European Medicines Agency

London, 4 May 2009
Product name: **SPRYCEL**
Procedure number: EMEA/H/C/709/II/10

SCIENTIFIC DISCUSSION

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

SCIENTIFIC DISCUSSION

Introduction

Sprycel (dasatinib) is a potent inhibitor of the BCR-ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c-KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. The Marketing Authorisation (MA) was granted in November 2006 for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate, and also 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.

At the time of the CHMP opinion for the initial Marketing Authorisation in September 2006, the Marketing Authorisation Holder (MAH) made a commitment (FUM 010) to provide data post-authorisation from two Phase 3 studies comparing the efficacy and safety of dasatinib administered once daily (QD) versus twice daily (BID) in subjects with chronic (CA180034) and advanced phase CML or Ph+ ALL (CA180035).

- FUM 010: *'The proposed posology should be reassessed when results of studies CA180034 and CA 180035 are available. Final Clinical Study Report (24 months follow-up) by June 2009*.'

6 months data from these studies have previously been evaluated as a part of variation EMEA/H/C/709/II/02 for which a positive CHMP opinion was adopted in July 2007, recommending the approval of a change in posology for chronic phase CML to 100 mg QD as starting dose, due to a more favourable benefit/risk ratio than the 70 mg BID originally approved.

The MAH has now submitted a type II variation application to update sections 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC with 24-months follow-up data from the Phase III studies CA180034 and CA180035. The Package Leaflet has beeen amended accordingly.
In addition, the MAH has taken the opportunity to provide an updated version of the RMP (version 6.0). Consequently, annex II has been updated to reflect the latest version agreed with the CHMP.

Clinical aspects

Clinical pharmacology

No additional studies on biopharmaceutical or clinical pharmacology have been submitted as part of this application.

Clinical Efficacy

This application is based upon two Phase 3 studies comparing the efficacy and safety of dasatinib administered once daily (QD) versus twice daily (BID) (current posology for the advanced phase CML and Ph+ ALL indications) in subjects with chronic phase CML (CA180034) and advanced phase CML or Ph+ ALL (CA180035).

Studies CA180034 and CA180035

In the **Phase 3 study (CA180034)** in subjects with chronic phase CML, dasatinib was administered QD or BID at a total daily dose (TDD) of 100 mg or 140 mg. The primary endpoint was the comparison of MCyR rates after a minimum follow-up of 6 months of dasatinib treatment when administered QD relative to BID in imatinib-resistant subjects. Secondary endpoints included: comparison of MCyR rates between the 2 TDDs of dasatinib; durability and time to MCyR; rate, duration, time to CHR; and major molecular response (MMR). Six hundred seventy subjects were

randomized (497 imatinib-resistant, according to the assessment on the baseline case report form, and 173 imatinib-intolerant) to receive dasatinib at either 100 mg or 140 mg TDD.

In the **Phase 3 study (CA180035)** in subjects with advanced phase CML or Ph+ ALL, dasatinib was administered either QD or BID at a TDD of 140 mg. The primary endpoint was the comparison of MaHR rates in all randomized subjects treated with dasatinib at 140 mg QD or 70 mg BID. Secondary endpoints included durability and time to MaHR and rate of MCyR. Six hundred eleven subjects with accelerated phase, myeloid blast phase, or lymphoid blast phase CML or with Ph+ ALL were randomized to receive dasatinib at either 140 mg QD or 70 mg BID.

In both studies, investigators were allowed to escalate subjects' doses to achieve better efficacy or to reduce subjects' doses to manage adverse events. Efficacy responses were determined from haematologic values, bone marrow cytology and cytogenetics, and in the presence or absence of extramedullary disease. All data presented represent data collected from any subject who was randomized. Response rates were estimated along with their 95% exact CIs based on the Clopper-Pearson method. Kaplan-Meier estimates of median duration of response were provided along with their 95% CIs. Duration on treatment is calculated as the time from the first dose to the last dose of study drug; medians are presented for both imatinib-resistant and imatinib-intolerant subjects treated in the studies. In addition, duration of response is presented for both imatinib-resistant and imatinib-intolerant subjects.

MMR in subjects with chronic phase CML was assessed by RQ-PCR determined as the ratio of BCR-ABL copies to a control gene. These ratios were expressed using a standardized methodology initially described in the International Randomized Study of Interferon and STI-571 (IRIS) trial and currently reported by an international panel of experts. Data are reported on the international scale after determining a laboratory specific conversion factor. Molecular data for the Phase 3 study (CA180034) were measured internally at a BMS facility using validated methodology. Results are reported in all treated subjects and in subjects who achieved a CCyR. Subjects assessed for MMR may have been tested at any time during the treatment period.

Progression-free survival (PFS) was defined as the time from randomization until the time disease progression was first documented by the investigator or death. Subjects who neither progressed nor died were censored on the date of their last cytogenetic or haematologic assessment.

RESULTS STUDY CA180034

The median duration of exposure in CA180034 was 22 months.
Efficacy was achieved across all treatment groups with the QD schedule demonstrating comparable efficacy (non-inferiority) to the BID schedule on the primary efficacy endpoint (difference in MCyR 1.9%; 95% confidence interval [-6.8%–10.6%]). Over half of the subjects with chronic phase CML who achieved MCyR did so within the first 6 months with most subjects achieving MCyR by 1 year. MMR in all treated subjects was reported in 33% to 35% of the subjects. MMR in assessed subjects with CCyR was reported in 66% to 72% of the subjects. Rates of projected duration of MCyR and CCyR, projected PFS, and projected overall survival showed little difference across dose and schedule. Similar findings were reported for subjects who were intolerant of or resistant to imatinib. (Please refer to Table 4.3.1.2 below)

Table 4.3.1.2: Efficacy in CA180034 with 2 Years Follow-up in Subjects with Chronic Phase CML

	100 mg QD	50 mg BID	140 mg QD	70 mg BID
	All N=167 (Imatinib-Resistant n=124)	All N = 168 (Imatinib-Resistant n=124)	All N = 167 (Imatinib-Resistant n=123)	All N = 168 (Imatinib-Resistant n=126)
	Percent (%) of Subjects			
Haematologic Response Rate[a] (%) (95% CI)				
CHR	92% (86–95)	92% (87-96)	87% (81-92)	88% (82-93)
Cytogenetic Response[b] (%) (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)
Duration of MCyR (%) (95% CI)				
1 year				
All Patients	97% (93–100)	94% (89-99)	89% (83-96)	93% (87-98)
Imatinib-resistant patients	96% (91–100)	93% (87-100)	84% (75-93)	92% (86-99)
18 months				
All Patients	93% (88–98)	88%(81-95)	82%(74-91)	88%(81-95)
Imatinib-resistant patients	94% (87–100)	89% (80-97)	74%(63-86)	86% (77-95))
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[c] in Assessed Subjects with CCyR (%) (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)
Progression-Free Survival (%) (95% CI)				
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)

Table 4.3.1.2: Efficacy in CA180034 with 2 Years Follow-up in Subjects with Chronic Phase CML

	100 mg QD	50 mg BID	140 mg QD	70 mg BID
	All N=167 (Imatinib-Resistant n=124)	All N = 168 (Imatinib-Resistant n=124)	All N = 167 (Imatinib-Resistant n=123)	All N = 168 (Imatinib-Resistant n=126)
	Percent (%) of Subjects			
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 (%) (95% CI)				
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] **Haematologic response criteria** (all responses confirmed after 4 weeks):
CHR (chronic CML): WBC ≤ institutional ULN, platelets < 450,000/mm^3, no blasts or promyelocytes in peripheral blood, < 5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood < 20%, and no extramedullary involvement.
[b] **Cytogenetic response criteria**: complete (0% Ph+ metaphases) or partial (> 0%–35%). MCyR (0%–35%) combines both complete and partial responses.
[c] Defined as BCR-ABL/control transcripts ≤0.1% by RQ-PCR in peripheral blood samples.
Source: Final CSR CA180034;[9] Clinical Summary of Efficacy[13]

In imatinib-intolerant subjects who received 100 mg QD, MCyR was achieved in 77%, CCyR in 67%, and MMR (in assessed subjects with CCyR) in 64%. Based on the Kaplan-Meier estimates, all subjects (100%) maintained MCyR for 1 year and 92% (95% CI: [80%–100%]) maintained MCyR for 18 months. 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.

RESULTS STUDY CA180035

With 2 years of follow-up in subjects with advanced phase CML and Ph+ ALL in the Phase 3 study (CA180035), haematologic and cytogenetic responses were achieved in subjects treated with dasatinib. Data from CA180035 establishing the optimal dosing schedule showed similar efficacy between the 140 mg QD and 70 mg BID schedules. With both schedules, long-term responses were identified in advanced phases of disease.

Table 4.3.3.1: Duration of Treatment in Dasatinib in Subjects with Advanced Phase CML (CA180035)

	Median Time on Study Therapy, Months			
	Accelerated CML	Myeloid Blast CML	Lymphoid Blast CML	Ph+ ALL
QD	15.4	3.3	3.4	3.4
BID	12.0	3.1	3.6	2.5

Accelerated Phase CML:
With 2 years of follow-up, most subjects with accelerated phase CML achieved haematologic responses. Efficacy results were similar between the 140 mg QD and 70 mg BID. Cytogenetic response rates in CA180035 were lower than haematologic responses (see Table 4.3.3.2 below). Most subjects who achieved MaHR did so within the first 6 months of treatment.10 Rates of projected duration of MaHR, projected PFS, and projected overall survival were high and showed little difference between the 2 schedules.

Myeloid Blast Phase CML:
Efficacy results with 2 years of follow-up were similar between the 140 mg QD and 70 mg BID schedules. In CA180035, approximately one-third of the subjects achieved haematologic and cytogenetic responses (see Table 4.3.3.2 below). In subjects with MaHR, the time to response was rapid and within the first 4 months of treatment. Rates of projected duration of MaHR, projected PFS, and projected overall survival showed little difference across the 2 schedules.

Lymphoid Blast Phase CML:
There was little difference in efficacy between the 140 mg QD and 70 mg BID schedules in subjects with lymphoid blast phase CML after 2 years of follow-up. In CA180035, more subjects achieved a MCyR compared with MaHR (Table 4.3.3.2). Most subjects who achieved MaHR did so within the first 2 months of treatment.10 Rates of projected duration of MaHR, projected PFS, and projected overall survival were lower compared with other advanced phases of CML reflecting the more aggressive nature of this disease phase.

Table 4.3.3.2: Efficacy in CA180035 with 2 Years Follow-up in Subjects with Advanced Phase CML

	140 mg QD			70 mg BID		
	Accelerated (n=158)	Myeloid Blast (n=75)	Lymphoid Blast (n=33)	Accelerated (n=159)	Myeloid Blast (n=74)	Lymphoid Blast (n=28)
MaHR (95% CI)	66% (59-74)	28% (18-40)	42% (26-61)	68% (60-75)	28% (19-40)	32% (16-52)
CHR (95% CI)	47% (40-56)	17% (10-28)	21% (9-39)	52% (44-60)	18% (10-28)	14% (4-33)
NEL (95% CI)	19% (13-26)	11% (5-20)	21% (9-39)	16% (11-23)	11% (5-20)	18% (6-37)
MCyR (95% CI)	39% (31-47)	28% (18-40)	52% (34-69)	43% (33-51)	30% (20-42)	46% (28-66)
CCyR (95% CI)	32% (25-40)	17% (10-28)	39% (23-58)	33% (26-41)	23% (14-34)	43% (25-63)

Ph+ ALL:
In subjects with Ph+ ALL with 2 years of follow-up, rates of MaHR were similar between the 140 mg QD and 70 mg BID schedules. In CA180035, cytogenetic responses were greater than haematologic

responses (see Table 4.3.3.3 below). Most subjects who achieved MaHR did so within the first 2 months of treatment. Rates of projected duration of MaHR, projected PFS, and projected overall survival were lower compared with other advanced phases of CML reflecting the more aggressive nature of this disease phase

Table 4.3.3.3: Efficacy in CA180035 with 2 Years Follow-up in Subjects with Ph+ALL

	140 mg QD (n=40)	70 mg BID (n=44)
MaHR (95% CI)	38% (23-54)	32% (19-48)
CHR (95% CI)	33% (19-49)	25% (13-40)
NEL (95% CI)	5% (1-17)	7% (1-19)
MCyR (95% CI)	70% (54-83)	52% (37-68)
CCyR (95% CI)	50% (34-66)	39% (24-55)

Dose modifications

Study CA180035 included 609 patients. Among the 304 patients who were randomized to the 140 mg QD starting dose of dasatinib, 110 (36%) were dose escalated (Table 1). Of the 110 subjects who dose escalated, 106 (96%) escalated to 180 mg, 3 to 200 mg, and 1 to 280 mg. Escalation higher than 180 mg QD was primarily due to dosing error or rising % blasts.

Table 1: Dose Modifications: All Treated QD

	N = 304
Subjects with Dose Escalations n (%)	110 (36.2)
Reason for First Escalation n (%)	
DOSING ERROR	3 (1.0)
HEMATOLOGIC TOXICITY	5 (1.6)
LOSS OF RESPONSE	19 (6.3)
NO CCYR AFTER 6 MONTHS	10 (3.3)
NO CHR, NEL OR RTC WITHIN 4 WEEKS	22 (7.2)
NO MCYR AFTER 3 MONTHS	15 (4.9)
NON-HEMATOLOGIC TOXICITY	0
OTHER	1 (0.3)
RISING % BLASTS	35 (11.5)

Of the 110 subjects who dose escalated to ≥ 180 mg QD due to either no response or partial response at the recommended starting dose, haematologic responses were reported in 10 subjects. Of the 10 subjects with haematologic response after dose escalation, 4 achieved a major haematologic response (MaHR). Cytogenetic responses were reported in 18 subjects who dose escalated due to no response or partial response at the recommended starting dose. An additional 7 subjects who had a loss of MCyR regained MCyR after dose escalation. Of these 25 subjects with a cytogenetic response after dose escalation, 17 achieved MCyR. Overall, with 3 of the 4 subjects with a MaHR also achieving a MCyR, a total of 18 (16%) out of 110 subjects benefited from dose escalation ≥ 180 mg QD. Changes in response following dose escalation are presented in Table 2.

Table 2: Hematologic and Cytogenetic Responses to Dose Escalation

Pre-escalation Response	Post-escalation Response	# of Subjects	Post-escalation MaHR or MCyR
No Response	Complete Hematologic	2	2 MaHR
No Evidence of Leukemia	Complete Hematologic	1	1 MaHR

Table 2: Hematologic and Cytogenetic Responses to Dose Escalation

Pre-escalation Response	Post-escalation Response	# of Subjects	Post-escalation MaHR or MCyR
Minor Hematologic	No Evidence of Leukemia	1	1 MaHR
No Response	Minor Hematologic	6	0
No Response	Complete Cytogenetic	1	1 MCyR
No Response	Partial Cytogenetic	4	4 MCyR
Partial Cytogenetic	Complete Cytogenetic	2	2 MCyR
Minor Cytogenetic	Complete Cytogenetic	1	1 MCyR
Minimal Cytogenetic	Complete Cytogenetic	2	2 MCyR
No Response	Minor Cytogenetic	2	0
No Response	Minimal Cytogenetic	6	0
Complete Cytogenetic	Complete Cytogenetic	4*	4 MCyR
Complete Cytogenetic	Partial Cytogenetic	2*	2 MCyR
Partial Cytogenetic	Partial Cytogenetic	1*	1 MCyR
Total		35	21**

* Patients who had a loss of major cytogenetic response, but regained major cytogenetic response after dose escalation.
** Of the 21 subjects with post-escalation MaHR or MCyR, 3 subjects with MaHR also achieved MCyR. Therefore, 18 unique subjects achieved benefit from dose escalation.

Discussion on Clinical Efficacy

The current dosing recommendation is 70 mg BID in subjects with advanced phase CML or Ph+ ALL based on three Phase 2 studies and one Phase 3 previously reported with 6 months of follow-up. With long-term follow-up in the dose optimization study (CA180035), efficacy data were similar between the 140 mg QD and 70 mg BID schedules, and comparable with responses reported at 6 months with 70 mg BID. With both schedules, long-lasting responses were identified. In subjects with Ph+ ALL with longer follow-up, haematologic and cytogenetic response rates were also similar between 140 mg QD and 70 mg BID schedules. The dose of 140 mg QD supports an overall superior benefit risk and should be recommended in this population.

Dose-escalation to 180 mg QD in subjects with no response or partial response at the recommended starting dose is considered justified based on dose modification guidelines utilized in Study CA180035 that resulted in response improvement without additional safety concerns.
Protocol CA180035 allowed dose escalation from 140 mg to 180 mg total daily dose for the advanced phase CML and Ph+ ALL patients for the following reasons:

- Rising % blasts on 2 consecutive haematologic assessments at least one week apart (i.e., from Day 15);
- No complete haematologic response (CHR), no evidence of leukaemia (NEL), or minor haematologic response (MiHR) within 4 weeks;
- No major cytogenetic response (MCyR) after 3 months;
- No complete cytogenetic response (CCyR) after 6 months;
- Loss of haematologic response on 2 consecutive assessments at least 1 week apart.

Clinical Safety

As part of this submission safety data are presented for the safety cohort (all treated subjects who received at least 1 dose of study drug). The safety prognosis for subjects resistant and intolerant to imatinib was expected to be similar; therefore, all of the safety analyses combined these 2 groups except for subgroup analyses by imatinib status.

Safety data are presented separately for subjects with chronic phase CML and advanced phase CML or Ph+ ALL. In subjects with chronic phase CML, data are displayed by 100 mg QD, 70 mg BID, other doses, and all doses. In advanced phase CML and in Ph+ ALL, data are presented for 140 mg QD, 70 mg BID, and total.

Exposure

Dasatinib-treated subjects with CML or Ph+ ALL were followed for 2 years. In CA180034, the median duration of study therapy was similar across the 4 treatment schedules (22 months for each schedule). In CA180035, the median duration of study therapy was similar between the QD (6.1 months; range 0.03 - 31.2 months) and BID (6.2 months; range 0.03 - 28.8 months) groups. Likewise, there was little difference between the groups in median duration when excluding interruptions (5.7 months and 5.2 months, respectively). The median duration of exposure in the overall population of 2,182 dasatinib-treated subjects with CML or Ph+ ALL was 15.01 months; 55% of the subjects were administered dasatinib for more than 12 months.

Common Drug-related adverse events

In Study CA180034 with 2 years of follow-up, the majority of treated subjects (645 [97%]) reported at least 1 AE, regardless of relationship to study drug. 9 Drug-related AEs were reported in 603 (91%) subjects. Drug-related AEs occurred less frequently in the 100 mg QD group (86%) compared with the other 3 treatment groups (range 92% to 94%). Similarly, drug-related Grade 3 to 5 AEs also occurred less frequently in the 100 mg QD group (36%) compared with the 140 mg QD, 50 mg BID, and 70 mg BID groups (range 42% to 53%). Common drug-related non-haematologic AEs (occurring ≥ 20% in at least 1 treatment group) were headache (23% to 32%), diarrhoea (26% to 31%), nausea (18% to 29%), fatigue (19% to 25%), dyspnoea (16% to 23%), and pleural effusion (14% to 25%).

In CA180035, most subjects in both the QD group and the BID group reported at least 1 AE, any grade, while on study drug (98% vs. 99%).10 Drug-related AEs (reported in ≥ 10% of subjects), were reported in the majority of subjects (90% in QD and 89% in BID). Drug-related AEs were similar between the QD and BID groups with 2 exceptions: pleural effusion (20% vs. 32%, respectively) and peripheral oedema (9% vs. 15%, respectively).

Of the overall population of 2,182 dasatinib-treated subjects, 1,864 (85%) experienced at least 1 drug-related AE over the course of the study. ADRs of clinical relevance included diarrhoea (33%), pleural effusion (27%), headache (25%), haemorrhage (16%), and infection (11%).

Two tables of selected adverse drug reactions (ADRs) reported in these Phase 3 dose-optimization studies have been updated in the proposed SPC. Uncommon and rare adverse drug reactions are also discussed and updated in the proposed SPC section 4.8.

Drug-related Adverse Events Leading to Discontinuation

In CA180034, 101 (15%) subjects reported AEs leading to discontinuation, any grade, during the study or up to 30 days after the last dose of study medication. Eighty-three (13%) subjects reported drug-related AEs leading to discontinuation. Fewer subjects in the 100 mg QD group (8%) reported drug-related AEs leading to discontinuation, any grade, compared with the 140 mg QD, 50 mg BID, and 70 mg BID groups (12% to 15%, respectively). The most common (≥ 2% incidence in at least 1 treatment group) drug-related AEs leading to discontinuation were pleural effusion, dyspnoea, and headache. Drug-related AEs leading to discontinuation, for all grades and for Grade 3 to 5, were less frequent in the 100 mg QD group vs. the other 3 treatment groups. This difference was largely due to fewer subjects with pleural effusion leading to discontinuation in the 100 mg QD group.

In CA180035, 192 (32%) subjects reported AEs leading to discontinuation, any grade, during the study or up to 30 days after the last dose of study medication. Drug-related AEs leading to discontinuation of study therapy were similar between the QD and BID groups (14% and 16%, respectively) with the exception of drug-related pleural effusion (2% vs. 5%, respectively). The most common (≥ 2% incidence in at least 1 treatment group) drug-related AE leading to discontinuation was pleural effusion.

Serious Adverse Events

In CA180034, 276 (42%) subjects reported SAEs, any grade, during the study or up to 30 days after the last dose of study medication. One hundred seventy-four (26%) subjects reported drug-related SAEs. Fewer subjects in the 100 mg QD group (19%) reported drug-related SAEs vs. the 140 mg QD, 50 mg BID, and 70 mg BID groups (25% to 33%). In particular, pleural effusion, gastrointestinal disorders, blood and lymphatic system disorders, and cardiac disorders were less frequent in the 100 mg QD group than in the other 3 treatment groups. Similarly, severe (Grade 3 to 5) drug-related SAEs were less frequent in the 100 mg QD group (13%) than in the other 3 treatment groups (16% to 25%). The most common (> 3% incidence in at least 1 treatment group) severe drug-related SAEs were pleural effusion, dyspnoea, febrile neutropenia, and thrombocytopenia.

In CA180035, 448 (74%) subjects reported SAEs, any grade, during the study or up to 30 days after the last dose of study medication. Two hundred seventy (44%) subjects reported drug-related SAEs. There was little difference (43% vs. 46%, respectively) in drug-related SAEs between the QD and BID groups. Notable common (>3% incidence in at least 1 treatment group) drug-related SAEs were pleural effusion, gastrointestinal haemorrhage, cerebral haemorrhage, pneumonia, febrile neutropenia, thrombocytopenia, and anaemia.

Deaths

In CA180034, 65 deaths were reported of which 26 were due to disease progression. Two of the 65 deaths were due to study drug toxicity (1 pulmonary oedema/CHF/neck pain/pleural effusion, 1 necrosis of the colon). Both deaths occurred within 30 days of the last dose of dasatinib. Of the 65 deaths, 16 occurred on-study or within 30 days of the last dose of dasatinib. Of these 16, deaths were less frequent in the QD group compared with the BID group (5 vs. 11 subjects, respectively).

In CA180035, 321 out of 609 subjects died of which over half were due to disease progression. Of the 321 deaths, 126 subjects died on-study or within 30 days of last dose of study therapy. For those deaths within 30 days of last dose of study therapy, a difference between the QD and BID groups was observed in infection (17% vs. 30%, respectively) and cardiovascular disease (3% vs. 11%, respectively).

Laboratory Abnormalities

In this heavily pretreated population of subjects, treatment with dasatinib was associated with severe (Grade 3 or 4) thrombocytopenia, neutropenia, and anaemia. There were few clinically meaningful non-haematologic changes in laboratory parameters reported on treatment with dasatinib with 2 years of follow-up, a result consistent with the initial filing. In CA180034 and CA180035, there were minimal differences between the treatment groups in the number of subjects with Grade 3 or 4 liver function and renal function abnormalities. In addition, electrolytes changes and coagulation parameters were similar between the groups in the two Phase 3 studies. There were few instances of Grade 3 or 4 laboratory values; the most common laboratory abnormality was Grade 3 or 4 hypophosphataemia.

An updated section of laboratory test abnormalities is provided in Section 4.8 of the proposed SPC.

Selected Safety Events

Safety issues of special importance in the dasatinib product information included the AEs of myelosuppression, fluid retention, bleeding-related events, and QT prolongation.

<u>Haematology</u>

With 2 years of follow-up, the occurrence of severe leukopaenia, thrombocytopenia, neutropenia, and anaemia were more frequent in subjects with advanced phase CML or Ph+ ALL than in chronic phase

CML. In subjects who reported severe myelosuppression, recovery generally occurred following brief (2 to 4 weeks) dose interruptions or reductions.
In CA180034, cytopenia was reported less frequently in the 100 mg QD group than in the other 3 treatment groups. More subjects in the 100 mg QD and 70 mg BID groups (55% and 54%, respectively) than in the 140 mg QD and 50 mg BID groups (40% and 36%, respectively) had their first occurrences of leukocytopenia after 8 weeks of treatment. In CA180035, more subjects in the BID group reported neutropenia and thrombocytopenia compared with the QD group. There was little difference between the QD and BID groups in the time to first occurrence of Grade 3 to 4 WBC, platelet, and ANC.

Fluid Retention

Dasatinib is associated with fluid retention. Fluid retention events were systematically identified in the dasatinib programme. Other events related to fluid retention were also examined including: 1) pleural effusion, 2) ascites, 3) pulmonary oedema, 4) congestive heart failure (CHF), 5) pulmonary hypertension, and 6) pericardial effusion.

In CA180034, fluid retention, any grade, was reported in 264 (40%) subjects. Of these 264 subjects, drug-related fluid retention occurred in 238 (36%) subjects. Pleural effusion, any grade and any relationship, was reported in 147 (22%) subjects. Few subjects reported severe (Grade 3 to 5) pleural effusions. The majority of cases of pleural effusion were drug-related (96%; 141/147). Fewer subjects in the 100 mg QD group reported pleural effusion (all grades) compared with the 140 mg QD, 50 mg BID, and 70 mg BID groups (14% vs. 25%, 23%, and 23%, respectively). The number of subjects with drug-related fluid-related events (including generalized oedema, pulmonary oedema, CHF/cardiac dysfunction, and pericardial effusion) was generally lower in the 100 mg QD group compared with the other 3 treatment groups.

In CA180035, fluid retention, any grade, was reported in 281 (46%) subjects. Of these 281 subjects, drug-related fluid retention occurred in 227 (37%) subjects. Pleural effusion, any grade and any relationship, was reported in 181 (30%) subjects. Few subjects reported severe (Grade 3 to 5) pleural effusions. The majority of cases of pleural effusion were drug-related (88%; 159/181) (Table 5.5.2B). Fewer subjects in the QD group reported drug-related pleural effusion compared with the BID group (20% vs. 32%, respectively). The number of subjects with drug-related fluid-related events (including generalized oedema, pulmonary oedema, CHF/cardiac dysfunction, and pericardial effusion) was lower in the QD group compared with BID group.

Bleeding-related Events

In CA180034, gastrointestinal bleeding, any grade, was reported in 40 subjects. Drug-related gastrointestinal bleeding occurred in 21 subjects. There was little difference in the rate of gastrointestinal bleeding between the 4 treatment groups.
In CA180035, drug-related gastrointestinal bleeding, any grade, was reported in 63 subjects. 10 Fewer subjects in the QD group (N = 25) compared with the BID group (N = 38) reported drug-related gastrointestinal bleeding.

QT Prolongation

A comprehensive evaluation of data from Phase 2 studies (N = 865) examined the possible effect of dasatinib on ECG parameters, particularly the QTc interval. The mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 to 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec. A total of 5 subjects (< 1%) reported a QTcF > 500 msec; 1 of these 5 subjects reported a QTcF > 500 msec on both Days 1 and 8. No events of torsade de pointes were reported.

Nine of the 1150 subjects with chronic phase CML had QTc prolongation reported as an adverse event. Of these 9 subjects, 7 were considered related to drug. None of the 9 subjects who reported QTc prolongation were from the 100 mg QD group compared with 8 subjects from the 70 mg BID group.

Ten of the 1032 subjects with advanced disease had QTc prolongation reported as an adverse event. Of these 10 subjects, 7 were considered drug-related. All 10 of the subjects who reported QTc prolongation were from the 70 mg BID group.

Overall, of the 2182 subjects treated with dasatinib in clinical trials, 21 (1%) subjects across the studies reported a QTcF > 500 msec, and 14 (<1%) had QTc prolongation reported as an adverse reaction. These data have been updated in the proposed SPC, accordingly (Sections 4.4 and 4.8).

Dose modifications

Analysis of safety showed no meaningful differences in subjects (advanced phase CML or Ph+ ALL) with dose escalation (≥ 180 mg QD) compared with those without dose escalation (≤ 140 mg QD) except for pleural effusion, which showed fewer events in subjects with dose escalation (Table 3).

Table 3: Summary of Safety - All Treated

System Organ Class Preferred Term	≥ 180 mg QD N = 110		≤ 140 mg QD N = 194	
	Any Grade	Severe (3 - 5)	Any Grade	Severe (3 - 5)
Myelosuppression:				
Platelet	97/110 (88)	76/110 (69)	175/189 (63)	137/189 (73)
ANC	92/110 (84)	68/110 (62)	167/189 (88)	132/189 (70)
WBC	89/110 (81)	53/110 (48)	161/189 (85)	107/189 (57)
Hypocalcemia	62/110 (56)	6/110 (6)	120/188 (64)	13/188 (7)
Hypophosphotemia	47/109 (43)	9/109 (8)	76/184 (41)	32/184 (17)
Hypomagnesemia	22/108 (20)	1/108 (< 1)	59/183 (32)	2/183 (1)
Drug-related AEs:				
Diarrhea	35 (32)	5 (5)	49 (25)	5 (3)
Fluid Retention	29 (26)	8 (7)	68 (35)	14 (7)
Pleural Effusion	12 (11)	7 (6)	48 (25)	12 (6)
Superficial Edema	17 (16)	1 (< 1)	29 (15)	0
Other Fluid Related	9 (8)	3 (3)	6 (3)	2 (1)
Pericardial Effusion	2 (2)	1 (< 1)	3 (2)	1 (< 1)
Pulmonary Edema	2 (2)	1 (< 1)	2 (1)	1 (< 1)
CHF/Cardiac Dysfunction	2 (2)	2 (2)	1 (< 1)	0
Generalized Edema	4 (4)	0	1 (< 1)	0
GI Bleeding	5 (5)	5 (5)	20 (10)	12 (6)

Discussion on Clinical Safety

Safety results after 2 years of follow-up were consistent with the safety profile reported with shorter follow-up. In chronic phase CML, fewer subjects in the 100 mg QD group reported drug-related non-haematologic toxicities, all grades, than subjects in the 70 mg BID. AEs of special interest including fluid retention, haemorrhage, and some cardiac disorders were reported in fewer subjects in the 100 mg QD group compared with the 70 mg BID group. Similarly, in subjects with advanced phase CML or Ph+ ALL, the QD schedule of administration was also associated with fewer drug-related non-haematologic toxicities (including AEs of special interest). Myelosuppression usually occurred early, especially in advanced stages of CML. Incidence and severity did not change over time.

Updated Risk Management Plan (RMP) version 6.0

The purpose of the RMP update is to provide 2-year post-approval safety data from the two studies for which results are discussed above. Changes to the RMP are summarized in the following table.

Summary of Changes to the Risk Management Plan	
Section	**Change**
Product Information (Product Details)	Under Dosage: Added the newly recommended starting dosage of 140 mg QD administered orally, for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ALL
Section 1.2.1: Exposure	Integrated updated clinical trial exposure information from CA180034 and CA180035 (N = 1271 subjects) with the overall safety cohort of 2,182 subjects Updated post-marketing (non-study) exposure with data through 31 March 2008
Section 1.3.2: Populations not Studied or with Limited Experience in the Pre-Authorisation Phase - Elderly	Provided findings (subjects ranging from 15 to 86 years of age) from a subsequent population pharmacokinetic PK (PPK) analysis, which updated the previous model with new data from a Phase 3 study (CA180034)
Section 1.3.7: Populations not Studied or with Limited Experience in the Pre-Authorisation Phase - Subjects of Different Racial and/or Ethnic Origins	Provided data (race/ethnic origin) from a subsequent PPK analysis, which updated the previous model with new data from a Phase 3 study (CA180034)
Section 1.3.8: Populations not Studied or with Limited Experience in the Pre-Authorisation Phase - Gender	Provided data (gender) from a subsequent PPK analysis, which updated the previous model with new data from a Phase 3 study (CA180034)

To be continued…next page

Summary of Changes to the Risk Management Plan	
Section	**Change**
Section 1.4.2: Post-Authorisation Experience - Regulatory Action	New regulatory information provided regarding updated safety data from two Phase 3 dose optimization studies (CA180034 and CA180035) with 24 months of follow-up
Section 1.5.2: Adverse Events/Adverse Reactions - Details of Important Identified and Potential Risks	Tables 1.5.2.1a through 1.5.2.1e updated with new information based on the integration of 2-year follow-up data from CA180034 and CA180035 with the overall safety cohort of 2,182 subjects
Section 1.8: Pharmacological Class Effects	Added references for published literature that present data showing that cardiotoxicity is not a class effect of Bcr-Abl tyrosine kinase inhibitors
Section 1.9.1: Additional EU Requirements - Potential for Overdose	Updated information on effect of overdosage of 280 mg per day reported for 1 week in two patients
Section 2.4: Overview of Study Protocols for the Pharmacovigilance Plan	Updated status of 'Single Dose Oral Phototoxicity Study in Hairless Mice' Deleted "Oral study of fertility and early embryonic development in rats (Seg. 1)" due to completion and submission of this nonclinical study (TYII 009, ongoing procedure that includes a revised RMP)
Section 2.5: For Updates to the EU-RMP	Summarized relevant updates to version 5 from two Phase 3 dose optimization studies (CA180034 and CA180035)
Section 2.6: Summary of Outstanding Actions, Including Milestones	Updated study status and the proposed and ongoing regulatory actions for completed protocols
Section 3.1: Summary of Planned Actions	Updated 'Description of Routine Activity' in Table 3.1 with the recommended starting dosage of 140 mg QD for accelerated and blast phase CML and for Ph+ ALL
Section 5: Summary of the Risk Management Plan	Updated 'Proposed Risk Minimization Activities' in Table 5 with 1) the recommended starting dosage of 140 mg QD for accelerated and blast
	phase CML and for Ph+ ALL, and 2) addition of QT prolongation as an uncommon cardiac adverse drug reaction in Section 4.8 of the Summary of Product Characteristics (SmPC)

CHMP's comment:
The revisions introduced in the RMP are relevant and fully adequate.

Changes to the Product Information

The MAH has suggested the following changes to the SPC:

Section 4.2

- Addition of newly recommended starting dosage of 140 mg QD administered orally, for accelerated, myeloid or lymphoid blast phase (advanced phase) CML or Ph+ ALL.
- Also a proposal for dose escalation and dose adjustments for undesirable effect (myelosuppression) is introduced.

Section 4.4

Myelosuppression

- Information related to Fluid retention has been updated and relocated to the "Fluid retention" subsection.

Bleeding

- Update of information related to CNS haemorrhage

Fluid retention

- Update of Information related to fluid retention.

QT Prolongation

- Update of information related to QT prolongation as an adverse reaction.

Section 4.8:

- Median duration of treatment updates
- Update to % of treatment discontinuation for adverse reactions.
- Rates of dose interruption and reduction in patients treated for chronic phase CML, advanced phase CML and Ph+ ALL
- Imatinib-intolerant patients and non-hematologic toxicity
- Update of % of patients with grade 3/4 fluid retention associated with the use of dasatinib
- Update of CNS haemorrhage fatal events.
- Median duration of treatment updates.
- Table 2a and 2b are updated with 2-year follow-up data from CA180034 and CA180035: for selected important ADRs
- Adverse reactions are proposed to merge revised Table 3 (ADRs $\geq$ 5%) data in the section Adverse Reactions, therefore providing for one list only of ADRs reported in clinical trials. Inclusion of new footnote "a" related to congestive heart failure/cardiac dysfunction, to be in line with the CCDS. Addition of electrocardiogram QT prolonged as uncommon ADR. Re-classification of frequencies of pulmonary hypertension, musculoskeletal stiffness, hyperuricaemia from uncommon to common ADR. Re-classification of frequency of temperature intolerance from rare to uncommon ADR.
- Laboratory test abnormalities – *haematology* is updated; table 3 (former table 4), Update of patient % experiencing grade 3/4 myelosuppression who permanently discontinued treatment from 1 to 5%: rationale for this updated provided as per cross-reference. *Biochemistry*; update to grade 3/4 elevations of transaminases, bilirubin and creatinine, and addition of hypokalemia, in line with CCDS. *Electrocardiogram*; information related to QT prolongation.

Section 4.9:

- Updated information on effect of overdosage of 280 mg per day reported for 1 week in two patients.

Section 5.1:

Phase II clinical trials in CML *Chronic Phase CML*

- The applicant takes the opportunity to amend the statement related to study CA180013 (approved 22 July 2008, procedure EMEA/H/C/000709/II/008), considered necessary, as the text was inaccurate.

Phase III Clinical Trials

- Updated number of imatinib-resistant patients in chronic phase CML (phase 2 clinical trial).
- Update to median duration of treatment.

Table 5: Efficacy in Phase III dose optimization study: chronic phase CML

- Update and reformatting of Table 5 (ex-table 6) with addition of clinically relevant efficacy responses, as Major Molecular Response data + Survival data (PFS and OS). Duration of MCyR included in text.
- Efficacy in patients intolerant to imatinib

Table 6: Efficacy in Phase III dose optimization study: advanced phase CML and Ph+ ALL

- Inclusion of new table (Table 6) presenting efficacy data in a Phase 3 dose-optimisation study for Advanced Phase CML and Ph+ ALL. Information on median duration of MaHR, PFS and OS (140mg QD vs. 70mg BID) for accelerated phase, myeloid blast phase and lymphoid blast phase CML, included in the text.

In addition, the MAH has made changes accordingly to sections 3 and 4 of the Package Leaflet, which are acceptable.

CHMP's comment:
The changes to the Product Information are supported by the data submitted and provide further useful information to the treating physicians.

Benefit /Risk assessment

This type II variation concerns an update of sections 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC with 24-months follow-up data from two Phase 3 studies comparing the efficacy and safety of dasatinib administered once daily (QD) versus twice daily (BID) (current posology for the advanced phase CML and Ph+ ALL indications) in subjects with chronic phase CML (CA180034) and advanced phase CML or Ph+ ALL (CA180035).

The current dosing recommendation is 70 mg BID in subjects with advanced phase CML or Ph+ ALL based on three Phase 2 studies and one Phase 3 previously reported with 6 months of follow-up. With long-term follow-up in the dose optimization study (CA180035), efficacy data were similar between the 140 mg QD and 70 mg BID schedules, and comparable with responses reported at 6 months with 70 mg BID. With both schedules, long-lasting responses were identified. In subjects with Ph+ ALL with longer follow-up, haematologic and cytogenetic response rates were also similar between 140 mg QD and 70 mg BID schedules. The dose of 140 mg QD supports an overall superior benefit risk and should be recommended in this population of advanced phase CML and Ph+ ALL.

Safety results after 2 years of follow-up were consistent with the safety profile reported with shorter follow-up. In chronic phase CML, fewer subjects in the 100 mg QD group reported drug-related non-haematologic toxicities, all grades, than subjects in the 70 mg BID. AEs of special interest including fluid retention, haemorrhage, and some cardiac disorders were reported in fewer subjects in the 100 mg QD group compared with the 70 mg BID group. Similarly, in subjects with advanced phase CML or Ph+ ALL, the QD schedule of administration was also associated with fewer drug-related non-haematologic toxicities (including AEs of special interest). Myelosuppression usually occurred early, especially in advanced stages of CML. Incidence and severity did not change over time.

Overall, data presented in the dossier confirm the selection of 140 mg QD as the recommended starting dose in subjects with advanced CML and Ph+ ALL. The proposed revised SPC Section 4.2 also includes a revised dose modification guideline:
- For Dose escalation: in patients who did not achieve a haematologic or cytogenetic response at the recommended starting dosage;
- For Dose adjustments for undesirable effects: with guidance including interruption, reduction, and escalation.

Based on the analyses provided the CHMP considers the dose escalation recommendation justified, as there is a subgroup of patients who derive efficacy benefit with the dose escalation to 180 mg QD. In addition, few differences in the safety profile were reported in subjects with dose escalation thereby demonstrating that the benefit in response received with dose escalation is not compromised by additional safety risks.

The CHMP consider the proposed changes to the SPC and the Package Leaflet acceptable. In addition, the MAH took the opportunity to provide an updated version of the RMP (version 6.0). The revisions introduced in the RMP are relevant and fully adequate. Consequently, annex II has been updated to reflect the latest version agreed with the CHMP.

CONCLUSION

On 22 January 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.