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Human Medicines Development and Evaluation

Assessment Report
For
Sprycel
(dasatinib)

Procedure No.: EMEA/H/C/000709/II/23

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Scientific discussion

1.1. Introduction

Chronic myeloid leukaemia (CML) is a haematopoietic stem cell disorder associated with a reciprocal translocation between chromosomes 9 and 22 to produce the Philadelphia chromosome. This chromosomal translocation results in a chimeric protein product BCR-ABL, which is a constitutively active form of the ABL tyrosine kinase. CML is a progressive myeloproliferative disease, which evolves through chronic, accelerated, and blast crisis phases.

The Philadelphia chromosome and resultant constitutively expressed BCR-ABL protein tyrosine kinase is present in > 90-95% of patients with CML and 20% - 30 % of adult patients with acute lymphoblastic leukemia.

The BCR-ABL tyrosine kinase inhibitor, imatinib, has become the standard of care for treatment-naive patients with chronic phase CML based upon the results of the pivotal Phase 3 International Randomised Interferon versus STI571 (IRIS) study. While not a cure, the clinical benefit provided by imatinib has led to reduced need for stem cell transplantation in this patient population. In newly diagnosed chronic phase CML (CP-CML) with 8 years of follow-up, imatinib was associated with a complete cytogenetic response (CCyR) in 82% of patients and an estimated 8-year event-free survival (EFS) and overall survival (OS) of 81% and 85%, respectively, with data approved and included in the Product Information of Glivec. Despite the results of the IRIS study, approximately 42% of patients discontinued imatinib during this 8-year experience due to either adverse events/safety, unsatisfactory therapeutic outcome, death or other reasons. With imatinib treatment, transformation to accelerated or blast phase stages of the disease with a significantly poorer prognosis still occurs in over 7% of patients over 5 years.

Imatinib resistance can result from mutation of the BCR-ABL gene or the over-expression of the BCR-ABL protein. Intolerance to imatinib is associated with adverse events (AEs) including fluid retention, QT prolongations, changes in liver function, thrombocytopenia, neutropenia and diarrhoea.

For patients who are intolerant or resistant to imatinib, therapeutic alternatives as dasatinib and nilotinib are approved as second line treatment.

Dasatinib is a potent, broad spectrum ATP-competitive inhibitor of 5 oncogenic tyrosine kinases/kinase families: BCR-ABL, SRC, c-KIT, PDGFR and ephrin receptor kinases. Dasatinib binds to the active and inactive conformations of the ABL kinase and confers inhibitory activity in ABL kinase domain mutations that render imatinib ineffective. Dasatinib is ~325-fold more potent than imatinib in inhibiting BCR-ABL in vitro.

On 23 December 2005, orphan designation (EU/3/05/339) was granted by the European Commission for dasatinib for the treatment of chronic myeloid leukaemia.

Sprycel (dasatinib) was granted a marketing authorisation in the European Union on 20 November 2006. It is currently indicated for the *treatment of adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesylate and for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy*. The currently approved posology is 100 mg administered QD (once daily) in subjects with chronic phase CML and 140 mg QD in subjects with advanced phase CML and Ph+ ALL.

In this type II variation (C.I.6.a), the Marketing Authorisation Holder (MAH) of Sprycel applied for a new indication in the treatment of adults with **newly** diagnosed chronic myeloid leukaemia (CML) in chronic phase.

Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) and the Package Leaflet have been updated. Annex II has been updated to include the updated version of the risk management plan (version 8.1).

The MAH also took the opportunity to include the marketing authorisation numbers of recently approved 80 mg and 140 mg strengths in Annexes I and IIIA.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/31/2010 for the following condition(s):

- Philadephia chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia
- Philadephia chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia

on the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

1.2. Non-clinical aspects

1.2.1. Introduction

The MAH did not conduct new non-clinical studies to support the use of dasatinib in the patient population covered by the new indication. The initial marketing authorisation application included most of the studies required for a long term use in patients with long life expectancy. Exception were the carcinogenicity studies which are currently ongoing, and the reproductive toxicity package from which only the embryo-fetal toxicity study has been performed in rats and rabbits.

1.2.2. Toxicology

Carcinogenicity

The MAH provided a very brief summary of the status of the recently-completed (in-life portion) carcinogenicity study in rats, as it is recognised these data are considered of relevance in view of the expected long treatment duration of newly diagnosed CML patients. This oral carcinogenicity study in rats was initiated in August 2007 as a commitment (based on Guideline ICH Topic S1B Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals), and the in-life portion of this study was completed in August 2009. Doses were 3 mg/kg/day (the presumed maximum tolerated dose), 1mg/kg/day, and 0.3 mg/kg/day (based on Guideline ICH Topic S1C(R2): Dose selection for carcinogenicity studies of pharmaceuticals). Peer review of the pathology data and microscope slides has been recently completed. Evaluations by the study pathologist and peer-review pathologist indicated that there was no evidence of dasatinib-related tumors. The final report is currently expected for submission at the latest by December 2010, as previously agreed with the CHMP (FUM 005).

Reproduction Toxicity

In embryofoetal development (Segment II) studies, dasatinib induced embryolethality with associated decreases in litter size in rats, and foetal skeletal alterations in both rats and rabbits. These effects in both rats and rabbits occurred at doses that did not produce maternal toxicity.

The current dasatinib SmPC reflects the embryo-lethality observed in previous embryo-foetal development and fertility and early embryonic development studies.

It is presently unknown whether dasatinib will be tolerated by late-gestation fetuses and neonates. The MAH committed to, prior to initiation of a large-scale study, perform preliminary range-finding study that begins dosing of cohorts of dams at different time points in development (Gestation Day 16, Lactation Day 0, and Lactation Day 4). Based on the outcome of this initial study the feasibility of conducting a definitive peri- and postnatal development study will be determined.

Ecotoxicity/environmental risk assessment

In this application, the MAH included an updated environmental risk assessment (ERA) report, summarised in the table below.

Table 1 – Summary of performed phase I and phase II tests

Substance (INN/Invented Name): Dasatinib					
CAS-number (if available): 863127-77-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.56			Potential PBT: N
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.56			not B
	BCF	n/a			
Persistence	DT50 or ready biodegradability	Not readily biodegradable after 28 days			P
Toxicity	NOEC or CMR	CMR			T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Refined	0.001 µg/L			>0.01 threshold: N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	Modified SCAS test	K_{oc} = 2430 (log K_{oc} = 3.38)			
Inherent Biodegradability in Water	OECD 302A	Negligible mineralization to CO_2 (0.4% over 21 days)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, whole\ system}$ = 79.7 and 131 days for higher and lower organic carbon content, respectively. % shifting to sediment = 14			Anaerobic conditions not tested
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC (growth rate)	0.073	mg/L	Pseudokirchneriella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.068	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC (survival)	0.018	mg/L	Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	>1000	mg/L	No inhibition seen at this dose
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	Chrironomus riparius

1.2.3. Discussion and conclusion on non-clinical aspects

The MAH did not conduct new non-clinical studies to support the use of dasatinib in the patient population covered by the new indication. This is acceptable as the initial marketing authorisation application included most of the studies required for a long term use in patients with long life expectancy.

Preliminary evaluation of the carcinogenicity data does not seem to pose immediate concern.

The enlargement of the population into "naive" patients with a longer lasting disease might lead to the identification of pregnant patients eligible for treatment during pregnancy, during the foetal period, after complete organogenesis. A preliminary range-finding study that begins dosing of cohorts of dams at different time points in development will be conducted as a post-authorisation commitment. Based on the outcome of this initial study the feasibility of conducting a definitive peri- and postnatal development study will be determined.

In this application, the MAH included an updated ERA report. The default PEC_{sw} value (0.7 ug/L) above the trigger limit (0.01 ug/L) led to a phase II analysis. Therefore, the risk of an adverse environmental impact from use of dasatinib was evaluated in Phase I, Phase II Tier A and Phase II Tier B - according to ERA CHMP guideline and supporting guidance by the European Chemicals Bureau: Technical Guidance Document (ECB: TGD). A revised PEC_{sw} value of 0.00021 µg/L was obtained by accounting for human metabolism (49.5% reduction) and refining F_{pen} (0.000015

instead of 0.01) based on patient use. It was not corrected to account for any environmental depletion mechanisms.

A terrestrial testing in tier B was not conducted as the K_{oc} value (2430) is below the 10,000 threshold. However, as dasatinib is not readily biodegradable and greater than 10% of dasatinib was measured in the sediment at day 14 a sediment toxicity study was conducted. Dasatinib is sensitive to light and this increases the removal potential of dasatinib in the aquatic environment. The assessment shows that dasatinib does not affect sludge micro-organisms, aquatic organisms (including sediment organisms), or bio-concentrate in aquatic species under the test conditions presented in this risk assessment. Of the three chronic toxicity studies conducted the fish was the most sensitive species (NOEC was 0.018 mg/L for the survival endpoint). Dasatinib fails to meet the bioconcentration criteria, one of the three criteria for the PBT assessment so it is not considered a PBT substance.

Taken together the PEC:PNEC ratios indicate that dasatinib is unlikely to be a concern for the aquatic environment and for the sediment compartment. Dasatinib is unlikely to bioaccumulate to any significant extent. Dasatinib may have a tendency to persist in some water-sediment systems. Dasatinib is not considered a PBT substance. Dasatinib is unlikely to adsorb to soil compartment.

1.3. Clinical aspects

1.3.1. Introduction

This application is supported by a Phase 3 study CA180056 comparing confirmed CCyR (cCCyR) rates within 12 months (the primary endpoint) in newly diagnosed chronic phase CML subjects treated with dasatinib 100 mg QD versus the approved standard of care imatinib 400 mg QD.

The MAH also intends to conduct a large prospective meta-analysis from a confirmatory set of ongoing studies with long-term data to establish overall clinical benefit with a minimum follow-up of 5 years. Protocol assistance on the pivotal study (CA180056) design and long-term clinical plans was given by the CHMP in July 2007 (EMEA/CHMP/SAWP/310852/2007).

Pharmacokinetics (PK) data on dasatinib from CA180056 were generated for population PK analysis and exposure-response analyses and were included in this application.

GCP

The pivotal Study CA180056 was performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

1.3.2. Clinical pharmacology

Pharmacokinetics

The MAH submitted a population PK (PPK) analysis performed with data on 1,216 subjects from 8 clinical studies in subjects with all phases of CML or Ph+ALL. Thus 7 studies with data from subjects resistant or intolerant to imatinib, and study CA180056 in 235 subjects with newly diagnosed CP-CML. PPK analysis has previously been performed on data from the 7 studies that enrolled resistant or intolerant to imatinib subjects.

The exposure-response (E-R) analysis for cCCyR was performed with data from only CA180056, and the E-R analysis for safety (pleural effusion, PE) used combined data from CA180034 and CA180056. These studies were selected based on their inclusion in the previous PPK and E-R analyses, with the addition of data from CA180056 for the E-R analyses on imatinib naive CP-CML subjects.

The model adequately characterised concentration-time data of dasatinib, and showed no statistically significant or clinically relevant differences in dasatinib PK between imatinib naive and imatinib previously treated patients.

The probability of achieving CCyR in newly diagnosed CP-CML patients decreased with increase in dose interruption duration, but was not related to dasatinib exposure (weighted average concentration) over the range produced by 100 mg QD.

The risk of pleural effusion in newly diagnosed and resistant or intolerant to imatinib CP-CML patients increased with dasatinib steady-state trough concentration and age.

Discussion and conclusion on clinical pharmacology

The concentration-time data of dasatinib in CML and Ph+ ALL patients were well described by a linear 2-compartment pharmacokinetic model with first-order absorption.

There were no statistically significant or clinically relevant differences in dasatinib pharmacokinetics between newly diagnosed CP-CML patients (1st-line) and patients resistant or intolerant to imatinib (2nd-line).

The results of the PPK analysis support the use of dasatinib as first line treatment in patients with newly diagnosed CP-CML.

1.3.3. Clinical efficacy

1.3.3.1. Introduction

The proposed new indication is supported by a single, multinational, open-label, randomised Phase 3 study (CA180056) comparing cCCyR rates within 12 months (the primary endpoint) in newly diagnosed chronic phase CML subjects treated with dasatinib 100 mg QD versus the approved standard of care imatinib 400 mg QD (Table 2).

Table 2 –Study Design for Study CA180056

Study number	Study Status	Brief title / Description of Endpoints / Key Data Summary
BMS-sponsored CA180056 (DASISION)	Ongoing (Global)	Pivotal (superiority) trial - Phase 3, open label, randomized trial comparing dasatinib 100 QD with imatinib 400 QD. Randomization stratified by Hasford score. Primary endpoint: cCCyR within 12 months Secondary endpoints: MMR rate at any time, time-to cCCyR (at any time), time-to MMR (at any time), and time-in cCCyR (at any time), PFS, and OS Other endpoints: Time-in and time-to responses within 12 months, Time-to treatment failure, Time-to maximal clinical benefit, Safety, Sparse PK sampling for E-R and exposure/safety analyses, BCR-ABL point mutations developing in both treatment arms, CCyR, CMR. Subjects enrolled at 108 sites in 26 countries: 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. N = 519 randomized, 516 treated, study is closed to enrollment. Database locked in January 2010.

A large prospective meta-analysis with > 1,500 subjects is planned to adequately assess long-term efficacy and safety and will include subjects with newly diagnosed chronic phase CML from CA180056 (BMS-sponsored study) and 2 ongoing non-BMS studies from cooperative groups (SPIRIT2 in the United Kingdom and SWOG 0325 in the US/Canada; Table 3). The goal of this meta-analysis is to provide the most reliable and accurate estimates of the differences in long-term efficacy and safety between subjects newly diagnosed with chronic phase CML and treated with dasatinib 100 mg QD vs. imatinib 400 mg QD.

Table 3 – Ongoing Non-BMS Studies in Newly Diagnosed Chronic Phase CML, to be included in the Meta-Analysis

Study number	Study Status	Brief title / Description of Endpoints / Key Data Summary
CA180072 (SWOG)	Ongoing (US/Canada)	Phase 2b, multicenter, open-label, and randomized clinical study comparing dasatinib 100 QD, imatinib 400 QD, and 800 mg QD. Randomization stratified by Hasford score. The study design included a fixed sample size. Power in this study was dependent on the magnitude of treatment difference between dasatinib and imatinib. Primary endpoint: Molecular response rate (defined as 4-log reduction in transcript level) within 12 months N= 400 planned, 403 enrolled, study is closed to enrolment as of 28-Feb-09. All 253 patients concurrently randomized to dasatinib and imatinib 400 mg QD will be included in the meta-analysis.
CA180216 (SPIRIT2)	Ongoing (UK)	Phase 3, multicenter, open-label, prospective randomized study comparing dasatinib 100 QD with imatinib 400 QD. Primary endpoint: EFS at 5 years follow up. An event was defined as the first occurrence of one of the following: death from any cause, disease progression as a result of loss of CHR, increasing WBC count, loss of MCyR, and progression to accelerated or blast phase CML. This definition is the same as PFS in CA180056 and CA180072. N= 810 planned; As of 8-Feb-2010, 156 subjects enrolled

1.3.3.2. Dose-response studies

In the main study CA180056, the selected dose of dasatinib was 100 mg QD. Activity at this dose level was first documented in the Phase 1 study CA180002 (submitted in the initial marketing authorisation application). In a Phase 2 study in chronic phase CML subjects (CA180013, submitted in the initial marketing authorisation application) the median average daily dose of dasatinib was 97 mg.

A Phase 3 dose optimisation study in chronic phase CML (CA180034) demonstrated comparable efficacy but fewer adverse events (AEs) in subjects treated with dasatinib at 100 mg QD vs. 70 mg twice daily (BID). This trial randomised 670 subjects to one of 4 doses: 100 mg QD, 50 mg BID, 140 mg QD, and 70 mg BID. With median treatment duration of 8 months, the response rates, duration of major cytogenetic response (MCyR) and PFS were similar among the 4 treatment groups. There was significantly less severe thrombocytopenia (22% on 100 mg QD and 37% on 70 mg BID) and pleural effusions (7% on 100 mg QD and 16% on 70 mg BID) in the 100 mg QD group. There were fewer dose interruptions and reductions on the 100 mg QD dose. Fewer subjects discontinued dasatinib due to study drug toxicity on this group as well (EMEA/H/C/709/II/02, Commission decision on 22 August 2007).

Based on these data, the 100 mg QD dose of dasatinib was selected for the pivotal study for this application.

1.3.3.3. Main Study CA180056

Methods

Study CA180056 (DASISION) is a phase 3 superiority open label, randomised trial comparing dasatinib 100 mg QD with the current standard of care, imatinib 400 mg QD.

Study Participants

Participants were subjects ≥ 18 years of age, newly diagnosed with chronic phase CML within the past 3 months based on cytogenetic test results of bone marrow, demonstrating the presence of the Philadelphia positive t(9;22) chromosomal translocation.

The main inclusion/exclusion criteria are as follows:

Main Inclusion criteria

- Subjects must have Ph+ CML in chronic phase, which was defined by the presence of all 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 leukemic involvement, with the exception of hepatosplenomegaly
  - Ph+ or variants must be demonstrated by BM cytogenetics.
- Previously untreated chronic phase CML

Main exclusion criteria

- Known pleural effusion at baseline
- Uncontrolled or significant cardiovascular disease, including any of the following:
  - A myocardial infarction (MI) within 6 months
  - Uncontrolled angina within 3 months
  - Congestive heart failure within 3 months
  - Diagnosed or suspected congenital long QT syndrome
  - Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointe)
  - Prolonged QTcF interval > 450 msec on pre-entry electrocardiogram (ECG)
- History of significant bleeding disorder unrelated to CML, including:
  - Diagnosed congenital bleeding disorders (e.g., von Willebrand's disease)
  - Diagnosed acquired bleeding disorder within one year (e.g., acquired anti-factor VIII antibodies)

Treatments

Dasatinib was administered orally at a dose of 100 mg QD. Subjects were permitted to adjust the time of administration as long as the drug was taken approximately every 24 hours. Dasatinib 50 mg tablets were administered as 2 tablets taken once per day.

Imatinib was administered orally at a dose of 400 mg QD. Each 400 mg dose was administered with a meal and taken with a large glass of water. Subjects were permitted to adjust the time of administration as long as the drug was taken approximately every 24 hours. Imatinib 400 mg tablets were administered as 1 tablet taken once per day.

Treatment was to continue until progression of disease or development of intolerable toxicity or subject's decision to withdraw.

Dose modifications were planned as described in Table 4. Dosing above 180 mg QD of dasatinib or 800 mg/day of imatinib was prohibited.

Table 4 – 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

No prior treatment for CML other than hydroxyurea or anagrelide was permitted before eligibility.

Objectives

The *primary objective* was to compare the best cCCyR rates within 12 months in newly diagnosed chronic phase CML subjects treated with dasatinib 100 mg QD versus imatinib 400 mg QD.

The *secondary objectives* were to compare Time in cCCyR overall (a measure of duration of cCCyR), Major molecular response (MMR) rate at any time, Time to cCCyR overall, Time to MMR overall, Progression-free survival (PFS), Overall survival (OS).

The *tertiary objectives* were:

- To describe the following efficacy parameters within 12 months: MMR, Confirmed major cytogenetic response rate (cMCyR), Confirmed complete hematologic response (cCHR), Time in and time to cCCyR.
- To describe the following study parameters overall: Best overall cCCyR, cMCyR, and cCHR rate, Times to cMCyR and cCHR, Time to treatment failure (TTF), Time to maximum clinical benefit (TMCB).
- To assess duration of cCCyR within 12 months, duration overall for cCCyR, cMCyR, MMR, and cCHR for each treatment group.
- To evaluate the toxicity profile for each treatment group.
- Pharmacokinetic assessment of dasatinib in relation to efficacy and safety variables.
- To explore the development of BCR-ABL point mutations in both treatment groups.

Outcomes/endpoints

The primary efficacy endpoint was the best cCCyR rate within 12 months. Secondary efficacy endpoints included time in cCCyR, MMR at any time, time to cCCyR overall, time to MMR overall, PFS and OS.

Sample size

For sample size estimation, the cCCyR rate within 12 months of dasatinib treatment was assumed to be 81%. With a 2-sided $\alpha = 0.05$ and power of 90%, a total of 518 subjects were needed to show a statistical significant difference in 12-month cCCyR rates between the 2 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% and 81%, respectively.

Randomisation

Randomisation was stratified by Hasford score. This is supported since it is possible by the means of Hasford score to identify low, intermediate, and high risk patients concerning survival.

Blinding (masking)

This was an open-label study.

Statistical methods

Response (cytogenetic, molecular, and hematologic) and event (e.g., AE of special interest) rates were estimated with their 2-sided, exact 95% confidence intervals (CIs) based on the Clopper and Pearson method. The difference in rates between the 2 treatment groups with their 2-sided 95% CI

was estimated using the Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for the stratification factor Hasford score. Test for differences in response rates used a 2-sided test stratified by Hasford score using CMH method.

The secondary endpoints will be reassessed again after 5 years using a hierarchical testing procedure. The power of these tests depends primarily on the number of observed events. Therefore, a reassessment seems reasonable, in particular if a considerable number of additional events is expected during the remaining follow-up.

The hierarchical test procedure maintains the overall significance level of the 5-years assessment. The 12-months assessment of the secondary endpoints may be considered as an interim analysis relative to the final assessment after 5 years, and the chosen significance level of 0.0001 ensures that this interim analysis has very little impact on the overall level significance in the final analysis.

Results

Participant flow

The subject disposition is summarised in the table below.

Table 5 – Subject Disposition - Enrolled Subjects in Study CA180056

	Number (%) of Subjects Enrolled Subjects: 547	
	Dasatinib 100 mg QD	**Imatinib 400 mg QD**
Randomised, n = 519	259	260
Treated, n = 516	258 (100)	258 (100)
Still on treatment, n = 428 (82%)	218 (85)	210 (81)
Discontinued	40 (16)	48 (19)
Disease progression	7 (3)	13 (5)
Treatment failure	6 (3)	10 (4)
Study drug toxicity	13 (5)	11 (4)
Adverse event unrelated	3 (1)	1 (<1)
Death	4 (2)	1 (<1)
Withdrew consent	2 (<1)	3 (1)
Pregnancy	2 (<1)	0
Lost to follow-up	0	3 (1)
Other reason	3 (1)	6 (2)

The participant flow had no major imbalances.

The number of treated subject n = 517 were equally distributed in the two treatment groups with 258 in each.

The number of discontinued subjects were lower in the dasatinib group [n= 40 (16%)] compared to the imatinib group [n=48 (19%)]. There was a trend towards higher disease progression and treatment failure in the imatinib group. Four deaths were reasons to discontinuation in the dasatinib group whereas one dead was reason to discontinuation in the imatinib group.

Recruitment

The first patient first visit occurred on 24 September 2007. The data cut-off date for the 12-month primary analysis was on 11 January 2010. The study is ongoing.

Conduct of the study

The amendments to the protocol were considered not to have major impact on the study results. Clinically relevant protocol deviations were reported for a total of 2 subjects, 1 from each treatment group for the reason "lacked criteria for Ph+ chronic phase CML".

Baseline data

Demographic summary and baseline characteristics are presented in the table below.

Table 6 – Baseline Disease and Demographics - Randomised Subjects in Study CA180056

	Dasatinib N = 259	**Imatinib N = 260**
Disease History: Median time from initial CML diagnosis (months, [range])	1 (0.03 - 9.72)	1 (0.10 - 8.02)
Median Age (years [range])	46.0 (18 - 84)	48.5 (18 - 78)
Gender (n [%])		
Male	144 (56)	163 (63)
Female	115 (44)	97 (37)
Race (n [%])		
White	132 (51)	143 (55)
Black/African American	2 (0.8)	1 (0.4)
Asian	108 (42)	95 (37)
Other	17 (7)	21 (8)
ECOG Performance (n [%])		
0	213 (82)	205 (79)
1	46 (18)	53 (20)
2	0	2 (0.8)
Baseline Hematology		
WBC (median; /mm^3)	25.1	23.5
Platelet (median; $10^3/mm^3$)	448	390
Hasford Score (n [%])		
Low	86 (33)	87 (34)
Intermediate	124 (48)	123 (47)
High	49 (19)	50 (19)

Numbers analysed

The number of subjects enrolled, randomised and analysed is provided in the table below.

Table 7 – Enrolled, randomised and treated Subjects in Study CA180056

	Number (%) of Subjects Enrolled Subjects: 547	
	Dasatinib 100 mg QD	**Imatinib 400 mg QD**
Randomised	259	260
Treated	258 (100)	258 (100)

Outcomes and estimation

Efficacy responses are summarised in the table below.

Table 8 – Efficacy Responses in Newly Diagnosed Chronic Phase CML: All Randomised Subjects

	Dasatinib N = 259	**Imatinib N = 260**
Primary Endpoint		
cCCyR rate within 12 months	199 (77%)	172 (66%)
p-value	p < 0.007*	
Secondary Endpoints		
MMR rate at any time	135 (52%)	88 (34%)
p-value	p < 0.00003*	
Time-to cCCyR		
Hazard ratio (99.99% CI)	1.55 (1.0 - 2.3)[a]	
p-value	p < 0.0001*	
Median (months) in subjects with cCCyR	3.1	5.6
Time-to MMR		
Hazard ratio (99.99% CI)	2.01 (1.2 - 3.4)[b]	
p-value	p < 0.0001*	
Median (months) in subjects with MMR	6.3	9.2
Time-in cCCyR at any time		
Hazard ratio (99.99% CI)	0.7 (0.4 - 1.4)[c]	
p-value	p < 0.035	
PFS at 12 months	96.4%	96.7%
OS at 12 months	97.2%	98.8%

* Considered statistically significant.

Note: All p values were adjusted for Hasford score.

[a] 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.

[b] 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.

[c] 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.

cCCyR - confirmed complete cytogenetic response, CI - confidence interval, MMR - major molecular response, OS - overall survival, PFS - progression-free survival

Primary endpoint: cCCyR

Dasatinib treatment produced a significantly ($p < 0.007$) higher cCCyR rate within 12 months (77%) compared with imatinib (66%) meeting the primary endpoint (Table 9).

Sensitivity analyses were pre-specified for the primary endpoint:

Table 9 – Rate of cCCyR within 12 Months with Newly Diagnosed Chronic CML

	Responders/All Subjects (%)		
Analyses (based on cCCyR within 12 months)	**Dasatinib**	**Imatinib**	**p-value**
All randomised subjects	199/259 (77)	172/260 (66)	0.007
All randomised with only assessments ≥ 20 metaphases	197/259 (76)	167/260 (64)	0.003
All randomised subjects (most conservative scenario)	199/259 (77)	177/260 (68)	0.025
All treated subjects	199/258 (77)	172/258 (67)	0.008
All evaluable subjects	199/258 (77)	172/256 (67)	0.011
Per-protocol subjects	198/257 (77)	171/255 (67)	0.011

Secondary endpoints

MMR at any time was significantly higher in dasatinib-treated subjects (n = 135, 52%) compared with imatinib-treated subjects (n = 88, 34%) (p < 0.00003; significance level = 0.0001).

The rate of complete molecular response (CMR) at any time was 8.5% vs. 4.2% in the dasatinib and imatinib treatment groups, respectively. This is the most sensitive way of evaluating the number of leukemic cells but CMR was not an endpoint.

The molecular response was achieved earlier in the dasatinib treated subjects compared to the imatinib treated subjects.

The secondary endpoint "***Time to cCyR at any time***" was met (p< 0.0001; significance level 0.0001) with a median of 3.1 and 5.6 months for the dasatinib and imatinib group respectively. Cytogenetic response was achieved earlier in the dasatinib treated subjects compared to the imatinib treated subjects.

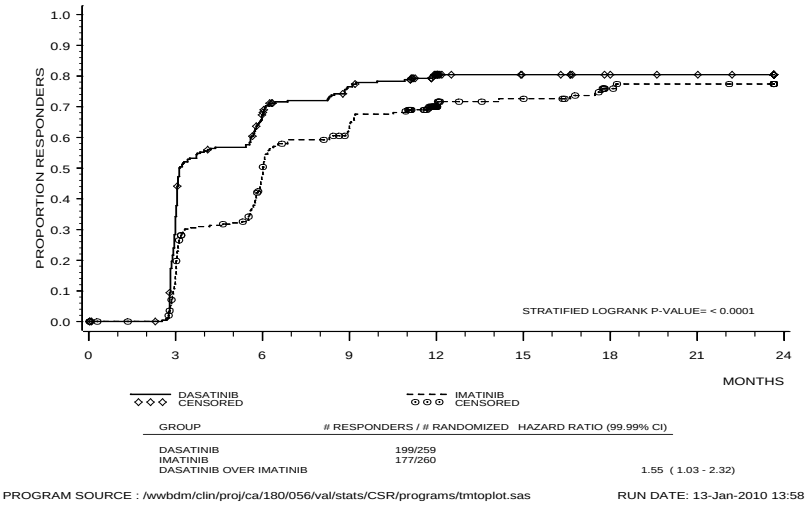

Figure 1 - Time to cCCyR at Any Time - All Randomised Subjects

The secondary endpoint "***Time to MMR***" was met (p< 0.0001; significance level 0.0001) with a median of 6.3 and 9.2 months for the Dasatinib and Imatinib group respectively. As MMR is more sensitive than cCCyR it is considered a very important endpoint.

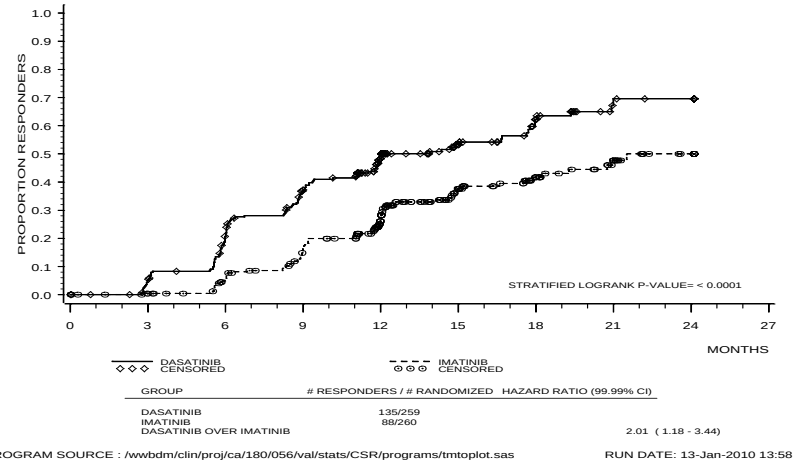

Figure 2 - Time to MMR at Any Time - All Randomised Subjects

The secondary endpoint "***Time in cCCyR (At Any Time): All Randomised Subjects***" is not met (stratified log-rank test, p < 0.035; tested at a significance level of 0.0001).

A trend for more durable cytogenetic responses with dasatinib compared with imatinib was seen though. With a hazard ratio of 0.7 indicating 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 in the same situation.

At the time of maturity of the secondary endpoints, "Time in cCCyR (At Any Time)" will be tested after a minimum of 5 years – as rank 2.

Duration of cCCyR (At Any Time) in Subjects with cCCyR was not defined as a key secondary endpoint but shows that the subjects with cCCyR only had very few events, 1/199 and 3/177 for dasatinib and imatinib respectively. It is still too early to assess the durability of response which was expected.

The time-dependent endpoints ***Overall survival*** and ***Progression-free Survival*** are difficult to interpret at this time. The number of events in OS and PFS was too low to allow a conclusion at the present time. With a minimum of 12 months follow-up PFS data are still immature. There were few progression events, 12 (5%) in the dasatinib group and 15 (6%) in the imatinib group.

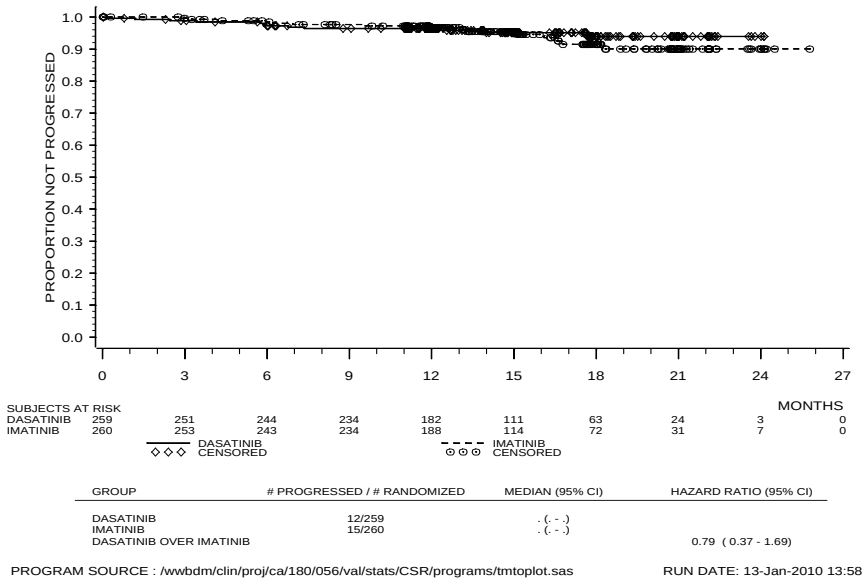

Figure 3 - Progression-Free Survival - All Randomised Subjects

The PFS at 12 months with Kaplan-Meier estimates were 96.4 % (CI: 94.1—98.7) and 96.7% (CI: 94.4-99.0%) for the dasatinib and imatinib group respectively. The secondary endpoint "PFS" will be tested after a minimum of 5 years – as rank 6.

No significant difference was seen in OS between the two treatment groups with OS at 12 months at 96.4% and 96.7% in the dasatinib and imatinib group respectively. The follow-up period in the pivotal study is too short to detect a difference in OS between the treatment groups. Maturation of overall survival results are anticipated at the 5 years follow-up.

Tertiary endpoints

Transformation to accelerated or blast phase of CML occurred less frequently in dasatinib treated subjects (5/259, 1.9%, all blastic phase) compared to imatinib treated subjects (9/260, 3.5%, all blastic phase). This endpoint was not mature yet but showed no detrimental effect of dasatinib.

One of the tertiary objectives was to explore the ***development of BCR-ABL point mutations*** in both treatment groups. The MAH stated that the mutations were assessed in subjects at the time of disease progression or at end of treatment (EOT). Some of these mutations have been reported to confer resistance to imatinib. Bone marrow samples were sequenced and reported by MolecularMD (Portland, OR). The spectrum of point mutations in the BCR-ABL gene at the time of progressive disease or EOT was described. Subjects were grouped by mutation status (i.e., no mutation, location, IC50 to imatinib) by mutation status and off-treatment reason, and by specific mutation.

In treated subjects who discontinued study therapy and had mutation data, 4/24 (17%) subjects in the dasatinib group and 5/35 (14%) in the imatinib group had mutations identified at the end of treatment. All mutations were outside the P-loop or activation loop. Among the 4 dasatinib-treated subjects, the T315I mutation (3) or F317L mutation (1) were identified. Mutations identified in 5 imatinib treated subjects were M244V (1), E355G (2), F359V (1), and 1 subject had 2 mutations (D276G and F359C). BCR/ABL mutations will also be assessed with yearly updates of the study results and with longer follow-up.

Ancillary analyses

In most subpopulations, rates of cCCyR within 12 months (primary efficacy endpoint) were higher in dasatinib-treated subjects compared with imatinib-treated subjects. In some subpopulations with a limited number of subjects enrolled (< 21 and ≥ 65 years of age, black and other races, North American region), no clinically meaningful comparisons can be made.

1.3.3.4. Analysis performed across trials (pooled analyses and meta-analysis)

In the final advice letter from the Protocol Assistance (July 2007), the CHMP agreed with the sponsor's proposal that the long-term clinical benefit of dasatinib can be derived from a prospectively designed meta-analysis of several individual well-controlled randomised clinical trials meeting pre-specified design specifications. The CHMP acknowledged that pooling data from a number of clinical trials represents the only realistic possibility of accurately determining the long-term clinical benefit of dasatinib. As the meta-analysis protocol was not available at the time of the Protocol Assistance procedure, this application included the Statistical Analysis Plan (SAP) for such meta-analysis. This SAP aims to pool data from the 3 individual studies and run a uniform model to assess treatment effect. The SAP is also designed to evaluate the consistency of such approach by investigating the heterogeneity in treatment effect and conducting sensitivity analyses on different subpopulations and endpoints.

No analyses performed across trials are found concerning efficacy yet.

1.3.3.5. Clinical studies in special populations

No clinical studies in special populations have been submitted in this application. Experience from the currently approved indication is reflected in the SmPC from earlier trials.

No subjects < 18 years old were included in the pivotal study. Efficacy and safety in children and adolescents under the age of 18 years has not been previously established either. Very few subjects more than 75 years old and even ≥ 66 years old have been studied in the proposed indication. The MAH provided adequate justification for this. The treatment of older patients should be similar to the overall patient population in the study. While the safety profile (overall rates of AEs) of dasatinib in the geriatric population was similar to that in the younger population, patients aged ≥ 65 years are more likely to experience fluid retention events and dyspnoea. This is consistent with the observations in the second-line treatment of CML with dasatinib (imatinib resistant/intolerant subjects) and is included in the SmPC, section 4.4 as well as in section 4.8 and it is considered that the treating physician should be aware of these potential differences in safety to effectively manage the treatment of the older patient.

Concerning renal impairment no clinical studies have been conducted. In the pivotal study, patients with serum creatinine concentration > 3 times upper limit of the normal range were excluded. 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.

Concerning hepatic impairment it is known from earlier findings from a single-dose pharmacokinetic study, patients with mild, moderate or severe hepatic impairment may receive the recommended starting dose. However, due to the limitations of the study, caution is recommended when administering dasatinib to patients with hepatic impairment.

1.3.3.6. Discussion on clinical efficacy

This application was supported by a single, multinational, open-label, randomised phase 3 study based on surrogate endpoints with a minimum of 12 months of follow up data. In addition a confirmatory set of studies with long-term data to establish overall clinical benefit, with a minimum of 5 years of follow up, is ongoing.

Although a confirmation trial would be desirable, the fact that this is a one-pivotal study application is in line with the available guidance (Points to consider on application with 1) meta-analyses; 2) one pivotal study, CPMP/EWP/2330/99) as there is a pharmacological rationale and a plausible hypothesis, previous data on efficacy (in second line in the same disease) is not unconvincing, the results do not show any indication of a potential bias, the treatment benefit is large enough to be clinically valuable, statistical evidence is strong, the trial seems to have internal validity and all important endpoints show similar findings.

The CHMP stated in the protocol assistance (EMEA/CHMP/SAWP/310852/2007) that in the proposed setting the long-term clinical benefit can be derived from a prospectively designed meta-analysis with individual studies meeting the design specifications of the meta-analysis. This is acceptable because of the small population of patients with CML and resulting difficulty in recruiting a large number of patients.

The open-label design is not considered to be of any concern as the majority of the endpoints are objectively determined i.e. cytogenetic, molecular and haematological endpoints.

The inclusion/exclusion criteria are adequate as they reflect the proposed indication and the anticipated risks involved in the treatment with dasatinib.

In the pivotal study subjects were randomized 1:1 stratified by Hasford score to receive either Dasatinib 100 mg QD or Imatinib 400 mg QD. The selection of the 100 mg QD dose of dasatinib in the study was based on previous dose-response studies and the phase 3 dose optimisation study in chronic phase CML (CA180034) and seems reasonable. The choice and posology of the imatinib control arm is acceptable as it is the current standard of care in the treatment of adult patients with newly diagnosed CML in chronic phase.

The primary endpoint in the pivotal trial (cCCyR at 12 months) was endorsed by the CHMP in the protocol assistance procedure. Cytogenetic response evaluated in an interim analysis at 12 month was used as surrogate primary endpoint when Glivec (Imatinib) was approved in first line treatment of CML (IRIS). In later analysis of the IRIS trial it was documented that CCyR at one year is predictive for PFS.

Using PFS or OS as primary endpoints is not considered feasible as it will take years before the results are mature. MMR could have been acceptable as a primary endpoint as it is a more sensitive way of measuring residual disease, and the previous protocol assistance recommended MMR as a secondary endpoint. But since the advice was given, progress has been made to standardise molecular monitoring, and consequently, the present approach is accepted, i.e. CCyR is considered a validated endpoint.

The secondary and tertiary endpoints are found relevant to support the primary endpoint.

In general, the statistical analyses were adequate and address the relevant question using valid tools. Comparisons of the secondary endpoints were performed at a significance level of 0.0001; this level allowed the testing for these endpoints without impacting the overall type I error. Using an extremely low significance level for the secondary endpoints ensures that these tests have essentially no impact on the overall significance level. Overall, the test strategy is satisfactory.

The baseline data were well balanced between the two treatment groups.

As for the results, dasatinib showed superiority to imatinib in first line treatment in subjects with CML in chronic phase. The primary endpoint, cCCyR rate within 12 months, is clearly met as dasatinib treatment produced a significantly ($p < 0.007$) higher cCCyR rate within 12 months compared with imatinib. The consistency of the results for the primary endpoint across subgroups supports the robustness of the data. The primary endpoint is supported by the secondary endpoints MMR at any time, Time to cCCyR at any time and Time to MMR. The MAH committed to provide yearly updates of the results from the trial.

1.3.3.7. Conclusions on clinical efficacy

Dasatinib 100 mg QD induced significantly higher rates of CCyR and MMR compared to imatinib 400 mg QD in adults with newly diagnosed CML in chronic phase. A faster time to remission was observed.

Long term data on PFS and OS issued from a meta-analysis of trial CA180056 and similar trials comparative with imatinib will be submitted as a post-authorisation commitment in order to provide a more definitive assessment of long-term efficacy of dasatinib.

1.3.4. Clinical safety

Patient exposure

The assessment of the safety of dasatinib with a minimum of 12 months of follow-up in adult subjects with newly diagnosed chronic phase CML is based on analyses of 516 treated subjects, 258 in the dasatinib arm and 258 in the imatinib arm. Safety data are presented for all treated subjects who received at least 1 dose of study drug.

There were no subjects under the age of 18 years participating in the study. The number of subjects ≥ 65 years old were rather small, n = 25 in the dasatinib group and n = 29 in the imatinib group. The average daily dose (mg/day) was 99.0 (21-136) in the dasatinib group and 400 (125-657) in the imatinib group.

Subjects with dose interruptions were higher in the dasatinib group (52.3 %) compared with the imatinib group (35.3 %). The reasons for the first dose interruption were hematologic toxicity (12.4%) and non-hematologic toxicity (8.5%) in the dasatinib group whereas the main reason in the imatinib group was hematologic toxicity. Subjects with dose reductions were also higher in the dasatinib group (23.3 %) compared with the imatinib group (14.0%) with mainly 1-2 reductions in both groups and mainly due to hematologic and non-haematologic toxicities. More subjects were having a dose escalation in the imatinib group compared to the dasatinib group (14.0 % vs. 5.4%) and were mainly due to "no CCyR" and "no CHR " in the imatinib and dasatinib group respectively .

Adverse events

Overall the AEs seen (>/= 10%, any grade, drug related) were either seen with a lower or equal frequency in the dasatinib group compared to the imatinib group except for pleural effusions seen in 26 subjects (10%) in the dasatinib group (only grade 1and 2) and not seen in any subjects in the imatinib group (Table 10).

Table 10 – Overall Safety Summary - All Treated Patients

	Number (%) of Subjects	
	Dasatinib N=258	**Imatinib N=258**
All AEs	239 (93)	239 (93)
Drug-related AEs (any Grade)	206 (80)	220 (85)
Diarrhea	45 (17)	45 (17)
Headache	30 (12)	27 (11)
Pleural Effusion	26 (10)	0
Rash	23 (9)	34 (13)
Nausea	20 (8)	51 (20)
Myalgia	15 (6)	30 (12)
Vomiting	12 (5)	26 (10)
Muscle Spasms	10 (4)	45 (17)
Eyelid Edema	2 (<1)	34 (13)
Drug-related Grade 3 or 4 AEs	78 (30)	61 (24)
Drug-related Fluid Retention (any Grade)	50 (19)	109 (42)
Pleural Effusion	26 (10)	0
Superficial edema	23 (9)	92 (36)
Generalized edema	5 (1.9)	16 (6.2)
Pericardial effusion	3 (1)	1 (<1)
On-study Laboratory Abnormalities		
Grade 3-4 Absolute Neutrophil Count	53 (21)	52 (20)
Grade 3-4 Hemoglobin	26 (10)	17 (7)
Grade 3-4 Platelets	49 (19)	27 (11)
Grade 3-4 ALT	1 (<1)	3 (1)
Grade 3-4 AST	1 (<1)	2 (1)
Grade 3-4 Total Bilirubin	3 (1)	0
Drug-related SAEs (any Grade)	20 (8)	13 (5)
Drug-related AEs Leading to Discontinuation (any Grade)	13 (5)	11 (4)
All Deaths	10 (4)	6 (2)

Overall the safety profiles of the two treatments are almost similar and no unexpected safety events for dasatinib were seen. However from the currently approved indications, pleural effusions are known to be associated with dasatinib, oedema and muscle cramps with imatinib and this is still evident.

Serious adverse event/deaths/other significant events

More ***deaths*** were seen in the dasatinib group, n = 10 (3.9%), compared to the imatinib group, n = 6 (2.3%).

The cause of the deaths in the dasatinib group were disease progression (n = 4), infection (n = 4) and myocardial infarction (MI, n = 2). Six of the subjects died within 30 days of the last dose of dasatinib (disease progression n = 1, infection n = 3, MI n = 2) and 4 died more than 30 days after last dose of dasatinib (disease progression n = 3 and infection n = 1).

The cause of the deaths in the imatinib group were disease progression (n = 4), MI (n = 1) and unknown (n = 1). Four of the subjects died within 30 days of the last dose of imatinib (disease progression n = 2, MI n = 1 and unknown n = 1) and 2 died more than 30 days after last dose of imatinib because of disease progression.

Death because of infection was only seen in the dasatinib group. None of these four subjects appeared to have significant leukopenia or neutropenia at the time of infection and were all receiving multiple antibiotics. Besides from that the causes of death were similar in the two treatment groups.

Serious adverse events (SAEs) (drug-related) were reported by 8% and 5% of subjects in the dasatinib and imatinib groups, respectively.

SAEs (drug-related) experienced by 2 or more subjects included pleural effusion (4 subjects, 2%), thrombocytopenia (3 subjects, 1%), and pyrexia (2 subjects, 0.8%) in the dasatinib group. SAEs (drug-related) reported by 2 subjects each in the imatinib group included febrile neutropenia (0.8%) and vomiting (0.8%). All other drug-related SAEs were reported by 1 subject each.

Grade 3 and 4 SAEs (drug-related) were reported by 4% of subjects in each treatment group.

Grade 3 and 4 SAEs (drug-related) reported by 2 or more subjects were thrombocytopenia (3 subjects, 1%) in the dasatinib group and febrile neutropenia (2 subjects, 0.8%) in the imatinib group. All other severe drug-related SAEs were reported by 1 subject each. Of the 4 SAEs of drug-related pleural effusion in dasatinib-treated subjects, none were severe.

Safety issues of special interest in the dasatinib arm

Fluid retention is a well known safety issue in patients treated with TKIs. Associations with pleural effusions with dasatinib treatment and oedema with imatinib treatment are observed in the currently approved indications.

In the pivotal study fluid retention (all grades) was seen more frequently with imatinib than dasatinib (42% vs. 19%). The most frequent fluid retention in the dasatinib group was pleural effusion (10.1%) and superficial oedema (8.9%). In the imatinib group it was superficial oedema (35.7%) and generalised oedema (6.2%). Other drug-related fluid retention AEs were reported for < 2% of the subjects in either group. The risk of fluid retention is reflected in the SmPC.

Most often the dasatinib treated subjects with pleural effusions were managed by interruption of dasatinib. Pleural effusion did not in general impair the ability of subjects to obtain a CCyR (88.5%) or achieve MMR (65.4%).

Pulmonary oedema was reported for 1 subject (0.4%) in the dasatinib group (Grade 1 and considered drug related). It is reflected in the SmPC. Pulmonary hypertension occurred in association with dasatinib and appeared as a consequence of other fluid retention events. It was reported as drug-related events in 3 (1.2%) in the dasatinib group. It is reflected in the SmPC as well.

Bleeding events (regardless of relationship to study treatment) was reported in 30 (11.6%) and 27 (10.5%) subjects in the dasatinib and imatinib groups, respectively. Severe (Grade 3 to 4) bleeding was reported in 3 (1.2%) and 4 (1.6%) subjects in the dasatinib and imatinib groups, respectively. Drug-related bleeding (consisting of GI bleeding, CNS bleeding, and other hemorrhage) was infrequent and comparable between groups. In the dasatinib group 13 subjects (5.1%) had bleeding of any grade (2 GI bleedings and 11 other hemorrhage). In the imatinib group 12 subjects, (4.7%) experienced bleeding of any grade (1 GI bleedings and 11 other hemorrhage). This despite a higher incidence of severe thromobocytopenia in the dasatinib group (dasatinib: 19.1%, imatinib: 10.5%). More information must be provided concerning the chronological relation of thrombocytopenia and hemorrhagic episodes, and the relation thrombocytopenia grade and bleeding.

Severe drug-related bleeding was reported in 1 (0.4%) dasatinib-treated subject and 2 (0.8%) imatinib-treated subjects.

As for the *cardiac events*, the protocol excluded subjects with significant recent cardiac events within 3 to 6 months prior to enrolment. However, nearly one quarter of the subjects had some degree of cardiac co-morbidity i.e. hypertension, hyperlipidemia, diabetes and peripheral artery disease.

AEs in the MedDRA SOC of cardiac disorders were more than twice as likely in subjects with cardiac co-morbidity at baseline compared with subjects without cardiac co-morbidity at baseline in both groups. Warnings are reflected in the SmPC.

The rates of cardiac events, regardless of relationship, were higher with dasatinib treatment compared to imatinib treatment (26 subjects, 10.1% vs. 18 subjects, 7.0%, respectively), the rates of drug-related cardiac events were infrequent in both treatment groups (dasatinib 13 subjects, 5.0%; imatinib 12 subjects, 4.7%).

In the dasatinib group the most frequent cardiac events were congestive heart failure/cardiac dysfunction (1.6%), palpitations (1.2%), arrhythmias (1.2%) and pericardial effusions (1.2%).

In the imatinib group the most frequent cardiac events were palpitations (1.6%), congestive heart failure/cardiac dysfunction (1.2%) and arrhythmias (0.8%).

One subject in each treatment group had QT prolongation and one person in the imatinib group only had ventricular arrhythmia. Of the 23 subjects with drug-related cardiac AEs all had resolution of their AEs, except for 3 subjects in the imatinib group (two with decreased ejection fraction and one with ventricular arrhythmia). Drug-related cardiac events led to discontinuation in 2 subjects, both treated with dasatinib (grade 3 pericardial effusions, grade 4 QT prolongation).

QTc(F) > 500 msec was seen in one subject in each treatment group. The median QTc (F) change from baseline was lower with dasatinib compared with imatinib (3.0 msec vs. 8.2 msec).

None of the subjects had a severe cardiac dysfunction with a LVEF < 20% during the study. Eleven subjects had mild or moderate cardiac dysfunction (10 of these from baseline). Seven of the 11 subjects had baseline cardiac risk factors including prior MI, congestive heart failure (CHF), hyperlipidaemia, diabetes or hypertension (4 dasatinib, 3 imatinib). Eight of the 11 subjects remain on study treatment (5 subjects in the dasatinib group and 3 subjects in the imatinib group).

The rate of abnormally elevated pulmonary artery systolic pressure was found in 15 subjects (5.8%) in the dasatinib group vs. 7 subjects (2.7%) in the imatinib group. Seven of the 15 subjects in the dasatinib group had a change of <= 20 mmHg from baseline, 4 subjects had a change of >20 mmHg and 4 subjects were not reported at baseline. There was only one subject in the imatinib group who had a change of >20 mmHg from baseline.

Laboratory findings

Concerning haematology, dasatinib differ from imatinib by higher rate of grade 3 to 4 thrombocytopenia (19.1% vs. 10.5%). Furthermore a higher proportion of subjects in the dasatinib group reported recurrent events of grade 3 to 4 thrombocytopenia (6.2% vs. 1.6%) compared with the imatinib group but without bleeding related to recurrent thrombocytopenia in the dasatinib group. The median duration of the first occurrence of grade 3 to 4 thrombocytopenia were 2.8 weeks vs. 3.4 weeks in the dasatinib and imatinib group respectively.

Grade 3 to 4 baseline hematologic abnormalities were found in 2.3% or less of randomised subjects. Most subjects had some degree of cytopenia on study; however, the majority was grade 1 or 2. Otherwise between the dasatinib and imatinib groups, the rates of grade 3 to 4 leukopenia (8.6% vs. 9.7%), neutropenia (20.7% vs. 20.2%), and anemia (10.2% vs. 6.6%) were comparable.

A total of 7 subjects (dasatinib: 4, imatinib: 3) reported grade 3 to 4 ALT and/or AST or total bilirubin levels during the study. Elevations in liver function tests led to study drug discontinuation in 2 subjects both from the imatinib group.

Grade 3 to 4 creatinine levels were reported for 3 subjects (1 dasatinib-treated subject and 2 imatinib-treated subjects).

With the exception of phosphorus, there were few cases on-study of Grade 3 to 4 levels in these other chemistries (calcium, magnesium, alkaline phosphatase, potassium, sodium, uric and acid) and little difference between the treatment groups. Hypophosphatemia, a known side effect of imatinib, was reported as grade 3 in 11 dasatinib-treated subjects (4.4%) and 54 imatinib-treated subjects (21.6%) and no grade 4 events were reported.

Safety in special populations

Concerning gender related differences, a higher proportion of AEs were seen in females compared to males (88.6% vs. 78.4%) as well as AEs leading to discontinuation (6.2% vs. 2.6%). A higher proportion of deaths were reported in males than in females (4.2% vs. 1.4%).

Concerning pregnancy there are no adequate and well controlled studies. It is furthermore unknown whether dasatinib is excreted in the human milk.

Safety related to drug-drug interactions and other interactions

It is well known that the following drugs may decrease dasatinib plasma concentrations: CYP3A4 inducers, antacids and H2 antagonists/proton pump inhibitors. Furthermore it is also well known that CYP3A4 substrates may have their plasma concentrations altered by dasatinib.

Discontinuation due to adverse events

Drug-related AEs leading to discontinuation of study drug were reported by 5% and 4% of subjects in the dasatinib and imatinib groups, respectively. Severe drug-related AEs leading to discontinuation were reported by 3 % in each treatment group.

Concerning drug-related AEs leading to discontinuation in more than one subject the MAH indicated that in the dasatinib group 4 subjects had cytopenias and 3 subjects had pleural effusion that led to discontinuation of study drug. In the imatinib group, 3 subjects had cytopenias that led to discontinuation of study drug. All other drug-related AEs inclusive severe drug-related AEs leading to discontinuation were reported by one subject each.

Post marketing experience

Dasatinib was first approved worldwide in June 2006 and is currently approved in over 60 countries worldwide. Based on routine pharmacovigilance activities conducted by BMS Global Pharmacovigilance and Epidemiology, review of postmarketing data confirms that dasatinib is tolerated. The safety profile of dasatinib remains favorable and similar to the profile established during clinical trials.

1.3.4.1. Discussion on clinical safety

The assessment of the safety of dasatinib with a minimum of 12 months of follow-up in adult subjects with newly diagnosed chronic phase CML is based on analysis of 516 treated subjects, 258 in the dasatinib arm and 258 in the imatinib arm. The number of randomized and treated subjects as well as the duration of therapy (14.01 and 14.28 months in the dasatinib and imatinib arm respectively) was overall well balanced.

The safety profiles of both dasatinib and imatinib did not indicate any new or unexpected major concerns.

Drug related non-haematological adverse events associated with both treatments were primary grade 1 or 2.

AEs are seen in 93% of the subjects in both treatment groups. Drug related AEs (any grade) are seen in 80% and 85% in the dasatinib and imatinib group respectively. Drug related grade 3-4 AEs was reported in 30% and 24 % in the dasatinib and imatinib group respectively.

Most frequent drug related AEs in the dasatinib group were: diarrhoea (17%), headache (12%) and pleural effusion (10%). Most frequent drug related AEs in the imatinib group were: superficial oedema (36%), nausea (20%), muscle spasms (17 %), diarrhoea (17%), rash (13%), eyelid oedema (13%), myalgia (12 %) and vomiting (10%).

AEs (drug related) seen with higher frequency in the dasatinib group compared to imatinib: pleural effusion (10 vs. 0 %) and headache (12 vs. 11%).

AEs (drug related) seen with higher frequency in the imatinib group compared to dasatinib: superficial oedema (36%), nausea (20%), muscle spasms (17 %), rash (13%), eyelid oedema (13%), myalgia (12 %) and vomiting (10%).

More deaths were seen in the dasatinib group (n = 10, (3.9%)) compared to the imatinib group (n = 6, (2.3%)). The cause of the deaths in the dasatinib group were disease progression (n = 4), infection (n = 4) and MI (n = 2). Six of the subjects died within 30 days of the last dose of dasatinib. The cause of the deaths in the imatinib group were disease progression (n = 4), MI (n = 1) and unknown (n = 1).

SAEs (drug-related) were reported by 8% and 5% of subjects in the dasatinib and imatinib groups, respectively. SAEs (drug-related) experienced by 2 or more subjects included pleural effusion (4 subjects, 2%), thrombocytopenia (3 subjects, 1%), and pyrexia (2 subjects, 0.8%) in the dasatinib group. SAEs (drug-related) reported by 2 subjects each in the imatinib group included febrile neutropenia (0.8%) and vomiting (0.8%). All other drug-related SAEs were reported by 1 subject each. Grade 3 and 4 SAEs (drug-related) were reported by 4% of subjects in each treatment group. Grade 3 and 4 SAEs (drug-related) reported by 2 or more subjects were thrombocytopenia in the dasatinib group and febrile neutropenia in the imatinib group.

Pleural effusions are known to be associated with dasatinib, oedema and muscle cramps with imatinib. These findings were confirmed in the pivotal study.

Other safety issues of special interests are those observed in association with dasatinib in currently approved indications or recognised events in other agents within this drug class i.e. myelosuppression, haemorrhage, cardiac disorders and QT-prolongation.

There were few cases of grade 3 to 4 levels in chemistries with the exception of phosphorus and little difference between the treatment groups. Hypophosphataemia, a known side effect of imatinib, was reported as grade 3 in 11 dasatinib-treated subjects (4.4%) and 54 imatinib-treated subjects (21.6%).

Drug-related AEs leading to discontinuation of study drug were reported by 5% and 4% of subjects in the dasatinib and imatinib groups, respectively. Severe drug-related AEs leading to discontinuation were reported by 3 % in each treatment group.

1.3.4.2. Conclusions on the clinical safety

Dasatinib is well tolerated. The safety profile of dasatinib has some differences compared to the safety profile of imatinib however it is not worse and acceptable in the proposed indication.

From the safety database all the adverse reactions reported in clinical trials and postmarketing have been included in the Summary of Product Characteristics.

1.4. Risk Management Plan

In this application, the MAH submitted an update to the risk management plan (version 8.1) which is considered acceptable.

Table 11 –Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation 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

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
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 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 reporting pregnancy-related malformative or feto/neonatal toxicity)	1) Potential risk information related to pregnancy in Section 4.6 of SmPC 2) Relevant information related to the Segment I nonclinical reproductive study findings are being added to Section 5.3 of SmPC

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Growth and development disorders and bone mineral metabolism disorders in pediatric patients	• Long-term safety assessments in leukemia pediatric studies (CA180018, CA180204, CA180226, and CA180Q36) for clinical evaluation of growth development disorders related to bone metabolism abnormalities in pediatric patients. • Routine PV activities with follow-up efforts targeted for information relevant for medical safety and causality assessments of growth development disorders related to bone maturation abnormality in pediatric patients	1) Updates to the IB regarding growth development disorders related to bone maturation abnormality in pediatric patients, if relevant data is available. 2) Update to the Product information, in applicable sections, in relation to paediatric use at the time of submission of the related application
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
Pediatric population	• Routine PV activities • Long-term safety monitoring of growth and development and bone mineral metabolism	SPRYCEL is not approved for use in paediatric patients. Information related to pediatric population in Section 4.2 of the SmPC, accordingly
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
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

1.5. Benefit-risk balance

Benefits

- Beneficial effects

The efficacy of dasatinib in newly diagnosed patients with CML-CP has been evaluated in a Phase III, open label, randomised superiority trial (study CA180056 or DASISION) comparing dasatinib 100 mg QD with imatinib 400 mg QD. A total of 519 patients were randomised, 259 patients in the dasatinib group and 260 patients in the imatinib group.

The open-label design is considered acceptable as the majority of the endpoints are objectively determined i.e. cytogenetic, molecular and haematological endpoints.

The primary endpoint was cCCyR rate at 12 months. This endpoint is widely accepted as a surrogate of clinical benefit and the adequacy of the primary surrogate endpoint stems from an analysis of the IRIS trial showing that CCyR at 1 year is predictive for PFS. This surrogate endpoint should be supported by time-dependent endpoints such as PFS and OS. In that context it should be taken into account that the overall 7-year survival rate for patients with newly diagnosed CML-CP treated with imatinib is now estimated to be 86 %.

Treatment with dasatinib produced a significantly ($p < 0.007$) higher cCCyR rate within 12 months (77%) compared with imatinib (66%) meeting the primary endpoint. The primary endpoint is supported by the secondary endpoints MMR at any time, Time to cCyR at any time and Time to MMR.

The PFS rates at 12 months are 96.4% (dasatinib) and 96.7% (imatinib), and the OS rates at 12 nonths are 97.2% (dasatinib) and 98.8 (imatinib). The PFS and OS data are still immature but will be provided post authorisation. Also, the rates of progression to CML-AP or CML-BC cannot be reliably assessed at this point in time.

Overall, study CA180056 convincingly demonstrates a favourable effect of dasatinib in comparison with imatinib in the first line treatment of patients with CML in chronic phase.

- Uncertainty in the knowledge about the beneficial effects

Efficacy in terms of cCCyR beyond 12 months is not known. Time-dependent endpoints are needed for a more definitive assessment of long term efficacy. At present OS and PFS are still immature but no detrimental effect is seen in the dasatinib group or the imatinib group. The MAH committed to provide yearly updates of the results from the trial.

If dasatinib substitutes imatinib as the preferred first-line treatment for CML-CP there is no evidence-based second-line therapy for patients failing dasatinib. However, this important clinical issue is not expected be resolved by the applicant at this point in time. However, the MAH committed to make proposals to prospectively collect response data (type, magnitude and duration) in patients receiving second line therapy after relapse or disease progression with dasatinib.

Risks

- Unfavourable effects

The observed safety profile for imatinib and dasatinib in the pivotal study was consistent with the known safety profile for both compounds. There were no new or unexpected major findings. Dasatinib is overall well tolerated. The safety profile of dasatinib has some differences compared to the safety profile of imatinib, however, it is not worse and acceptable in the proposed indication.

Pleural effusions are known to be associated with dasatinib, oedema and muscle cramps with imatinib. These findings were confirmed in the pivotal study. Pleural effusion was the most common fluid retention in the dasatinib group (10% vs. 0%) but discontinuation overall due to pleural effusion is infrequent. All pleural effusions were grade 1 to 2. Most often the dasatinib treated subjects with pleural effusions were managed by interruption of dasatinib but diuretic, dose reduction, corticosteroids and one thoracocentesis were also used. Three subjects discontinued due to pleural effusion. Pleural effusion did not in general impair the ability of subjects to obtain a CCyR or achieve MMR.

With regards to haematological toxicity dasatinib differ from imatinib by higher rate of grade 3 to 4 thrombocytopenia (19.1% vs. 10.5%). Most subjects had some degree of cytopenia on study; however, the majority was grade 1 or 2.

Another safety issues to be mentioned is the rate of abnormally elevated pulmonary artery systolic pressure (> 40 mmHg) which was found in 5.8% in the dasatinib group vs. 2.7% in the imatinib group.

- Uncertainty in the knowledge about the unfavourable effects

When pleural effusions (or other conditions) are treated with interruption of dasatinib or dose reduction it is not known if the duration of efficacy is sustained or the subjects will progress earlier. This, although the subjects in general did not have their ability to obtain a CCyR impaired in the pivotal study.

Also, the etiological relevance of dasatinib treatment to cardiac dysfunction, including cardiac failure, conduction disturbances, ischemia and myocardial infarction doesn't seem well defined or quantified.

The relation of haemorrhage to thrombocytopenia or to other haemostatic defect secondary to dasatinib is not fully clarified.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The higher cCCyR within 12 months achieved with dasatinib as compared to imatinib are very promising results indicating substantial higher efficacy for the second generation TKI dasatinib as compared with the hitherto standard of care of patients with newly diagnosed CMP-CP.

The observed safety profile for dasatinib in the pivotal study was consistent with the known safety profile. There are so far no indications that dasatinib has any detrimental effects on OS as compared to imatinib.

- Benefit-risk balance

In conclusion treatment of first line CML-CP subjects show clear superiority of efficacy in the dasatinib group compared to the imatinib group. Long term efficacy results are warranted, and should be submitted postapproval. The safety profile of dasatinib is in some aspects different from that of imatinib but not worse, and overall manageable.

1.5.1. Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Sprycel is not similar to Glivec and Tasigna within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 (See appendix 1).

1.6. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Sprycel in the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase was favourable and therefore recommended the granting of this extension of indication.

In addition, the CHMP, with reference to Article 8 of Regulation (EC) No 141/2000, considers Sprycel not to be similar (as defined in Article 3 of Commission Regulation (EC) No 847/2000) to Glivec and Tasigna for the same therapeutic indication.

Furthermore, the CHMP takes note that the agreed Paediatric Investigation Plan is not fully completed yet as only some of the measures are completed.

User consultation

The MAH provided a justification for not performing a consultation with target patients groups, for the submitted application. In line with EMA guideline, and within the scope of the current proposed changes, the MAH considered as not necessary to conduct another consultation with target patient groups for the package leaflet of SPRYCEL (dasatinib) for this pertaining Type II new indication, and proposed to perform a readability test based on an approved PL (resulting from this Type II variation and the recently completed line extension EMEA/H/C/709/X/22, commission decision on 30 September 2010) for its inclusion into the upcoming 5-year renewal application. The justification provided by the MAH was endorsed.