depending on response and toxicities. Randomized subjects were stratified by Hasford risk score into low, intermediate, and high risk groups. Of the 519 randomized subjects, 428 (82.5%) were still on-study at the cut-off date for the submitted data of 10 January 2010. The diagnostic criteria for CML-CP were consistent with clinical practice. In addition, patients were required to have no evidence of extramedullary leukaemic involvement, with the exception of hepato-splenomegaly, and Ph+ or variants must have been demonstrated by bone marrow cytogenetics. The exclusion criteria were extensive and have the potential to limit the generalisability of the results.

The open-label design of the study exposes it to the well known biases associated with studies of this type. However, the objective pre-specified primary and secondary efficacy endpoints mitigate the risks of bias in this study. Nevertheless, there appears to be no significant reason why the study could not have been conducted using a double-blind design for at least 12 months. The use of imatinib as an active control rather than the use of a placebo control is acceptable given that this drug is generally considered to be first-line treatment for CML-CP. The primary efficacy endpoint of cCCyR response within 12 months is an acceptable surrogate for long-term clinical benefit.

The limitations of the current Australian submission include presentation of only one pivotal study examining the efficacy and safety of dasatinib for the treatment of newly diagnosed adult patients with CML-CP in subjects followed-up for 12 months. However, this is considered to be acceptable in view of the extensive safety data available for dasatinib for up to 36 months of follow-up derived from its use as a second line agent for the treatment of patients with CML-CP resistant to or intolerant of prior treatment with imatinib. The population PK study suggests that there are no notable differences in the PKs of dasatinib in imatinib naive and imatinib experienced subjects with CML. The submission of a single pivotal study with only 12 month follow-up data to support registration for the target condition in the target population would have been difficult to

justify in the absence of existing long-term efficacy and safety data on the use of dasatinib for the treatment of CML-CP resistant to or intolerant of prior treatment with imatinib.

Benefit Risk Assessment

Benefits

Overall, it is considered that the pivotal study has satisfactorily established superior efficacy of dasatinib 100 mg QD (n=259) compared with imatinib 400 mg QD (n=260) in adult patients with newly diagnosed CML-CP with at least 12 months of follow-up data. The primary efficacy endpoint in the pivotal study was the cCCyR rate within 12 months. This endpoint is considered to be an acceptable surrogate for long-term clinical benefit (such as PFS or OS). The study showed that subjects treated with dasatinib 100 mg QD had a statistically significantly higher cCCyR rate within 12 months than subjects treated with imatinib 400 mg QD (76.8% [n=199] versus 66.2% [n=172], respectively, p=0.0067). *Post hoc* analysis of the 95% CI of the difference between the two cCCyR rates confirmed the results of the primary analysis: difference = 10.6% [95% CI: 3.0%, 18.4%]. All sensitivity analyses of the difference in cCCyR rates within 12 months between the two treatments were statistically significant and supported the primary efficacy analysis. Disease progression was reported in only four subjects with a cCCyR (1/199 dasatinib, 3/177 imatinib). Based on the Kaplan-Meier estimates in subjects with cCCyR, the estimated rate of remaining in cCCyR at 12 months was 97.4% [95% CI: 92.5%, 100%] in the dasatinib group and 99.1% [95% CI: 97.2, 100%] in the imatinib group.

The pivotal study included a number of pre-specified secondary efficacy endpoints and interim analyses were presented for these parameters. As the study is ongoing the definitive analysis of the pre-specified efficacy endpoints will take place when the data are mature (after subjects have been followed-up for at least 5 years). The results of the interim analyses of the secondary efficacy endpoints in pre-specified rank order of importance showed that subjects treated with dasatinib compared with imatinib: were 30% less likely to have disease progression after achieving a cCCyR or never achieving a cCCyR (p=0.035 but not statistically significant at pre-specified significance level of p=0.0001); had a greater MMR rate at any time (52.1% versus 33.8%, statistically significant, $p < 0.0001$); were 55% more likely to achieve a cCCyR at any time (statistically significant, $p < 0.0001$); were twice as likely to achieve a MMR at any time (statistically significant, $p < 0.0001$); had a similar rate of progression free survival at 12 months (96.4% versus 96.7%); and had a marginally lower rate of overall survival at 12 months (97.2% versus 98.8%). In all subjects, disease progression occurred in 5% (n=12) and 6% (n=15) of subjects in the dasatinib and imatinib groups, respectively. Transformation to accelerated or blast phase occurred in 1.9% (5/259) and 3.5% (9/260) of subjects in the dasatinib and imatinib groups, respectively. Overall, the secondary efficacy analyses are considered to support the superiority of dasatinib over imatinib. The 12 month follow-up data for disease free progression and overall survival are similar in the two treatment groups, but the follow-up period is too short to make meaningful comparisons between treatments for these two clinical endpoints.

The pivotal study included numerous tertiary efficacy endpoints including cytogenetic, haematological, molecular and clinical outcomes. However, analyses of these endpoints had not been adjusted for multiplicity of testing. Consequently, the study wide significance level of p=0.05 was not maintained by the tertiary efficacy analyses. It is considered that the statistical results observed for tertiary efficacy endpoints analyses are nominal rather than actual and the results should be considered to be exploratory rather than definitive.

Risks

Safety data in the pivotal study were collected from 516 treated patients with a minimum of 12 months of follow-up (258 in both treatment groups). The median of the average daily dasatinib doses was 99 mg [range: 21 mg, 36 mg] and the median of the average daily imatinib doses was 400 mg [range: 125 mg, 657 mg]. The median treatment duration in both groups was 14 months. There were no long-term safety data for dasatinib for the treatment of patients with newly diagnosed CML-CP. However, there are previously evaluated safety data for dasatinib in 2,182 patients for the treatment of imatinib resistant or intolerant CML or Ph+ ALL with a minimum of 24 months of follow-up.

In both the dasatinib and imatinib treatment groups, nearly all subjects experienced at least one or more AE (any grade) (92.6% [n=239] in each group), while severe Grade 3 or 4 AEs occurred more commonly in the dasatinib group than in the imatinib group (36.4% [n=94] versus 30.6% [n=79], respectively). The high rates of AEs in both treatment groups did not translate into correspondingly high discontinuation rates due to AEs (any grade AEs 7.4% [n=19] dasatinib versus 6.2% [n=18] imatinib, and Grade 3 or 4 AEs 4.3% [n=11] in both groups). The difference between reported AEs and discontinuations due to AEs suggest that most AEs in both treatment groups were managed by dose reductions and/or dose interruptions and/or symptomatic treatment rather than dose discontinuation. Both dose interruptions and dose reductions occurred more commonly in dasatinib treated subjects than in imatinib treated subjects. First dose reductions in the dasatinib and imatinib groups due to haematological toxicities were 12.4% and 8.1%, respectively, and to non-haematological toxicities were 8.5% and 4.7%, respectively. First dose interruptions in the dasatinib and imatinib groups due to haematological toxicities were 26.7% and 18.6%, respectively, and to non-haematological toxicities 19.0% and 11.6%, respectively.

Although the overall AE rates (any grade) were identical in the two treatment groups the pattern differed with non-haematological AEs occurring more commonly in the imatinib group and haematological AEs occurring more commonly in the dasatinib group. Non-haematological AEs (any grade) occurring with a frequency of at least 5% in the imatinib group and at least 5% more frequently than in the dasatinib group were nausea (21.7% versus 11.6%), vomiting (16.7% versus 10.9%), arthralgia (14.3% versus 7.0%), pain in extremity (12.4% versus 5.8%), muscle spasms (19.8% versus 3.8%), peripheral oedema (19.8% versus 5.4%) and eyelid oedema (13.6% versus 0.8%). Non-haematological AEs (any grade) occurring with a frequency of at least 5% in the dasatinib group and at least 5% more frequently than in the imatinib group were cough (17.1% versus 8.1%) and pleural effusion (10.1% versus 0.4%). Grade 3 or 4 non-haematological AEs occurring with

a frequency ≥ 1% in the imatinib group and more commonly than in the dasatinib group were diarrhoea (1.6% versus 1.2%) and weight increased (1.9% versus 1.2%). There were no Grade 3 or 4 non-haematological AEs occurring with a frequency≥ 1% in the dasatinib group and more commonly than in the imatinib group. Non-haematological AEs (any grade) resulting in discontinuation in two (0.8%) or more subjects in either of the two treatment groups (dasatinib versus imatinib) were disease progression (2.3% [n=6] versus 0.8% [n=2]), pleural effusion (1.2% [n=3] versus 0% [n=0]) and chest pain (0.8% [n=2] versus 0% [n=0]).

Haematological laboratory results showed that myelosuppression was more common in the dasatinib than in the imatinib group. The haematological toxicities (Grade 1-4) of anaemia, neutropaenia, thrombocytopaenia and leucopaenia all occurred more commonly in dasatinib treated subjects compared with imatinib treated subjects: anaemia 90.2% (n=231) versus 84.0% (n=216); neutropaenia 65.6% (n=168) versus 58.0% (n=149); thrombocytopaenia 70.7% (n=181) versus 62.3% (n=160); and leucopaenia 67.6% (n=173) versus 63.8% (n=164). Grade 3 or 4 severe anaemia occurred more commonly in the dasatinib group than in the imatinib group (10.2% [n=26] versus 6.6% [n=17]), as did Grade 3 or 4 severe thrombocytopaenia (19.1% [n=49] versus 10.5% [n=27]), while Grade 3 or 4 severe neutropaenia occurred with similar frequencies in both groups (20.7% [n=53] dasatinib versus 20.2% [n=52] imatinib) and Grade 3 or 4 severe leucopaenia occurred marginally more commonly in the imatinib group than in the dasatinib group (9.7% [n=25] versus 8.6% [n=22]). Overall, total discontinuations due to myelosuppression were small (7 [1.4%] subjects). Discontinuations due to thrombocytopaenia occurred in five subjects (3 dasatinib versus 2 imatinib), while one subject discontinued due to leucopaenia (dasatinib) and one due to neutropaenia (imatinib). The proportion of subjects receiving transfusions was greater in the dasatinib group (10.1%) than in the imatinib group (5.8%), with most transfusions being packed red blood cells followed by platelets and fresh frozen plasma. There were no deaths due to haematological toxicities in the pivotal study.

SAEs (any grade) occurred more frequently in the dasatinib group (17.4% [n=45]) than in the imatinib group (13.2% [n=34]), as did Grade 3 or 4 severe SAEs (10.5% [n=27] versus 8.2% [n=21]). The most commonly occurring SAEs (any grade) reported with a frequency of ≥ 1% in the dasatinib (versus imatinib) group were pleural effusions (1.6% versus 0%), thrombocytopaenia (1.6% versus 1.2%), abdominal pain (1.2% versus 0.4%), pneumonia (1.2% versus 0.8%), and disease progression (1.2% versus 1.2%). The only Grade 3 or 4 severe SAEs reported with a frequency of≥ 1% occurring in the dasatinib group (versus imatinib) were thrombocytopaenia (1.6% versus 0.8%) and abdominal pain (1.2% versus 0%). Death was reported in 16 subjects at the date of the database lock: ten (3.9%) in the dasatinib group and six (2.3%) in the imatinib group. The ten deaths in the dasatinib group were considered to be due to disease progression (n=4), infection (n=4), and myocardial infarction (n=2). The six deaths in the imatinib group were considered to be due to disease progression (n=4), myocardial infarction (n=1), and “other” (n=1).

In addition to myelosuppression, other AEs of particular interest included fluid retention, bleeding and cardiac disorders. *Fluid retention* AEs (any grade) occurred more than twice as commonly in the imatinib group than in the dasatinib group (46.9% [n=121] versus 22.1% [n=55]), but Grade 3 or 4 severe AEs were uncommon in both groups (0.4% [n=1] versus 1.2% [n=3], respectively). The most common fluid retention AE in both treatment groups was superficial oedema (10.9% dasatinib versus 39.9% imatinib). Pleural effusions occurred notably more commonly in the dasatinib group than in the imatinib group (10.1% versus 0.4%, respectively). Similarly, fluid retention due to CHF/cardiac dysfunction, pericardial effusion and pulmonary hypertension all occurred more commonly in the dasatinib group (1.6% to 2.7%) than in the imatinib group (1.2% to 1.6%). Generalised oedema was more common in the imatinib group (7.0%) than in the dasatinib group (1.9%). *Cardiac disorders*, occurred more commonly in the dasatinib group than in the imatinib group (10.5% [n=27] versus 7.4% [n=19]), as did Grade 3 or 4 severe cardiac disorders (1.6% [n=4] versus 0.4% [n=1]). CHF / cardiac dysfunction occurred more commonly in the dasatinib group than in the imatinib group (2.7% [n=7] versus 1.6 % [n=4]), while MIs occurred in one subject from each group. In both treatment groups, cardiac disorders occurred about twice as commonly in subjects with a baseline history of cardiac disease than in subjects without such a history. *Bleeding events* (any grade) occurred with similar frequencies in both the dasatinib and imatinib groups (11.6% [n=30] and 11.2% [n=29], respectively), while Grade 3 or 4 severe bleeding events were uncommon in both groups (1.3% [n=3] and 1.6% [n=4], respectively).

Liver and renal function laboratory abnormalities were uncommon in both treatment groups and did not significantly differ between the two groups. The only non-haematological laboratory abnormalities of note were Grade 3 hypophosphataemia (4.4% [n=11] dasatinib versus 21.6% [n=54] imatinib), and Grade 3 hypokalaemia (0% [n=0] dasatinib versus 2.3% [n=6] imatinib). There were no notable differences between the two treatment groups as regards on-treatment changes in vital signs, ECGs or ECHOs. Subjects aged ≥ 65 years experienced AEs more commonly than subjects aged < 65 years in both treatment groups. In both treatment groups, AEs occurred more frequently in females than in males, while SAEs occurred more frequently in males than in females. Discontinuations due to AEs occurred with similar frequencies in males and females in the dasatinib group, but in the imatinib group the frequency was higher in females than in males.

Safety Specifications

The sponsor proposes to investigate the long-term clinical benefit of dasatinib in adult patients with newly diagnosed CML-CP from a prospectively designed meta-analysis pooling the results from three on-going studies to assess treatment effect in > 1,500 subjects. The safety and efficacy data from this meta-analysis should be submitted to the TGA for evaluation as soon as they become available. In addition, the safety and efficacy data from the on-going pivotal study in subjects with at least 5 years of follow-up should be submitted to the TGA as soon as the results become available.

Benefit-Risk Balance

The pivotal study is considered to have satisfactorily established superior efficacy of dasatinib 100 mg compared with imatinib 400 mg QD for the treatment of adult patients with newly diagnosed chronic Ph+ CML-CP. The primary efficacy endpoint analysis suggests that treatment with dasatinib 100 mg QD is likely to result in better long-term clinical outcomes of disease free progression and overall survival than imatinib 400 mg QD. However, it is possible that resistance to dasatinib might emerge with long-term treatment and this will only be determined by the proposed long-term follow studies. No new safety signals were observed for dasatinib in subjects with a minimum of 12 months of follow-up and a median duration of treatment of 14 months. Haematological toxicities (myelosuppression) were more common in the dasatinib group than in the imatinib group, while the reverse was observed for most non-haematological toxicities. Both serious adverse events and deaths occurred more commonly in the dasatinib group than in the imatinib group. Treatment discontinuations due to AEs were marginally higher in the dasatinib group than in the imatinib group, but most adverse events appear to have been adequately managed by dose reductions and/or dose interruptions and/or appropriate symptomatic treatment rather than treatment discontinuation.

On balance, the overall safety profile of dasatinib for the treatment of patients with newly diagnosed CML is considered to be acceptable. No new or unexpected safety signals associated with dasatinib were observed in the pivotal study. However, the marginally higher rates of treatment discontinuations due to AEs, and the higher rates of both first dose interruptions and first dose reductions due to non-haematological and haematological toxicities in dasatinib treated subjects suggests that the drug is less well tolerated than imatinib in patients with newly diagnosed CML-CP. Nevertheless, the risks of dasatinib are well known and appear to be manageable with dose modification and/or symptomatic treatment. Overall, it is considered that the risk benefit balance for dasatinib 100 mg QD for the treatment of adults with Ph+ CML-CP is favourable.

Conclusions

It is considered that the submission has satisfactorily established the efficacy and safety of dasatinib for the treatment of adults with newly diagnosed Ph+ CML-CP. It is recommended that dasatinib be approved for treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase. It is recommended that the starting dose of dasatinib for this indication be 100 mg QD.

Recommended Conditions of Registration

It is recommended that the final 5-year follow-up results from the pivotal study [CA180056] be submitted to the TGA for evaluation as soon as the data become available. This should be a condition of registration.

It is recommended that the results from the long-term meta-analysis of data from the BMS sponsored pivotal [CA180056] and the two ongoing non-BMS sponsored studies from co-operative groups (SPIRIT2 in the UK and SWOG 0325 in the USA/Canada) in adult patients

with newly diagnosed Ph+ CML-CP be submitted to the TGA for evaluation as soon as they become available. This should be a condition of registration.

Product Information

The recommended wording of the indication has been modified from that proposed by the sponsor to more closely align it with the population included in the pivotal study. The recommended wording of the indication is

> *"The treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase".*

V. Pharmacovigilance Findings

Risk Management Plan

The following is a summary of the RMP submitted by the sponsor to the Office of Product Review (OPR), TGA, for review (Table 14).

Table 14: Safety concerns, Proposed Pharmacovigilance (PV) actions and Proposed Risk Minimization Activities.

Safety concern	Proposed PV activities	Proposed risk minimization activities
Important Identified Risks		
Myelosuppression	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	1) The revised recommended starting dosage for chronic phase CML is 100 mg QD 2) Warning in Section 4.4 of the SmPC 3) Dose adjustment guidelines in Section 4.2 of the SmPC 4) Presented as ADRs (e.g., myelosuppression, pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anemia) in Section 4.8 of SmPC
Fluid retention	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	1) The revised recommended starting dosage for chronic phase CML is 100 mg QD and the recommended starting dosage for accelerated and blast phase CML and for Ph+ ALL is 140 mg QD 2) Warning in Section 4.4 of the SmPC 3) Presented as ADRs (e.g., pleural effusion, ascites, pulmonary edema, pericardial effusion, superficial edema) and specific risk information (including time to onset, reversibility, and clinical management) for pleural effusion observed in the newly diagnosed CML in chronic phase in Section 4.8 of SmPC
Bleeding-related events	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	1) The revised recommended starting dosage for chronic phase CML is 100 mg QD and the recommended starting dosage for accelerated and blast phase CML and for Ph+ ALL is 140 mg QD 2) Warning in Section 4.4 of the SmPC (including clarification that the effects of dasatinib on platelet activation may also contribute to bleeding in addition to the thrombocytopenia) 3) Presented as ADRs (e.g., hemorrhage, petechiae, epistaxis, gastrointestinal

Table 14 continued.

Safety concern	Proposed PV activities	Proposed risk minimization activities
		hemorrhage, CNS bleeding) in Section 4.8 of SmPC (including clarification that the effects of dasatinib on platelet activation may also contribute to bleeding in addition to the thrombocytopenia), and (iv) nonclinical findings in Section 5.3 of SmPC
QT prolongation	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	1) Warning in Section 4.4 of the SmPC, 2) Added as an uncommon cardiac ADR in Section 4.8 of the SmPC 3) Presented as laboratory test abnormalities in Section 4.8 of SmPC 4) Nonclinical findings in Section 5.3 of SmPC
Important Potential Risks		
Severe hepatotoxicities	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	ADRs (e.g., hepatitis, cholestasis) and laboratory test abnormalities (e.g., elevation of transaminases and bilirubin) are presented in Section 4.8 of SmPC to warn physicians of the risks of potential severe hepatotoxicities
Direct cardiotoxic effects (e.g., cardiomyopathy)	• Routine PV activities • Targeted follow-up efforts for individual case reports of relevant serious cardiac events (e.g., CHF, cardiomyopathy, myocardial ischemic events) to collect additional clinical and diagnostic information and to provide comprehensive data assessment and reporting in PSUR • Comprehensive data analysis for relevant new and important cardiac risk information in the annual updates of CA180056	1) The revised recommended starting dosage for chronic phase CML is 100 mg QD and the recommended starting dosage for accelerated and blast phase CML and for Ph+ ALL is 140 mg QD 2) Warning in Section 4.4 of the SmPC (including information for CHF/cardiac dysfunction and fatal MI and precautionary statement indicating that patients treated with dasatinib who have risk factors or a history of cardiac disease should be monitored carefully) 3) Events of CHF/cardiac dysfunction and MI with fatal outcome listed as ADRs in Section 4.8 of SmPC
Pregnancy-related malformative or feto/neonatal toxicity	• Routine PV activities (including closely follow-up of all pregnancy cases and targeted follow-up on cases	1) Potential risk information related to pregnancy in Section 4.6 of SmPC 2) Relevant information related to the

Table 14 continued.

Safety concern	Proposed PV activities	Proposed risk minimization activities
	reporting pregnancy-related malformative or feto/neonatal toxicity)	Segment I nonclinical reproductive study findings are being added to Section 5.3 of SmPC
Important Missing Information		
Carcinogenicity	• Routine PV activities • Additional information from ongoing clinical trials • The results from a rat carcinogenicity study will be submitted by Dec 2010, as stated in the letter of undertaking (FUM Module 4 - 3).	Information related to carcinogenesis in Section 5.3 of SmPC
Other Potential Concerns		
Drug interactions: dasatinib and potent CYP3A4 inhibitors or CYP3A4 substrates	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	1) Warning in Section 4.4 of the SmPC 2) Drug interaction information in Section 4.5 of the SmPC

Safety concern	Proposed PV activities	Proposed risk minimization activities
Drug interactions: dasatinib and other highly protein-bound medicinal products	• Routine PV as listed in the current RMP • Additional information from ongoing clinical trials	Drug interaction information in Section 4.5 of the SmPC

Routine pharmacovigilance (PV) practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified.

There is no objection to the sponsor implementing the proposed application of routine pharmacovigilance activities for the ongoing safety concerns as detailed above. However, it is not clear from the information provided in the RMP how the sponsor proposes to monitor exposure to dasatinib during pregnancy and pregnancy outcomes with particular attention to abnormal pregnancy outcomes and congenital anomalies. It is recommended to the Delegate that the sponsor be required to provide details to the OPR of how they plan to follow up reports of pregnancy and related malformative or feto/neonatal toxicity, in particular if the sponsor is planning to have a pregnancy registry and if so, if Australian women will be included in the registry. It is not expected at this stage that the sponsor should update the RMP with this additional information.

The application of routine risk minimisation activities for each of the identified safety concerns is acceptable. Where the sponsor had indicated that a change had been made to

the Summary of Product Characteristics (SmPC), the Australian PI was checked. The changes made to the EU SmPC were reflected in the Australian PI.

With regard to the proposed routine risk minimisation activities, the draft product information is considered satisfactory.

With regard to the proposed routine risk minimisation activities, the draft consumer medicine information is considered satisfactory.

The sponsor addressed the recommendations outlined in the OPR evaluation. Of note, it was recommended that the sponsor provide the OPR with details of how they plan to follow up on reports of pregnancy and related malformative or feto/neonatal toxicity. The sponsor provided details of their follow up procedures.

The OPR were satisfied with the sponsor's response.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics (PK)

The submission included a population PK analysis based on a total of 1216 patients from seven studies in CML and Ph+ ALL patients receiving dasatinib in the second-line setting, and one study in the first line setting. PK of the drug in the first line setting were found to be comparable to that previously observed in the second line setting (Figure 1).

An analysis of 235 subjects in the first line setting examined the relationship between dasatinib exposure and efficacy (as measured by the complete cytogenetic response rate – CCyR). Prolonged dose interruptions were associated with a reduction in efficacy (see Figure 2).

A further analysis based on 802 subjects in both the first and second line settings examined the relationship between dasatinib exposure and the incidence of pleural effusion, a known adverse effect of dasatinib. Increased dasatinib exposure resulted in an increased risk of pleural effusion. Increased age also increased the risk.

Efficacy

Evidence for efficacy comes from a single, Phase III randomised controlled trial (Study CA180056 aka the **DASISION** study). The study has been published[19].

[19] Kantarjian H *et al.* (2010) Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukaemia. *N Engl J Med* 362:2260-70.

Subjects enrolled in the trial had previously untreated CML in chronic phase. They were randomised to receive either:

- Dasatinib 100 mg once daily; or
- Imatinib 400 mg once daily.

The dose of imatinib used is the same as that registered for the first-line treatment of CML in Australia.

The primary endpoint for the study was the percentage of patients who achieved a complete cytogenetic response (CCyR) after 12 months. The CCyR had to be confirmed by bone marrow cytogenetics on two separate occasions at least 28 days apart. CCyR rate is a surrogate endpoint. The sponsor's justification for using this as an endpoint was reviewed by the clinical evaluator and found to be acceptable. Also, the TGA has adopted Appendix 2 to the EMA guideline on anticancer agents[20]. This guideline discusses appropriate endpoints for studies in haematological malignancies and recommends CCyR rate at 12 months as an appropriate endpoint for trials of first-line therapy in CML.

The data presented for the study derive from an analysis conducted when all subjects had been followed up for a minimum of 12 months. Confirmed CCyR rate at 12 months was improved with dasatinib (76.8% versus 66.2%; p = 0.0067). Median time to CCyR was also shorter (3.1 versus 5.5 months).

The results from the analysis of multiple other secondary and exploratory endpoints generally favoured the dasatinib arm. Results for survival and progression-free survival were not mature as very few patients had experienced disease progression or died. The study is ongoing and a final analysis of these secondary endpoints will be conducted after all subjects have had a minimum of 5 years of follow-up.

Safety

The overall safety profile of the two drugs in the pivotal study, in terms of the incidence of adverse events, is summarised in the following table:

Table 15: Overall Safety Profiles.

	Dasatinib	**Imatinib**
Adverse events (any grade)	92.6 %	92.6 %
Related adverse events (any grade)	79.8 %	85.3%
Grade 3 or 4 adverse events	36.4 %	30.6 %
Related Grade 3 or 4 adverse events	30.2 %	23.6 %
Serious adverse events	17.4 %	13.2 %
Related serious adverse events	7.8 %	5.0 %
Discontinuations due to adverse events	7.4 %	6.2 %
Deaths	10	6
Related deaths	1	1

These data suggest that the two drugs have similar overall toxicity, with a small increase in serious adverse events and Grade 3 or 4 adverse events with dasatinib. Dose

[20] Appendix 2 to the Guideline on the evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95 Rev. 3) on Confirmatory studies in Haematological Malignancies. 18 February 2010. EMA/CHMP/EWP/520088/2008 (previously EMEA/CHMP/EWP/520088/2008)

interruptions and reductions were also more common with dasatinib treatment (CER p 67).

In terms of individual toxicities, dasatinib was associated with increased incidences of haematological events, pleural and pericardial effusion, congestive heart failure and pulmonary hypertension. Imatinib was associated with a higher incidence of overall fluid retention events, especially superficial oedema (p32), as well as nausea and vomiting and musculoskeletal events.

Risk Management Plan

A satisfactory RMP has been negotiated with the sponsor by the TGA's Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

1. Overall-risk benefit
   The pivotal study has demonstrated that dasatinib has superior efficacy compared to imatinib in the first-line treatment of CML, on the surrogate endpoint of CCyR. The safety profile of the two drugs is similar, with perhaps a small increase in serious/Grade 3 or 4 adverse events with dasatinib. There are some differences between the two drugs in the pattern of individual adverse events. Overall it appears that the risk-benefit profile of dasatinib is comparable to that of imatinib, and that it is therefore favourable.

2. Long-term efficacy outcomes
   Current standard treatment of CML involves the initial use of imatinib followed by the second-line use of dasatinib or nilotinib if disease relapse occurs. If dasatinib is used in the first line setting, there is no established second line TKI that can be used on disease relapse. Imatinib is unlikely to be effective in the second line setting. Long-term survival could be better with the current sequential use of two drugs rather than the use of single agent dasatinib. This question will only be answered with long term follow-up from the pivotal study included in this submission and other ongoing Phase III trials. Given the early evidence of superior efficacy provided by the pivotal study in this submission, the Delegate considered it would be reasonable, as recommended by the clinical evaluator, to approve the first-line indication with a condition of registration that the sponsor provides the long-term follow-up data when available.

The Delegate proposed to approve the application. The advice of the Advisory Committee for Prescription Medicines (ACPM) is requested.

Response from Sponsor

Bristol-Myers Squibb Australia Pty Ltd have reviewed the evaluation report from the Clinical Evaluator and Delegate's Request for ACPM Advice and have noted that both the evaluator and Delegate have recommended approval of the application to extend the approved indications to include the treatment of adults with newly diagnosed chronic myeloid leukaemia (CML) in chronic phase. The company has noted that the Delegate has referred the application to ACPM to seek their advice in relation to the extended indication.

Please note that a change to the indication from the original application was made following recommendation by the Clinical Evaluator from "…treatment of adults aged 18 years or over with newly diagnosed chronic myeloid leukaemia (CML)" to "treatment of

adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase".

The company has reviewed the Delegate's response and provides a response to issues raised below.

Overall Risk-Benefit

The sponsor would like to confirm that Study CA180056 demonstrated superior efficacy in newly diagnosed chronic phase CML based on the primary endpoint confirmed complete cytogenic response (cCCyR). The study reported both cCCyR and unconfirmed CCyR rates in newly diagnosed chronic phase CML patients treated with dasatinib versus imatinib. Cytogenetic response (CyR) was based on the number of Ph+ metaphases reported by conventional bone marrow (BM) cytogenetics. A confirmed response (cCyR) is defined as two separate cytogenetic analyses performed at least 28 days apart. The primary endpoint for Study CA180056 is a cCCyR within 12 months. Unconfirmed CCyR was also reported. Dasatinib treatment produced a significantly ($p < 0.007$) higher cCCyR rate (76.8% versus 66.2%) and a higher CCyR rate (83.4% versus 71.5%) within 12 months compared to imatinib. Both confirmed and unconfirmed cytogenetic response rates were higher in dasatinib treated patients and the study demonstrated superior efficacy in first line CML based on the primary endpoint cCCyR.

Long-Term Efficacy Outcomes

The sponsor agrees longer follow-up is needed to confirm long-term survival is better in patients treated with dasatinib (second generation TKI) compared to imatinib (first generation TKI). However, there is strong evidence to support Sprycel's position as first line treatment in newly diagnosed chronic myeloid leukemia in the chronic phase (CML-CP). This is based upon randomized, Phase III data showing a statistically significant and clinically relevant increase in the rate of "optimal responses," defined by the European LeukemiaNet[21] as CCyR within 12 months of treatment, compared to imatinib. In addition, the randomized data also show a significant improvement in the rate of MMR, time to CCyR and time to MMR. The surrogate endpoint of CCyR has been demonstrated in multiple independent studies to correlate with long-term outcome, including PFS and OS, these data provide high level evidence for the position of Sprycel in the initial treatment of newly diagnosed CML-CP patients. In a 5-year update of the IRIS trial, a landmark analysis demonstrated that among patients who did or did not achieve a CCyR within 12 months, 97% and 81%, respectively, were free from progression to accelerated or blast phase CML at 5 years ($p<0.001$)[22]. Similarly, a large single institution experience in the United Kingdom demonstrated that among patients who did or did not achieve a CCyR within 12 months, the 5-year PFS was 96% and 74% ($p=0.007$), respectively, and 5-year overall survival (OS) was 98% and 74% ($p=0.03$), respectively[23]. Another report of a single institution's experience demonstrated a strong association between 12-month CCyR and PFS.[24] In this report of 276 chronic phase CML patients, 78% achieved a CCyR by month 12

[21] Baccarani, M., J. Cortes *et al*. (2009). "Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet." *J Clin Oncol* 27(35): 6041-51.
[22] Druker BJ, Guilhot F, O'Brien SG, *et al*. (2006). Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. *N Engl J Med* 355:2408-17.
[23] De Lavallade H, Apperley JF, Khorashad JS, *et al*. (2008). Imatinib for newly diagnosed patients with chronic myeloid leukemia: Incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol* 26:3358-3363.
[24] Kantarjian H, O'Brien S, Shan J, *et al*. (2008). Cytogenetic and molecular responses and outcome in chronic myelogenous leukemia: need for new response definitions? *Cancer* 112:837-45.

on imatinib. Among the patients with a CCyR, 97% remained progression-free after 5 years. Major molecular response (MMR) is an important goal of therapy and has been established as a good predictor of long-term response. Evidence from the IRIS trial showed that MMR at 18 months was a better predictor for excellent long-term outcomes, with an event-free survival (EFS) at 72 months of 98% and 89% (p = 0.0137) in those with an MMR (≤ 0.1%) compared with those with a BCR ABL/control gene ratio of > 0.1%-< 1%, respectively.[25] Similarly, in the IRIS trial, patients who achieved CCyR and MMR after 18 months of imatinib had an estimated 100% rate of PFS at 60 months follow-up. Achieving an optimal response (CCyR at 12 months, MMR at 18 months) can predict survival close to 100% after 6 to 7 years (ELN Guidelines)[21]. In addition, the use of dasatinib as standard therapy in first line may further reduce the need for subsequent therapies. In Study CA180056, results showed that nearly half the subjects in the dasatinib treatment group discontinued due to disease progression or treatment failure compared with the imatinib treatment group (5% versus 9% in the dasatinib and imatinib groups, respectively). For those patients who do require subsequent therapy, several treatment options are available. For patients with intolerance to dasatinib, published data suggest the lack of cross-intolerance between imatinib and dasatinib.[26] Thus, dasatinib-intolerant patients will still have the option of imatinib treatment. There is growing literature that other tyrosine kinase inhibitors may provide efficacy after dasatinib resistance or intolerance. In one study, 60 CML patients with imatinib resistance or intolerance who failed to respond to dasatinib were given nilotinib 400 mg twice daily (BID). The MCyR rate was 43% among patients with chronic phase with a median duration of MCyR of 18 months (range 3-23 months).[27] A separate series of patients published from M.D. Anderson Cancer Center described 14 patients who failed treatment with imatinib and dasatinib and then received nilotinib 400 mg BID. The MCyR, CCyR, and MMR rates were 21%, 14% and 21%, respectively.[28] Thus, other tyrosine kinase inhibitor (TKI) treatment may offer an additional option of subsequent therapy after dasatinib treatment.

Additionally, although not established, there are many emerging therapies that may provide a therapeutic option after dasatinib in the future (like AP24534 (ponatinib), omacetaxine, DCC-2036, KW-2449). Thus, the greater efficacy of dasatinib compared with imatinib, as shown in the 12-month data provided, may reduce the need for subsequent therapies for CML and translate into improved long-term outcomes. For those patients who will require subsequent treatment, several potentially efficacious options exist, and consideration should be given to other treatments under development. Based on this, the

[25] Hughes TP, Branford S, White DL, *et al.* (2008). Impact of early dose intensity on cytogenetic and molecular responses in chronic- phase CML patients receiving 600 mg/day of imatinib as initial therapy. *Blood* 112:3965-73.
[26] Hochhaus A, Kantarjian HM, Baccarani M, *et al.* (2007). asatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 1 09:2303-9.; Khoury HJ, Goldberg SL, Mauro MJ, *et al*. (2008). Dasatinib lack of cross intolerance to imatinib in patients (pts) with chronic myelogenous leukemia chronic phase (CML-CP) intolerant to imatinib: a retrospective analysis of safety [abstract 7015]. *J Clin Oncol*. 26(15s):375s.; A randomized multicenter open-label study of BMS-354825 versus imatinib mesylate (Gleevec,® Glivec®) 800 mg/d in subjects with chronic phase Philadelphia chromosome positive chronic myeloid leukemia who have disease that is resistant to imatinib at a dose of 400 - 600 mg/d. Final Study Report - 2-year Follow-up (CA180017). Bristol-Myers Squibb Research and Development; 2008.
[27] Giles FJ, Abruzzese E, Rosti G, *et al.* (2010). Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy. *Leukemia*. 4:1299-1301.
[28] Garg RJ, Kantarjian H, O'Brien S, *et al.* (2009). The use of nilotinib or dasatinib after failure to 2 prior tyrosine kinase inhibitors: long-term follow-up. *Blood* 114:4361-68.

sponsor believes the benefit/risk ratio remains favourable for dasatinib in first-line treatment of chronic phase CML, and agrees longer follow-up on Study CA180056 will be needed to confirm this. The sponsor agrees to submission of these data when they are available.

Conclusion

Overall, the sponsor concurs with the Clinical Evaluator and Delegate's evaluation and agreed to submit follow-up data from Study CA180056 when they become available.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Bristol-Myers Squibb Australia Pty Ltd to register dasatinib (Sprycel) tablet 20, 50, 70 and 100 mg for an extension of indications to include:
Sprycel (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase.

In making this recommendation, the ACPM considered that the pivotal study has demonstrated that dasatinib has superior efficacy compared to imatinib in the first-line treatment of CML, on the surrogate endpoint of complete cytogenetic response rate (CCyR). However, a small increase in serious/Grade 3 or 4 adverse events with dasatinib was suggested by the data.

The ACPM agreed with the Delegate, that the submitted evidence of safety and efficacy supported a favourable benefit-risk profile for this product for the proposed indication. The ACPM noted the relationship between dasatinib exposure and efficacy (as measured by CCyR) and safety. Prolonged dose interruptions were associated with a reduction in efficacy while increased exposure increased the incidence of pleural effusion, a known adverse effect.

The use of surrogate endpoints is always somewhat problematic and it was acknowledged that the relationship between measures of transcript clearance, CCyR and cure has not yet been defined.

It was noted that a satisfactory RMP has been negotiated with the sponsor by the TGA's Office of Product Review.

Long term efficacy outcomes, however, are unclear. This question will only be answered with long term follow-up from the pivotal study included in this submission and other ongoing phase III trials.

The ACPM considered the specific conditions of registration should include:

- Submission of long-term follow-up data when available.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Sprycel tablet containing dasatinib 30mg, 50mg, 70mg and 100mg in bottle and blister pack for the new indication:

> *For the treatment of adults aged 18 years and over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase.*

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

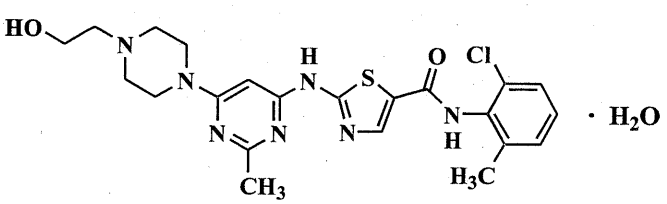
PRODUCT INFORMATION

SPRYCEL®

NAME OF THE MEDICINE
SPRYCEL® (Dasatinib)

DESCRIPTION

SPRYCEL® (Dasatinib) is a potent inhibitor of multiple oncogenic kinases, cellular enzymes involved in the transmission of growth signals from the cell membrane to the nucleus. The chemical name for dasatinib is *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The CAS number for dasatinib monohydrate is 863127-77-9. The molecular formula is $C_{22}H_{26}C1N_7O_2S \bullet H_2O$, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib drug substance has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water (0.008 mg/mL) at 24 ± 4 ºC. The pH of a saturated solution of dasatinib in water is about 6.0. Two basic ionization constants (pK_a) were determined to be 6.8 and 3.1, and one weakly acidic pK_a was determined to be 10.8. The solubilities of dasatinib in various solvents at 24 ± 4 ºC are as follows: slightly soluble in ethanol (USP), methanol, polyethylene glycol 400, and propylene glycol; very slightly soluble in acetone and acetonitrile; and practically insoluble in corn oil.

SPRYCEL® film coated tablets contain the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hydroxpropyl cellulose and magnesium stearate. The tablet coating contains: hypromellose, titanium dioxide and polyethylene glycol.

PHARMACOLOGY

Mechanism of Action

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nanomolar or subnanomolar concentrations. Dasatinib also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of kinase's active conformation.

Dasatinib has been demonstrated to inhibit the survival/proliferation of human leukaemic cell lines *in vitro*, and to inhibit the growth of human CML (chronic myeloid leukaemia) xenografts in SCID mice, in both imatinib-sensitive and resistant models of the disease. Antileukaemic activity was seen in dasatinib-treated mice in a model of CML with CNS involvement. Non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR-ABL independence, most BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving SRC-family kinases (LYN and FYN) and P-glycoprotein (multi-drug resistance protein 1) overexpression.

PHARMACOKINETICS

The pharmacokinetics of SPRYCEL® (dasatinib) were evaluated in 229 healthy subjects and in 84 patients with leukaemia.

Absorption

Dasatinib is rapidly absorbed in patients following oral administration. The absolute bioavailability of dasatinib has not been determined. Peak concentrations were observed between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUC_τ) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg twice daily (BID).

Data from a study of 54 healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following consumption of a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. Consumption of a low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects are unlikely to be clinically significant.

Distribution

In patients, SPRYCEL® has a large apparent volume of distribution (2505 L) suggesting that the drug is extensively distributed in the extravascular space.

Metabolism

Dasatinib is extensively metabolized in humans. In a study of 8 healthy subjects administered 100 mg of [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the drug. The overall mean terminal half-life of dasatinib is approximately

5-6 hours. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.

Elimination

Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [^{14}C]-labelled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the administered radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the administered dose in urine and faeces, respectively, with the remainder of the dose being metabolites.

Special Populations

Pharmacokinetic analyses of demographic data indicate that there are no clinically relevant effects of age and gender on the pharmacokinetics of SPRYCEL®.

The pharmacokinetics of SPRYCEL® have not been evaluated in paediatric patients.

The effect of hepatic impairment on the single-dose pharmacokinetics of dasatinib was assessed in 8 moderately hepatic-impaired subjects who received a 50 mg dose and 5 severely hepatic-impaired subjects who received a 20 mg dose compared to matched healthy subjects who received a 70 mg dose of dasatinib. The mean C_{max} and AUC of dasatinib adjusted for the 70 mg dose was decreased by 47% and 8%, respectively, in subjects with moderate hepatic impairment compared to subjects with normal hepatic function. In severely hepatic-impaired subjects, the mean C_{max} and AUC adjusted for the 70 mg dose was decreased by 43% and 28% respectively, compared to subjects with normal hepatic function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 27 months. Responses were durable across all phases of CML and Ph+ ALL.

Four single-arm, uncontrolled, open-label Phase II clinical trials were conducted to determine the safety and efficacy of SPRYCEL® in patients with CML in chronic, accelerated, or myeloid blast phase, who were either resistant or intolerant to imatinib.

One randomized, comparative trial was conducted in chronic phase patients who failed initial treatment with 400 or 600 mg imatinib. The starting dose of SPRYCEL® was 70 mg twice daily. Dose modifications were allowed for improving activity or management of toxicity.

Two randomised, open-label Phase III trials were conducted to evaluate the efficacy of SPRYCEL® administered once daily compared with SPRYCEL® administered twice daily. In addition, one open-label, randomised, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML.

The efficacy of SPRYCEL® is based on haematological and cytogenetic response rates. Durability of response and estimated survival rates provide additional evidence of SPRYCEL® clinical benefit.

A total of 2,440 patients were evaluated in clinical trials; of these 23% were ≥ 65 years of age and 5% were ≥ 75 years of age.

Chronic Phase CML - Newly Diagnosed

An international open-label, multi-centre, randomised, comparative Phase III study was conducted in adult patients with newly diagnosed chronic phase CML. Patients were randomised to receive either SPRYCEL® 100 mg once daily or imatinib 400 mg once daily. The primary end-point was the rate of confirmed complete cytogenetic response (cCCyR) within 12 months. Secondary endpoints included time in cCCyR (measure of durability of response), time to cCCyR, major molecular response (MMR) rate, time to MMR, progression free survival (PFS) and overall survival (OS). Other relevant efficacy results included CCyR and complete molecular response (CMR) rates.

A total of 519 patients were randomised to a treatment group: 259 to SPRYCEL® and 260 to imatinib. Baseline characteristics were well balanced between the two treatment groups with respect to age (median age was 46 years for the SPRYCEL® group and 49 years for the imatinib group with 10% and 11% of patients 65 years of age or older, respectively), gender (women 44% and 37%, respectively), and race (Caucasian 51% and 55%; Asian 42% and 37%, respectively). At baseline, the distribution of Hasford Scores was similar in the SPRYCEL® and imatinib treatment groups (low risk: 33% and 34%; intermediate risk 48% and 47%; high risk: 19% and 19%, respectively).

With a minimum of 12 months follow-up, 85% of patients randomised to the SPRYCEL® group and 81% of patients randomised to the imatinib group were still receiving first-line treatment. Discontinuation due to disease progression occurred in 3% of SPRYCEL®-treated patients and 5% of imatinib-treated patients.

Efficacy results are presented in Table 1. A statistically significantly greater proportion of patients in the SPRYCEL® group achieved a cCCyR compared with patients in the imatinib group within the first 12 months of treatment. Efficacy of SPRYCEL® was consistently demonstrated across different subgroups, including age, gender, and baseline Hasford score.

Table 1: Efficacy Results in Newly Diagnosed Patients with Chronic Phase CML (12-month data)

	SPRYCEL® n= 259	imatinib n= 260	p-value
	Response rate (95% CI)		
Cytogenetic Response within 12 months			
cCCyR[a]	76.8% (71.2–81.8)	66.2% (60.1–71.9)	p< 0.007*
CCyR[b]	85.3% (80.4-89.4)	73.5% (67.7-78.7)	—
Major Molecular Response[c]	52.1% (45.9–58.3)	33.8% (28.1–39.9)	p< 0.00003 *
	Hazard Ratio (99.99% CI)		
Time-to cCCyR	1.55 (1.0-2.3)		p< 0.0001*
Time-to MMR	2.01 (1.2-3.4)		p< 0.0001*
Durability of cCCyR	0.7 (0.4-1.4)		p< 0.035**

[a] Confirmed complete cytogenetic response (cCCyR) is defined as a response noted on two consecutive occasions (at least 28 days apart).

[b] Cytogenetic response (CCyR) is based on a single bone marrow cytogenetic evaluation. The CCyR results refer to best unconfirmed cytogenic response within 12 months for any number of metaphases.

[c] Major molecular response (at any time) was defined as BCR-ABL ratios ≤ 0.1% by RQ-PCR in peripheral blood samples standardized on the International scale.

*Adjusted for Hasford Score and indicated statistical significance at a pre-defined nominal level of significance.
**Not significant.
CI = confidence interval

For time-to cCCyR, a hazard ratio of 1.55 indicates that a patient treated with SPRYCEL is 55% more likely to achieve a cCCyR at any time compared to a patient treated with imatinib. Similarly, for time-to MMR, a hazard ratio of 2.01 indicates a patient treated with SPRYCEL is more than two times more likely to achieve a MMR at any time compared to a patient treated with imatinib. For durability of cCCyR (time-in response), a hazard ratio of 0.7 indicates a patient treated with SPRYCEL is 30% less likely to have disease progression after achieving a cCCyR (or never achieving a cCCyR) compared to a patient treated with imatinib.

Median time to cCCyR was 3.1 months in the SPRYCEL® group and 5.6 months in the imatinib group in patients with a confirmed CCyR. Median time to MMR was 6.3 months in the SPRYCEL® group and 9.2 months in the imatinib group in patients with a MMR. The rates of cCCyR in the SPRYCEL® and imatinib treatment groups, respectively, within 3 months (54% and 30%), 6 months (70% and 56%), and 9 months (75% and 63%) were consistent with the primary endpoint. The rates of MMR in the SPRYCEL® and imatinib treatment groups, respectively, within 3 months (8% and 0.4%), 6 months (27% and 8%), 9 months (39% and 18%), and 12 months (46% and 28%) were also consistent with the primary endpoint. The rate of CMR (i.e. at least 4.5-log reduction from a standardised baseline value BCR-ABL ratio≤ 0.0032%) at any time was 8.5% versus 4.2% in the SPRYCEL® and imatinib treatment groups, respectively.

Progression was defined as increasing white blood cells despite appropriate therapeutic management, loss of CHR, partial CyR or CCyR, progression to accelerated phase or blast

phase, or death. The estimated 12-month PFS rate was 96.4% (CI: 94.1% - 98.7%) and 96.7% (CI: 94.4% - 99.0%) for the SPRYCEL® and imatinib treatment groups, respectively. Transformation to accelerated or blast phase occurred less frequently with SPRYCEL® (n = 5; 1.9%) than with imatinib-treated patients (n = 9; 3.5%).

Data described below are from studies using a starting dosage of 70 mg twice daily. See DOSAGE AND ADMINISTRATION for the recommended starting dosages for chronic phase CML, accelerated phase CML, myeloid and lymphoid blast phase CML, and Ph+ALL.

Chronic Phase CML - Resistance or Intolerance to Prior Imatinib Therapy

Two clinical trials were conducted in patients resistant or intolerant to imatinib; the primary efficacy endpoint in these trials was Major Cytogenetic Response (MCyR):

1. An open-label, randomised, comparative multi-centre study was conducted in patients who failed initial treatment with 400 or 600 mg imatinib. They were randomised (2:1) to either SPRYCEL® (70 mg twice daily) or imatinib (400 mg twice daily). Crossover to the alternative treatment arm was allowed if patients showed evidence of disease progression or intolerance that could not be managed by dose modification. The primary endpoint was MCyR at 12 weeks. Results are available for 150 patients: 101 were randomised to SPRYCEL® and 49 to imatinib (all imatinib-resistant). The median time from diagnosis to randomisation was 64 months in the SPRYCEL® group and 52 months in the imatinib group. All subjects were extensively pretreated. Prior complete haematologic response (CHR) to imatinib was achieved in 93% of the overall patient population. A prior MCyR to imatinib was achieved in 28% and 29% of the patients in the dasatinib and imatinib arms, respectively. Median duration of treatment was 23 months for dasatinib (with 44% of patients treated for > 24 months to date) and 3 months for imatinib (with 10% of patients treated for >24 months to date). Ninety-three percent (93%) of patients in the SPRYCEL® arm and 82% of the patients in the imatinib arm achieved a CHR prior to cross-over. At 3 months, a MCyR occurred more often in the SPRYCEL® arm (36%) than in the imatinib arm (29%). Notably, 22% of patients reported a complete cytogenetic response (CCyR) in the SPRYCEL® arm while only 8% achieved a CCyR in the imatinib arm. With longer treatment and follow-up (median of 24 months), MCyR was achieved in 53% of the SPRYCEL®-treated patients (CCyR in 44%) and 33% of the imatinib-treated patients (CCyR in 18%) prior to crossover. Among patients who had received imatinib 400 mg prior to study entry, MCyR was achieved in 61% of patients in the SPRYCEL® arm and 50% in the imatinib arm.

Based on the Kaplan-Meier estimates, the proportion of patients who maintained MCyR for 1 year was 92% (95% CI: [85%-100%]) for SPRYCEL® (CCyR 97%, 95% CI: [92%-100%]) and 74% (95% CI: [49%-100%]) for imatinib (CCyR 100%). The proportion of patients who maintained MCyR for 18 months was 90% (95% CI: [82%-98%]) for SPRYCEL® (CCyR 94%, 95% CI: [87%-100%]) and 74% (95% CI: [49%-100%]) for imatinib (CCyR 100%).

Based on the Kaplan-Meier estimates, the proportion of patients who had progression-free survival (PFS) for 1 year was 91% (95% CI: [85%-97%]) for SPRYCEL® and 73% (95% CI: [54%-91%]) for imatinib. The proportion of patients who had PFS at 2 years was 86% (95% CI: [78%-93%]) for SPRYCEL® and 65% (95% CI: [43%-87%]) for imatinib.

A total of 43% of the patients in the dasatinib arm, and 82% in the imatinib arm had treatment failure, defined as disease progression or cross-over to the other treatment (lack of response, study drug intolerance, etc.).

The rate of major molecular response (defined as BCR-ABL/control transcripts $\leq 0.1\%$ by RQ-PCR in peripheral blood samples) prior to crossover was 29% for SPRYCEL® and 12% for imatinib.

2. An open-label, single-arm, multi-centre study was conducted in patients resistant or intolerant to imatinib (i.e. patients who experienced significant toxicity during treatment with imatinib that precluded further treatment).

A total of 387 patients received dasatinib 70 mg twice daily (288 resistant and 99 intolerant). The median time from diagnosis to start of treatment was 61 months. The majority of the patients (53%) had received prior imatinib treatment for more than 3 years. Most resistant patients (72%) had received > 600 mg imatinib. In addition to imatinib, 35% of patients had received prior cytotoxic chemotherapy, 65% had received prior interferon, and 10% had received a prior stem cell transplant. Thirty-eight percent of patients had baseline mutations known to confer imatinib resistance. Median duration of treatment on SPRYCEL® was 24 months with 51% of patients treated for > 24 months to date. Efficacy results are reported in Table 2. MCyR was achieved in 55% of imatinib-resistant patients and 82% of imatinib-intolerant patients. With a minimum of 24 months follow-up, 21 of the 240 patients who had achieved a MCyR had progressed and the median duration of MCyR had not been reached.

Based on the Kaplan-Meier estimates, 95% (95% CI: [92%-98%]) of the patients maintained MCyR for 1 year and 88% (95% CI: [83%-93%]) maintained MCyR for 2 years. The proportion of patients who maintained CCyR for 1 year was 97% (95% CI: [94%-99%]) and for 2 years was 90% (95% CI: [86%-95%]). Fifty-two percent (52%) of the imatinib-resistant patients with no prior MCyR to imatinib (n = 188) achieved a MCyR with SPRYCEL®.

There were 45 different BCR-ABL mutations in 38% of patients enrolled in this trial. Complete haematologic response or MCyR was achieved in patients harbouring a variety of BCR-ABL mutations associated with imatinib resistance except T315I. The rates of MCyR at 2 years were similar whether patients had any baseline BCR-ABL mutation, P-loop mutation, or no mutation (63%, 61% and 62%, respectively).

Among imatinib-resistant patients, the estimated rate of PFS was 88% (95% CI: [84%-92%]) at 1 year and 75% (95% CI: [69%-81%]) at 2 years. Among imatinib-intolerant patients, the estimated rate of PFS was 98% (95% CI: [95%-100%]) at 1 year and 94% (95% CI: [88%-99%]) at 2 years.

The rate of major molecular response at 24 months was 45% (35% for imatinib-resistant patients and 74% for imatinib-intolerant patients).

Accelerated Phase CML

An open-label, single-arm, multi-centre study was conducted in patients intolerant or resistant to imatinib. A total of 174 patients received SPRYCEL® 70 mg twice daily (161 resistant and 13 intolerant to imatinib). The median time from diagnosis to start of treatment was 82 months. Median duration of treatment on SPRYCEL® was 14 months with 31% of patients

treated for >24 months to date. The rate of major molecular response (assessed in 41 patients with a CCyR) was 46% at 24 months. Efficacy results are reported in Table 2.

Myeloid Blast Phase CML

An open-label, single-arm, multi-centre study was conducted in patients intolerant or resistant to imatinib. A total of 109 patients received SPRYCEL® 70 mg twice daily (99 resistant and 10 intolerant to imatinib). The median time from diagnosis to start of treatment was 48 months. Median duration of treatment on SPRYCEL® was 3.5 months with 12% of patients treated for >24 months to date. The rate of major molecular response (assessed in 19 patients with a CCyR) was 68% at 24 months. Efficacy results are reported in Table 2.

Lymphoid Blast Phase CML and Ph+ ALL

An open-label, single-arm, multi-centre study was conducted in patients with lymphoid blast phase CML or Ph+ ALL who were resistant or intolerant to prior imatinib therapy. A total of 48 patients with lymphoid blast CML received SPRYCEL® 70 mg twice daily (42 resistant and 6 intolerant to imatinib). The median time from diagnosis to start of treatment was 28 months. Median duration of treatment on SPRYCEL® was 3 months with 2% treated for >24 months to date. The rate of major molecular response (all 22 treated patients with a CCyR) was 50% at 24 months. In addition, 46 patients with Ph+ ALL received SPRYCEL® 70 mg twice daily (44 resistant and 2 intolerant to imatinib). The median time from diagnosis to start of treatment was 18 months. Median duration of treatment on SPRYCEL® was 3.0 months with 7% of patients treated for >24 months to date. The rate of major molecular response (all 25 treated patients with a CCyR) was 52% at 24 months. Efficacy results are reported in Table 2. Of note, major haematologic responses (MaHR) were achieved quickly (most within 35 days of first SPRYCEL® administration for patients with lymphoid blast CML, and within 55 days for patients with Ph+ ALL).

Table 2: Efficacy in Phase II SPRYCEL® Single-Arm Clinical Studies[a]

	Chronic (n=387)	Accelerated (n=174)	Myeloid Blast (n=109)	Lymphoid Blast (n=48)	Ph+ ALL (n=46)
Haematologic Response Rate[b] (%)					
MaHR (95% CI)	n/a	**64% (57-72)**	**33% (24-43)**	**35% (22-51)**	**41% (27-57)**
CHR (95% CI)	**91% (88-94)**	50% (42-58)	26% (18-35)	29% (17-44)	35% (21-50)
NEL (95% CI)	n/a	14% (10-21)	7% (3-14)	6% (1-17)	7% (1-18)
Duration of MaHR (%; Kaplan-Meier Estimates)					
1 Year	n/a	79% (71-87)	71% (55-87)	29% (3-56)	32% (8-56)
2 Years	n/a	60% (50-70)	41% (21-60)	10% (0-28)	24% (2-47)
Cytogenetic Response[c] (%)					
MCyR (95% CI)	**62% (57-67)**	40% (33-48)	34% (25-44)	52% (37-67)	57% (41-71)
CCyR (95% CI)	54% (48-59)	33% (26-41)	27% (19-36)	46% (31-61)	54% (39-69)
Survival (%; Kaplan-Meier Estimates)					
Progression-Free					
1 Year	91% (88-94)	64% (57-72)	35% (25-45)	14% (3-25)	21% (9-34)
2 Years	80% (75-84)	46% (38-54)	20% (11-29)	5% (0-13)	12% (2-23)
Overall					
1 Year	97% (95-99)	83% (77-89)	48% (38-59)	30% (14-47)	35% (20-51)
2 Years	94% (91-97)	72% (64-79)	38% (27-50)	26% (10-42)	31% (16-47)

Note: Data described in this table are from using a starting dosage of 70 mg twice daily. See DOSAGE AND ADMINISTRATION for the recommended starting dosage.

[a] Numbers in bold font are the results of primary endpoints

[b] Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic responses: (MaHR) = complete haematologic response (CHR) + no evidence of leukaemia (NEL).
CHR (chronic CML): WBC ≤ institutional ULN, platelets < 450 x 10^9/L, no blasts or promyelcytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.
CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥ 1.0 x 10^9/L , platelets ≥ 100 x 10^9/L , no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L, or platelets ≥ 20 x 10^9/L and ≤ 100 x 10^9/L.

[c] Cytogenetic response criteria: complete (0% Ph+ metaphases) or partial (> 0%-35%). MCyR (0%-35%) combines both complete and partial responses.

n/a = not applicable C1 = confidence interval ULN = upper limit of normal range

The outcome of patients with bone marrow transplantation after SPRYCEL® has not been fully evaluated.

Phase III Clinical Trials in patients with CML in chronic, accelerated, or myeloid blast phase, and Ph+ ALL who were resistant or intolerant to imatinib

Two randomised, open-label studies were conducted to evaluate the efficacy of SPRYCEL® administered once daily compared with SPRYCEL® administered twice daily: The results described in Table 3 are based on a minimum of 24 months follow-up after the start of dasatinib therapy.

In the study in chronic phase CML, the primary endpoint was MCyR (once daily vs. twice daily) in imatinib-resistant patients. The main secondary endpoint was MCyR by total daily dose level in the imatinib-resistant patients. Other secondary endpoints included duration of MCyR, progression-free survival, and overall survival. A total of 670 patients, of whom 497 were imatinib-resistant, were randomised to the SPRYCEL® 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily group. Median duration of treatment was approximately 22 months (range <1 -31 months).

Efficacy results are presented in Table 3. Efficacy was achieved across all SPRYCEL® treatment groups with the once daily schedule demonstrating comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy end-point (difference in MCyR 1.9%; 95% confidence interval [-6.8% - 10.6%]). The main secondary end-point of the study also showed comparable efficacy (non-inferiority) between the 100 mg total daily dose and the 140 mg total daily dose (difference in MCyR -0.2%; 95% confidence interval [-8.9% - 8.5%]).

Table 3: Efficacy of SPRYCEL® in Phase III Dose-Optimisation Study: Chronic Phase CML

	100 mg once daily	50 mg twice daily[a]	140 mg once daily[a]	70 mg twice daily[a]
All Patients	**n = 167**	n = 168	n = 167	n = 168
Imatinib-Resistant Patients	**n = 124**	n = 124	n = 123	n = 126
Haematologic Response Rate[b] (%) (95% CI)				
CHR	**92% (86-95)**	92% (87-96)	87% (81-92)	88% (82-93)
Cytogenetic Response[c] (%) (95% CI)				
MCyR				
All Patients	**63% (56-71)**	61% (54-69)	63% (55-70)	61% (54-69)
Imatinib-Resistant Patients	**59% (50-68)**	56% (47-65)	58% (49-67)	57% (48-66)
CCyR				
All Patients	**50% (42-58)**	50% (42-58)	50% (42-58)	54% (46-61)
Imatinib-Resistant Patients	**44% (35-53)**	42% (33-52)	42% (33-52)	48% (39-57)
Major Molecular Response[d] (%) (95% CI)				
All Patients	**69% (58-79)**	70% (59-80)	72% (60-82)	66% (54-76)
Imatinib-Resistant Patients	**72% (58-83)**	69% (54-81)	63% (48-76)	64% (50-76)
Survival (% [95% CI]; Kaplan-Meier Estimates)				
Progression-Free				
1 Year				
All Patients	**90% (86-95)**	86% (81-92)	88% (82-93)	87% (82-93)
Imatinib-Resistant Patients	**88% (82-94)**	84% (77-91)	86% (80-93)	85% (78-91)
2 Years				
All Patients	**80% (73-87)**	76% (68-83)	75% (67-82)	76% (68-83)
Imatinib-Resistant Patients	**77% (68-85)**	73% (64-82)	68% (59-78)	72% (63-81)
Overall Survival				
1 Year				
All Patients	**96% (93-99)**	96% (93-99)	96% (93-99)	94% (90-98)
Imatinib-Resistant Patients	**94% (90-98)**	95% (91-99)	97% (93-100)	92% (87-97)
2 Years				
All Patients	**91% (86-96)**	90% (86-95)	94% (90-97)	88% (82-93)
Imatinib-Resistant Patients	**89% (84-95)**	89% (83-94)	94% (89-98)	84% (78-91)

[a] Not a recommended starting dosage of SPRYCEL® for chronic phase CML

[b] **Haematologic response criteria** (all responses confirmed after 4 weeks):

Complete haematologic response (CHR) (chronic CML): WBC ≤ institutional ULN, platelets < 450 x 10^9/L, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.

[c] **Cytogenetic response criteria**: complete (0% Ph+ metaphases) or partial (>0%–35%). MCyR (0%–35%) combines both complete and partial responses.

[d] Major molecular response criteria: Defined as BCR-ABL/control transcripts ≤ 0.1% by RQ-PCR in peripheral blood samples.

Molecular response was evaluated in a subset of assessed patients who had a CCyR

CI = confidence interval; ULN = upper limit of normal range.

Based on the Kaplan-Meier estimates, the proportion of patients treated with SPRYCEL® 100 mg once daily who maintained MCyR for 24 months was 87% (95% CI: [78%-97%]) and 88% (95% CI: [81% - 95%]) for patients treated with 70 mg of SPRYCEL® twice daily.

Efficacy was also assessed in patients who were intolerant to imatinib. In this population of patients who received 100 mg once daily, MCyR was achieved in 77%, CCyR in 67%, and

major molecular response (in assessed subjects with CCyR) was 64%. Based on the Kaplan-Meier estimates, all imatinib-intolerant patients (100%) maintained MCyR for 1 year and 85% (95% CI: [69%-100%]) maintained MCyR for 2 years. The estimated rate of PFS in this population was 97% (95% CI: [92%-100%]) at 1 year and 87% (95% CI: [76%-99%]) at 2 years. The estimated rate of overall survival was 100% at 1 year and 95% (95% CI: [88%-100%]) at 2 years.

In the Phase III, randomized, open-label study in patients with advanced phase CML and Ph+ALL, whose disease was resistant to or who were intolerant to imatinib, the primary endpoint was MaHR. A total of 611 patients were randomised to either the SPRYCEL® 140 mg once daily or 70 mg twice daily group. Median duration of treatment was approximately 6 months (range <1-31 months).

The once daily schedule demonstrated comparable efficacy (non-inferiority) to the twice daily schedule on the primary efficacy endpoint (difference in MaHR 0.8%; 95% confidence interval [-7.1%- 8.7%]). The response rates are presented in Table 4.

Table 4: Efficacy of SPRYCEL® in Phase III Dose-Optimisation Study: Advanced Phase CML and Ph+ ALL

	140 mg Once Daily				**70 mg Twice Daily**[a]			
	Accelerated (n= 158)	**Myeloid Blast (n= 75)**	**Lymphoid Blast (n= 33)**	**Ph+ALL (n= 40)**	**Accelerated (n= 159)**	**Myeloid Blast (n= 74)**	**Lymphoid Blast (n= 28)**	**Ph+ALL (n= 44)**
MaHR [b]	**66%**	**28%**	**42%**	**38%**	68%	28%	32%	32%
(95% CI)	**(59-74)**	**(18-40)**	**(26-61)**	**(23-54)**	(60-75)	(19-40)	(16-52)	(19-48)
CHR [b]	**47%**	**17%**	**21%**	**33%**	52%	18%	14%	25%
(95% CI)	**(40-56)**	**(10-28)**	**(9-39)**	**(19-49)**	(44-60)	(10-28)	(4-33)	(13-40)
NEL [b]	**19%**	**11%**	**21%**	**5%**	16%	11%	18%	7%
(95% CI)	**(13-26)**	**(5-20)**	**(9-39)**	**(1-17)**	(11-23)	(5-20)	(6-37)	(1-19)
MCyR [c]	**39%**	**28%**	**52%**	**70%**	43%	30%	46%	52%
(95% CI)	**(31-47)**	**(18-40)**	**(34-69)**	**(54-83)**	(35–51)	(20-42)	(28-66)	(37-68)
CCyR	**32%**	**17%**	**39%**	**50%**	33%	23%	43%	39%
(95% CI)	**(25-40)**	**(10-28)**	**(23-58)**	**(34-66)**	(26-41)	(14-34)	(25-63)	(24-55)

[a] Not a recommended starting dosage for advances phase CML and Ph+ALL.
[b] Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response (MaHR) = complete haematologic response (CHR) + no evidence of leukaemia (NEL).
CHR: WBC ≤ institutional ULN, ANC ≥ 1.0 x 10^9/L, platelets ≥ 100 x 10^9/L, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤ 5%, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
NEL: same criteria as for CHR but ANC ≥ 0.5 x 10^9/L and < 1.0 x 10^9/L, or platelets ≥ 20 x 10^9/L and ≤ 100 x 10^9/L.
[c] MCyR combines both complete (0% Ph+ metaphases) and partial (> 0%-35%) responses.
CI = confidence interval ULN = upper limit of normal range.

The median duration of MaHR in patients with accelerated phase CML was not reached for either group; the median PFS was 25 months and 26 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; and the median overall survival was not reached for the 140 mg once daily group and 31 months for the 70 mg twice daily group. In patients with myeloid blast phase CML, the median duration of MaHR was 8 months and 9 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months for both groups; and the median overall survival was 8 months for both groups. In patients with lymphoid blast phase CML, the median duration of MaHR was

5 months and 8 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 5 months for both groups, and the median overall survival was 11 months and 9 months, respectively.

In patients with Ph+ALL, the median duration of MaHR was 5 months and 12 months for the 140 mg once daily group and the 70 mg twice daily group, respectively; the median PFS was 4 months and 3 months respectively, and the median overall survival was 7 months and 9 months, respectively.

INDICATIONS

SPRYCEL® (dasatinib) is indicated for the treatment of adults aged 18 years or over with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia in the chronic phase.

SPRYCEL® (dasatinib) is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.

SPRYCEL® is indicated for the treatment of adults aged 18 years or over with Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

CONTRAINDICATIONS

Use of SPRYCEL® is contraindicated in patients with hypersensitivity to dasatinib or to any other component of SPRYCEL®.

PRECAUTIONS
General

Myelosuppression

Treatment with SPRYCEL® is associated with thrombocytopenia, neutropenia and anaemia. Their occurrence is more frequent in patients with advanced phase 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 SPRYCEL® temporarily or dose reduction (see DOSAGE and ADMINISTRATION and ADVERSE EFFECTS: Laboratory Abnormalities). CTC Grade 3 or 4 (severe) cases of anaemia were managed with blood transfusions.

In a Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with SPRYCEL® 100 mg once daily than in patients treated with SPRYCEL® 70 mg twice daily (See Table 9).

Bleeding

In the Phase III study in patients with newly diagnosed chronic phase CML, 1 patient (< 1%) receiving SPRYCEL® compared to 2 patients (1%) receiving imatinib had Grade 3 or 4

haemorrhage. In clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe CNS haemorrhage, including fatalities, occurred in < 1% of patients receiving SPRYCEL®**.** Eight cases were fatal and 6 of them were associated with Common Toxicity Criteria (CTC) Grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4% of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruptions and transfusions. Other cases of Grade 3 or 4 haemorrhage occurred in 2% of patients with resistance or intolerance to prior imatinib therapy. Most bleeding reactions in these patients were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, in *vitro* and *in vivo* platelet assays suggest that SPRYCEL® treatment reversibly affects platelet activation.

Patients were excluded from participation in the initial SPRYCEL® (dasatinib) clinical studies if they took medications that inhibit platelet function or anticoagulants. In subsequent trials, the use of anticoagulants, acetylsalicylic acid, and non-steroidal anti-flammatory drugs (NSAIDs) was allowed concurrently with SPRYCEL® if the platelet count was > 50 – 75 x 10^9/L. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention

SPRYCEL® is associated with fluid retention. In the Phase III clinical study in patients with newly diagnosed chronic phase CML, Grade 3 or 4 fluid retention was reported in 2 patients (1%) in each of the dasatinib and the imatinib-treatment groups (ADVERSE EFFECTS). In clinical studies in patients with resistance or intolerance to prior imatinib therapy, Grade 3 or 4 fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe congestive heart failure/cardiac dysfunction was reported in 2% of patients. In these studies, Grade 3 or 4 ascites and generalized oedema were each reported in < 1% of patients and Grade 3 or 4 pulmonary oedema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnoea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require oxygen therapy and thoracentesis. Fluid retention reactions were typically managed by supportive care measures that include diuretics or short course of steroids. While the safety profile of SPRYCEL® in the elderly population was similar to that in the younger population, patients aged 65 years and older are more likely to experience pleural effusion, congestive heart failure, gastrointestinal bleeding, and dyspnoea, and should be monitored closely. Fluid retention reactions were reported less frequently in patients treated with once daily schedule than in patients treated with twice daily schedule in two Phase III dose-optimisation studies.

QT Prolongation

In vitro data showing inhibition of the hERG K+ channel expressed in mammalian cells and action potential prolongation in rabbit Purkinje fibres by dasatinib and a number of its metabolites suggest that dasatinib has the potential to prolong cardiac ventricular repolarisation (QT interval).

In 258 SPRYCEL® -treated patients and 258 imatinib-treated patients in the Phase III study in newly diagnosed chronic phase CML, 1 patient (< 1%) in each group had QTc prolongation reported as an adverse reaction. The median changes in QTcF from baseline were 3.0 msec in SPRYCEL® -treated patients compared to 8.2 msec in imatinib-treated patients. One patient (< 1%) in each group experienced a QTcF > 500 msec. In 865 patients with leukaemia treated

with SPRYCEL® in Phase II, single-arm clinical studies, the mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4-6 msec; the upper 95% confidence intervals for all mean changes from baseline were <7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy treated with SPRYCEL®, 14 (< 1%) had QT prolongation reported as an adverse reaction. Twenty-one (21) of these patients (1%) experienced a QTcF >500 msec.

SPRYCEL® should be administered with caution in patients who have or may develop prolongation of QTc. These include patients with hypokalaemia or hypomagnesaemia, patients with congenital long QT syndrome, patients taking anti-arrhythmic medicines or other medicinal products which lead to QT prolongation and cumulative high dose anthracycline therapy. Hypokalaemia or hypomagnesaemia should be corrected prior to SPRYCEL® administration.

Cardiac Adverse Reactions

SPRYCEL® was studied in a randomised trial of 519 patients with newly diagnosed CML in chronic phase which included patients with prior cardiac disease. The cardiac adverse reactions of congestive heart failure/cardiac dysfunction and fatal myocardial infarction were reported in patients taking SPRYCEL®. Adverse cardiac reactions were more frequent in patients with risk factors or a previous medical history of cardiac disease. Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately.

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

Lactose Content

SPRYCEL® contains 135 mg of lactose monohydrate in a 100 mg daily dose and 189 mg of lactose monohydrate in a 140 mg daily dose.

Interactions with Other Medicines

Drugs that may increase dasatinib plasma concentrations

CYP3A4 Inhibitors: *In vitro*, dasatinib is a CYP3A4 substrate. Concomitant use of SPRYCEL® and substances that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving treatment with SPRYCEL®, systemic administration of a potent CYP3A4 inhibitor is not recommended. 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 may increase metabolism and decrease dasatinib plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or

Hypericum perforatum, also known as St. John's Wort) with SPRYCEL® is not recommended. In healthy subjects, the concomitant use of SPRYCEL® and rifampicin, a potent CYP3A4 inducer, resulted in a five-fold decrease in dasatinib exposure. In patients for whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used.

Antacids: Non-clinical data demonstrate that the solubility of dasatinib is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with SPRYCEL® reduced the AUC of a single dose of SPRYCEL® by 55% and the Cmax by 58%. However, when antacids were administered 2 hours prior to a single dose of SPRYCEL®, no relevant changes in SPRYCEL®, concentration or exposure were observed. Thus, antacids may be administered up to 2 hours prior to or 2 hours following SPRYCEL®. Simultaneous administration of SPRYCEL® with antacids should be avoided.

Histamine-2 Antagonists /Proton Pump Inhibitors: Long-term suppression of gastric secretion by Histamine-2 Antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of Histamine-2 Antagonists or proton pump inhibitors with SPRYCEL® is not recommended. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of SPRYCEL® reduced dasatinib exposure by 61%. The use of antacids should be considered in place of Histamine-2 Antagonists or proton pump inhibitors in patients receiving SPRYCEL® therapy.

Drugs that may have their plasma concentration altered by dasatinib

CYP3A4 Substrates: In a study in healthy subjects, a single 100 mg dose of SPRYCEL® increased exposure to simvastatin, a known CYP3A4 substrate, by 20%. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving SPRYCEL®. (See PHARMACOLOGY).

In vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

Hepatic Impairment

Based on the findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose (see DOSAGE and ADMINISTRATION and PHARMACOKINETICS- Special Populations). Due to the limitations of this clinical study, caution is recommended when SPRYCEL® is administered to patients with hepatic impairment.

Renal Impairment

There are currently no clinical studies with SPRYCEL® in patients with impaired renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine > 3 times the upper limit of the normal range, and clinical studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range). Dasatinib and its metabolites are minimally excreted via the kidney. Since the

renal excretion of unchanged dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Carcinogenicity studies were not performed with dasatinib.

Genotoxicity

Dasatinib was not mutagenic when tested in *in vitro* bacterial cell assays (Ames test) and was not clastogenic in an *in vivo* rat micronucleus study. Clastogenicity was observed with dasatinib *in vitro* in assays with Chinese hamster ovary cells in the absence and presence of metabolic activation.

Effects on Fertility

No specific studies have been conducted in animals to evaluate the effects of dasatinib on fertility. Dasatinib caused atrophy/degeneration of the testis in rats and monkeys and an increase in the number of corpora lutea in the ovaries in rats at doses producing plasma exposure levels below or close to that anticipated in patients receiving SPRYCEL® therapy.

Pregnancy

Pregnancy Category D

Dasatinib may cause foetal harm when administered to a pregnant woman. In non-clinical studies, at exposure levels that are readily achievable in humans receiving therapeutic doses of SPRYCEL® serious embryo foetal toxicity was observed in both pregnant rats and rabbits. Malformations and foetal death were observed in rats treated with dasatinib.

SPRYCEL® is therefore not recommended for use in women who are pregnant or contemplating pregnancy. Women must be advised to avoid becoming pregnant while on therapy. If SPRYCEL® is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL®, the patient should be apprised of the potential hazard to the foetus.

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

Use in Lactation

It is unknown whether SPRYCEL® is excreted in human milk. Women who are taking SPRYCEL® should not breastfeed.

Paediatric Use

The safety and efficacy of SPRYCEL® in patients <18 years of age have not been established.

Geriatric Use

In the newly diagnosed chronic phase CML study, 25 patients (10%) were 65 years of age and older and 7 patients (3%) were 75 years of age and older. Of the 2,182 patients in clinical studies of SPRYCEL® with resistance or intolerance to prior imatinib therapy, 547 (25%) were 65 years of age and older and 105 (5%) were 75 years of age and older. While the safety profile of SPRYCEL® in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience pleural effusion (43% vs. 24%), congestive heart failure (6% vs. 2%), gastrointestinal bleeding (12% vs. 7%), and dyspnoea (37% vs. 20%) and should be monitored closely. No differences in efficacy were observed between older and younger patients. However, in the two randomized studies in patients with chronic phase CML, the rates of major cytogenetic response (MCyR) were lower among patients aged 65 years and older.

ADVERSE EFFECTS

The data described below reflect exposure to SPRYCEL® in 2,440 patients in clinical trials, including 258 patients with newly diagnosed chronic phase CML with a minimum of 12 months follow-up (starting dose 100 mg once daily) and 2,182 patients with imatinib resistant or intolerant CML or Ph+ALL with a minimum of 24 months follow-up (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy for patients with resistance or intolerance to imatinib was 15 months (range <1-36 months). Of the 2,440 patients treated, 23% patients were ≥ 65 years of age, while 5% were ≥ 75 years of age.

In the Phase III study of patients with newly diagnosed chronic phase CML the median duration of therapy was 14 months (range 0.03 – 24 months) for SPRYCEL® and 14 months (range 0.3 – 26 months) for imatinib; the median average daily dose was 99 mg and 400 mg, respectively.

The majority of patients treated with SPRYCEL®, regardless of dose or schedule, experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade.

In the Phase III study in patients with newly diagnosed chronic phase CML, treatment was discontinued for drug-related adverse reactions in 5% of SPRYCEL®-treated patients and 4% of imatinib-treated patients. Among patients with resistance or intolerance to imatinib therapy, the rates of discontinuation for adverse reactions were 15% in chronic phase CML, 16% in accelerated phase CML, 15% in myeloid blast phase CML, and 8% in lymphoid blast phase CML and 8% in Ph+ ALL. In the Phase III dose-optimisation study in patients with chronic phase CML, the rate of discontinuation for drug-related adverse reaction was lower for patients treated with 100 mg once daily than for those treated with 70 mg twice daily (10% and 16%, respectively). The rates of dose interruption and reduction were also lower for patients with chronic phase CML treated with 100 mg once daily than for those treated with 70 mg twice daily. Less frequent dose reductions and interruptions were also reported for patients with advanced phase CML and Ph+ALL treated with 140 mg once daily than for those treated with 70 mg twice daily.

The majority of imatinib-intolerant patients in chronic phase CML were able to tolerate treatment with SPRYCEL®. In clinical studies in chronic phase CML, 10 of the 215 imatinib-intolerant patients had the same Grade 3 or 4 non-haematological toxicity with SPRYCEL® as

they did with prior imatinib; 8 of the 10 patients were managed with dose reduction and were able to continue SPRYCEL® treatment.

The most frequently reported adverse reactions reported in SPRYCEL®-treated patients with newly diagnosed chronic phase CML were fluid retention (including pleural effusion), diarrhoea, headache, rash and musculoskeletal pain. The most frequently reported adverse reactions in SPRYCEL®-treated patients with resistance or intolerance to prior imatinib therapy were fluid retention (including pleural effusion), diarrhoea, headache, nausea, skin rash, dyspnoea, haemorrhage, fatigue, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of SPRYCEL®-treated patients with resistance or intolerance to prior imatinib therapy.

Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as "fluid retention."

In the newly diagnosed chronic phase CML study, Grade 1 and 2 pleural effusion were reported in 26 patients (10%) receiving SPRYCEL® (see Table 5). The median time to onset was 28 weeks (range 4-88 weeks). This reaction was usually reversible and managed by interrupting SPRYCEL® treatment and using diuretics or other appropriate supportive care measure (see DOSAGE AND ADMINISTRATION and PRECAUTIONS). The pleural effusion was adequately managed such that 23 patients (88%) were able to continue on SPRYCEL®.

The use of SPRYCEL®is associated with fluid retention with Grade 3 and 4 cases in 10% of patients with resistance or intolerance to prior imatinib therapy. Grade 3 or 4 pleural and pericardial effusion were reported in 7% and 1% of patients. Severe congestive heart failure/cardiac dysfunction was reported in 2% of patients. Grade 3 or 4 ascites and generalised oedema were each reported in <1%. One percent of patients experienced Grade 3 or 4 pulmonary oedema. Fluid retention reactions were typically managed by supportive care measures that include diuretics or short courses of steroids (See PRECAUTIONS).

Bleeding drug-related events, ranging from petechiae and epistaxis to Grade 3 or 4 gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking SPRYCEL®. In the Phase III study in patients with newly diagnosed chronic phase CML, 1 patient (< 1%) receiving SPRYCEL® compared to 2 patients (1%) receiving imatinib had Grade 3 or 4 haemorrhage. In clinical studies in patients with resistance or intolerance to prior imatinib therapy, severe CNS haemorrhage occurred in < 1% of patients. Eight (8) cases were fatal and 6 of them were associated with CTC Grade 4 thrombocytopenia. Grade 3 or 4 gastrointestinal haemorrhage occurred in 4% of patients with resistance or intolerance to prior imatinib therapy and generally required treatment interruption and transfusions. Other Grade 3 or 4 haemorrhage occurred in 2% of patients with resistance or intolerance to prior imatinib therapy. Most bleeding related events in these patients were typically associated with Grade 3 or 4 thrombocytopenia. Additionally, *in vitro* and *in vivo* platelet assays suggest that SPRYCEL® treatment reversibly affects platelet activation.

Treatment with SPRYCEL® is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML.

QT Prolongation: in the Phase III study in patients with newly diagnosed chronic phase CML, one patient (< 1%) of the SPRYCEL®-treated patients, and one patient (< 1%) of the imatinib-treated patients had a QTcF > 500 msec (see PRECAUTIONS).

In 5 Phase II clinical studies in patients with resistance or intolerance to prior imatinib therapy, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 patients receiving SPRYCEL® 70 mg twice daily. QT interval was corrected for heart rate by Fridericia's method. At all post-dose time points on day 8, the mean changes from baseline in QTcF interval were 4 – 6 msec, with associated upper 95% confidence intervals < 7 msec. Of the 2,182 patients with resistance or intolerance to prior imatinib therapy who received SPRYCEL® in clinical studies, 14 (< 1%) had QTc prolongation reported as an adverse reaction. Twenty-one patients (1%) experienced a QTcF > 500 msec (see PRECAUTIONS).

Patients with risk factors or a history of cardiac disease should be monitored carefully for signs or symptoms consistent with cardiac dysfunction and should be evaluated and treated appropriately (see PRECAUTIONS).

In clinical trials with patients with resistance or intolerance to prior imatinib therapy, it was recommended that treatment with imatinib be discontinued at least 7 days before starting treatment with SPRYCEL®.

The comparative frequency of adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of the patients with newly diagnosed chronic phase CML are presented in Table 5.

Table 5: Adverse Reactions Reported in ≥ 10% of Patients with Newly Diagnosed Chronic Phase CML

	All Grades		Grade 3/4	
	SPRYCEL® n= 258	imatinib n= 258	SPRYCEL® n= 258	imatinib n= 258
Preferred Term	Percent (%) of Patients			
Fluid Retention	19	42	1	1
Superficial localised oedema	9	36	0	< 1
Pleural effusion	10	0	0	0
Generalised oedema	2	6	0	0
Pericardial effusion	1	< 1	< 1	0
Congestive heart failure/ cardiac dysfunction[a]	2	1	< 1	< 1
Pulmonary hypertension	1	0	0	0
Pulmonary oedema	< 1	0	0	0
Diarrhoea	17	17	< 1	1
Nausea	8	20	0	0
Vomiting	5	10	0	0
Headache	12	10	0	0
Rash[b]	11	17	0	1
Fatigue	8	10	< 1	0
Musculoskeletal pain	11	14	0	< 1
Myalgia	6	12	0	0
Muscle inflammation	4	17	0	< 1
Haemorrhage[c]	5	5	< 1	1
Gastrointestinal bleeding	1	< 1	< 1	0
Other bleeding[d]	4	4	0	1

[a] Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased and left ventricular dysfunction.
[b] Includes erythema, erythema multiforme, rash, rash generalised, rash macular, rash papular, rash pustular, skin exfoliation and rash vesicular.
[c] Important adverse reaction of special interest with < 10% frequency.
[d] Includes conjunctival haemorrhage, ear haemorrhage, ecchymosis, epistaxis, eye haemorrhage, gingival bleeding, haematoma, haematuria, haemoptysis, intra-abdominal haematoma, petechiae, scleral haemorrhage, uterine haemorrhage and vaginal haemorrhage.

In the Phase III dose-optimisation study in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy (median duration of treatment approximately 23 months), the incidence of pleural effusion and congestive heart failure/cardiac dysfunction was lower in patients treated with SPRYCEL® 100 mg once daily than in those treated with SPRYCEL® 70 mg twice daily (Table 6a). Myelosuppression was also reported less frequently with the 100 mg once daily (see Laboratory Abnormalities, Table 9).

Table 6a: Selected Adverse Drug Reactions Reported in Phase III Dose-Optimisation Study: Chronic Phase CML

	100 mg once daily n = 165		140 mg once daily[a] n = 163		50 mg twice daily [a] n = 167		70 mg twice daily [a] 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**							
Diarrhoea	27	2	30	4	31	2	27	4
Fluid Retention	34	4	40	7	37	5	40	10
Superficial Oedema	18	0	17	1	19	0	19	1
Pleural Effusion	18	2	26	5	24	4	24	5
Generalised Oedema	3	0	5	0	0	0	2	0
Congestive heart failure/cardiac dysfunction[b]	0	0	4	1	1	1	5	3
Pericardial effusion	2	1	6	2	5	2	2	1
Pulmonary Oedema	0	0	0	0	1	1	3	1
Pulmonary hypertension	0	0	1	0	1	0	1	1
Haemorrhage	11	1	14	1	10	4	16	2
Gastrointestinal bleeding	2	1	2	0	5	3	4	2

[a] Not a recommended starting dosage of SPRYCEL® for chronic phase CML
[b] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

In the Phase III dose-optimisation study in patients with advanced phase CML and Ph+ ALL (median duration of treatment of 14 months (range <1-36 months) for accelerated phase CML; 3 months (range <1-32 months) for myeloid blast CML; 4 months (<1 – 22 months) for lymphoid blast CML; and 3 months (<1 – 29 months) for Ph+ALL), fluid retention (pleural effusion and pericardial effusion) was reported less frequently in patients treated with SPRYCEL® 140 mg once daily than in those treated with 70 mg twice daily (Table 6b).

Table 6b: Selected Adverse Drug Reactions Reported in Phase III Dose-Optimisation Study: Advanced Phase CML and Ph+ ALL

	140 mg once daily n = 304		70 mg twice daily [a] n = 305	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Preferred Term	**Percent (%) of Patients**			
Diarrhoea	28	3	29	4
Fluid Retention	33	7	43	11
Superficial oedema	15	<1	19	1
Pleural Effusion	20	6	34	7
Generalised oedema	2	0	3	1
Congestive heart failure/ cardiac dysfunction[b]	1	0	2	1
Pericardial effusion	2	1	6	2
Pulmonary oedema	1	1	3	1
Ascites	0	0	1	0
Pulmonary hypertension	0	0	1	<1
Haemorrhage	23	8	27	7
Gastrointestinal bleeding	8	6	12	6

[a] Not a recommended starting dosage of SPRYCEL® for advanced phase CML or Ph+ALL.
[b] Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

The following adverse reactions, excluding laboratory abnormalities, were reported in patients in SPRYCEL® clinical trials. These reactions are presented by system organ class and by frequency.
Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations
Common: weight decreased, weight increased
Cardiac disorders
Common: congestive heart failure/cardiac dysfunction[a], pericardial effusion, arrhythmia (including tachycardia), palpitations
Uncommon: myocardial infarction (including fatal outcomes), electrocardiogram QT prolonged, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly
Rare: cor pulmonale, myocarditis, acute coronary syndrome
Blood and lymphatic system disorders
Common: febrile neutropenia, pancytopenia
Rare: aplasia pure red cell

Nervous system disorders
Very common: headache
Common: neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Uncommon: CNS bleeding[b], syncope, tremor, amnesia
Rare: cerebrovascular accident, transient ischemic attack, convulsion, optic neuritis
Eye disorders
Common: visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Uncommon: conjunctivitis
Ear and labyrinth disorders
Common: tinnitus
Uncommon: vertigo
Respiratory, thoracic and mediastinal disorders
Very common: pleural effusion, dyspnoea
Common: cough, pulmonary oedema, pulmonary hypertension, lung infiltration, pneumonitis
Uncommon: bronchospasm, asthma
Rare: acute respiratory distress syndrome
Gastrointestinal disorders
Very common: diarrhoea, vomiting, nausea, abdominal pain
Common: gastrointestinal bleeding, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Uncommon: pancreatitis, upper gastrointestinal ulcer, oesophagitis, ascites, anal fissure, dysphagia
Rare: protein-losing gastroenteropathy
Renal and urinary disorders
Uncommon: renal failure, urinary frequency, proteinuria
Skin and subcutaneous tissue disorders
Very common: skin rash[c]
Common: alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon: acute febrile neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome
Musculoskeletal and connective tissue disorders
Very common: musculoskeletal pain
Common: arthralgia, myalgia, muscle inflammation, muscular weakness
Uncommon: musculoskeletal stiffness, rhabdomyolysis, blood creatine phosphokinase increased
Rare: tendonitis
Metabolism and nutrition disorders
Common: anorexia, appetite disturbances
Uncommon: hyperuricaemia, hypoalbuminaemia
Infections and infestations
Very common: infection (including bacterial, viral, fungal, non-specified)
Common: pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection
Uncommon: sepsis (including fatal outcome)
Injury, poisoning, and procedural complications
Common: contusion

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Uncommon: tumour lysis syndrome
Vascular disorders
Very common: haemorrhage[d]
Common: hypertension, flushing
Uncommon: hypotension, thrombophlebitis
Rare: livedo reticularis
General disorders and administration site conditions
Very common: fluid retention, fatigue, superficial oedema[e], pyrexia
Common: asthenia, pain, chest pain, generalised oedema, chills
Uncommon: malaise, temperature intolerance
Immune System Disorders
Uncommon: hypersensitivity (including erythema nodosum)
Hepatobiliary disorders
Uncommon: hepatitis, cholecystitis, cholestasis
Reproductive system and breast disorders
Uncommon: gynecomastia, irregular menstruation
Psychiatric disorders
Common: depression, insomnia
Uncommon: anxiety, confusional state, affect lability, libido decreased

a. Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure.
b. Includes cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, hemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.
c Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation and urticaria vesiculosa.
d.Excludes gastrointestinal bleeding and CNS bleeding; these ADRs are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.
e Includes auricular swelling, conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, genital swelling, gravitational oedema, lip oedema, localised oedema, macular oedema, oedema genital, oedema mouth, oedema peripheral, orbital oedema, penile oedema, periorbital oedema, pitting oedema, scrotal oedema, swelling face and tongue oedema.

Postmarketing Experience

The following additional adverse events have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders:	atrial fibrillation/atrial flutter[a]
Vascular disorders:	thrombosis/embolism (including pulmonary embolism, deep vein thrombosis)[b]
Respiratory, thoracic and mediastinal disorders:	interstitial lung disease
Gastrointestinal disorders:	fatal gastrointestinal hemorrhage[c]

a. Typically reported in elderly patients or in patients with confounding factors including significant underlying or concurrent cardiac or cardiovascular disorders, or other significant comorbidities (eg, severe infection/sepsis, electrolyte abnormalities).

b. Typically reported in patients with underlying malignancies or other confounding risk factors, including cardiovascular disorders, history of surgery, or other comorbidities.

c. Typically reported in patients with progressive underlying malignancies (eg. advanced phase CML or Ph+ ALL) or severe or life-threatening comorbidities (eg, severe gastrointestinal disorders, infection or sepsis, thrombocytopenia).

Laboratory Abnormalities

Haematology and Biochemistry in patients with newly diagnosed chronic phase CML

The comparative frequency of Grade 3 and 4 laboratory abnormalities in patients with newly diagnosed chronic phase CML is presented in Table 7. There were no discontinuations of SPRYCEL® therapy due to these biochemical laboratory parameters.

Table 7: CTC Grade 3/4 Laboratory Abnormalities in Patients with Newly Diagnosed Chronic Phase

	SPRYCEL® n= 258	imatinib n= 258
	Percent (%) of Patients	
Haematology Parameters		
Neutropenia	21	20
Thrombocytopenia	19	11
Anaemia	10	7
Biochemistry Parameters		
Hypophosphataemia	4	21
Hypokalaemia	0	2
Hypocalcaemia	< 1	< 1
Elevated SGPT (ALT)	< 1	1
Elevated SGOT (AST)	< 1	1
Elevated Bilirubin	1	0
Elevated Creatinine	< 1	1

CTC grades: neutropenia (Grade 3 $\geq 0.5 - < 1.0 \times 10^9$/l, Grade 4 $< 0.5 \times 10^9$/l); thrombocytopenia (Grade 3 $\geq 25 - < 50 \times 10^9$/l, Grade 4 $< 25 \times 10^9$/l); anaemia (haemoglobin Grade 3 $\geq 65 - < 80$ g/l, Grade 4 < 65 g/l); elevated creatinine (Grade 3 > 3 – 6 × upper limit of normal range (ULN), Grade 4 > 6 × ULN); elevated bilirubin (Grade 3 > 3 – 10 × ULN, Grade 4 > 10 × ULN); elevated SGOT or SGPT (Grade 3 > 5 – 20 × ULN, Grade 4 > 20 × ULN); hypocalcaemia (Grade 3 < 7.0 – 6.0 mg/dl, Grade 4 < 6.0 mg/dl); hypophosphataemia (Grade 3 < 2.0 – 1.0 mg/dl, Grade 4 < 1.0 mg/dl); hypokalaemia (Grade 3 < 3.0 – 2.5 mmol/l, Grade 4 < 2.5 mmol/l).

Haematology and Biochemistry in patients with resistance or intolerance to prior imatinib therapy:

Table 8 shows laboratory findings from SPRYCEL® clinical trials in which 2,182 patients received SPRYCEL® for a median of 15 months.

Table 8: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies in Patients with Resistance or Intolerance to Prior Imatinib Therapy

	Chronic (n=1150)	Accelerated (n=502)	Myeloid Blast (n=280)	Lymphoid Blast (n=115)	Ph+ ALL (n=135)
	Percent (%) of Patients				
Hematology Parameters					
Neutropenia	47	69	80	83	75
Thrombocytopenia	41	72	82	86	71
Anaemia	19	55	75	51	42
Biochemistry Parameters					
Hypophosphataemia	10	14	20	19	21
Hypokalaemia	3	10	20	13	16
Hypocalcaemia	2	8	16	14	9
Elevated SGPT (ALT)	1	4	6	7	7
Elevated SGOT (AST)	1	1	4	5	4
Elevated Bilirubin	1	1	4	7	2
Elevated Creatinine	1	1	4	2	0

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25–<50 × 10^9/L, Grade 4 <25 × 10^9/L); anaemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcaemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphataemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalaemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

Myelosuppression was commonly reported in all patient populations. In newly diagnosed chronic phase CML, myelosupression was less frequently reported than in chronic phase CML patients with resistance or intolerance to prior imatinib therapy. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anaemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML.

In patients who experienced Grade 3 or 4 myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 1.6% of newly diagnosed chronic phase CML patients and in 5% of patients with resistance or intolerance to prior imatinib therapy.

Grade 3 or 4 elevations in transaminases or bilirubin and Grade 3 or 4 hypocalcaemia, hypokalaemia, and hypophosphataemia were reported in all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. In general, decreased calcium levels were not associated with clinical symptoms. Patients developing Grade 3 or 4 hypocalcaemia often had recovery with oral calcium supplementation.

In the Phase III dose-optimisation study in patients with chronic phase CML, the frequency of neutropenia, thrombocytopenia and anaemia was lower in the SPRYCEL® 100 mg once daily than in the SPRYCEL® 70 mg twice daily group. Laboratory abnormalities reported in the Phase III dose-optimisation study are shown in Table 9.

Table 9: CTC Grades 3/4 Laboratory Abnormalities in Phase III Dose –Optimization Study *(Chronic Phase CML)

	100 mg QD (n=165)	140 mg QD[a] (n=163)	50 mg BID[a] (n=167)	70 mg BID[a] (n=167)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	36	44	47	46
Thrombocytopenia	23	41	36	38
Anaemia	13	19	18	19
Biochemistry Parameters				
Hypophosphataemia	10	6	9	9
Hypokalaemia	2	4	2	4
Hypocalcaemia	1	3	0	3
Elevated SGPT (ALT)	0	1	1	1
Elevated SGOT (AST)	1	1	1	0
Elevated Bilirubin	1	1	0	1
Elevated Creatinine	0	1	0	1

a Not a recommended starting dosage of SPRYCEL® for chronic phase CML.
CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10^9/L, Grade 4 <0.5 × 10^9/L); thrombocytopenia (Grade 3 ≥25–<50 ×10^9/L, Grade 4 <25 × 10^9/L); anaemia (haemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10× ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcaemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphataemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalaemia (Grade 3<3.0-2.5 mmol/L, Grade 4<2.5 mmol/L.

DOSAGE AND ADMINISTRATION

The recommended starting dosage of SPRYCEL® (dasatinib) for chronic phase CML is 100 mg administered orally once daily (QD). The recommended starting dosage of SPRYCEL® for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally once daily and should be taken consistently either in the morning or the evening.

In clinical studies, treatment with SPRYCEL® was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a CCyR has not been investigated.

To achieve the recommended dose, SPRYCEL® is available as 20 mg, 50 mg, 70 mg and 100 mg film-coated tablets. Dose increase or reduction is recommended based on patient response and tolerability.

Dose escalation

In clinical studies in adult CML and Ph+ ALL patients, dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage.

Dose adjustment for adverse reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Platelet transfusion and red cell transfusion were used as appropriate. Haematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications are summarized in Table 10.

Table 10: Dose Adjustments for Neutropenia and Thrombocytopenia		
Chronic Phase CML (starting dose 100 mg once daily)	ANC* <0.5 x 10^9/L and/or Platelets <50 x 10^9/L	1. Stop SPRYCEL® until ANC ≥1.0 x10^9/L and platelets ≥50 x 10^9/L 2. Resume treatment with SPRYCEL® at the original starting dose 3. If platelets <25 x10^9/L and/or recurrence of ANC <0.5 x 10^9/L for >7 days, repeat step 1 and resume SPRYCEL® at a reduced dose of 80 mg once daily for second episode. For third episode further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue (for patients resistant or intolerant to prior therapy including imatinib).
Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily)	ANC* <0.5 x 10^9/L and/or Platelets <10 x 10^9/L	1. Check if cytopenia is related to leukaemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukaemia, stop SPRYCEL® until ANC ≥1.0 x 10^9/L and platelets ≥20 x 10^9/L and resume at the original starting dose 3. If recurrence of cytopenia, repeat step 1 and resume SPRYCEL® at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode) 4. If cytopenia is related to leukaemia, consider dose escalation to 180 mg once daily
*ANC: absolute neutrophil count		

Non-haematological adverse reactions

If a severe non-haematological adverse reaction develops with SPRYCEL® use, treatment must be withheld until the event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

Paediatric population: The safety and efficacy of SPRYCEL® in children and adolescents below 18 years of age have not yet been established. No data are available (see PRECAUTIONS).

Elderly population: No clinically relevant age-related pharmacokinetic differences have been observed in these patients. No specific dose recommendation is necessary in the elderly (see PRECAUTIONS).

Hepatic impairment: Patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, caution is recommended when SPRYCEL® is administered to patients with hepatic impairment. (see PRECAUTIONS).

Renal impairment: No clinical trials were conducted with SPRYCEL® in patients with decreased renal function (the study in patients with newly diagnosed chronic phase CML excluded patients with serum creatinine > 3 times the upper limit of the normal range, and studies in patients with chronic phase CML with resistance or intolerance to prior imatinib therapy excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range). Since the renal clearance of dasatinib and its metabolites is <4%, a decrease in total body clearance is not expected in patients with renal insufficiency (see PRECAUTIONS).

Method of Administration: To be administered orally. Tablets must not be crushed or cut in order to minimize risk of dermal exposure, they must be swallowed whole. SPRYCEL® can be taken with or without a meal and should be taken consistently either in the morning or the evening.

OVERDOSAGE

Experience with overdose of SPRYCEL® in clinical studies is limited to isolated cases. Overdosage of 280 mg per day for one week was reported in two patients and both developed a significant decrease in platelet counts. Since SPRYCEL® is associated with severe myelosuppression, patients who ingested more than the recommended dosage should be closely monitored for myelosuppression and given appropriate supportive treatment.

In case of overdose, immediately contact the Poisons Information Centre on 131126 for advice.

PRESENTATION

SPRYCEL® (dasatinib) tablets are available as film-coated, white to off-white, biconvex, round tablets with “BMS” debossed on one side and “527” (20 mg), or “524” (70 mg) on the other side.

The 50 mg tablets are oval shaped and debossed “BMS” on one side and “528” on the other side.

The 100 mg tablets are oval shaped and debossed “BMS 100” on one side and “852” on the other side.

20 mg, 50 mg and 70 mg Tablets are available in bottles or blisters of 60 tablets. 100 mg Tablets are available in bottles or blisters of 30 tablets.

Not all pack sizes may be marketed.

Storage Conditions

SPRYCEL® (dasatinib) tablets should be stored below 30 °C.

Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered.

Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

SPRYCEL® (dasatinib) tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However, if tablets are crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed and/or broken tablets.

NAME AND ADDRESS OF SPONSOR:

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POISON SCHEDULE

Prescription Medicine

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Therapeutic Goods Administration

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