European Medicines Agency

London, 3 July 2008
Product name: **SPRYCEL**
Procedure number: EMEA/H/C/709/II/08

SCIENTIFIC DISCUSSION

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III. SCIENTIFIC DISCUSSION

3.1. 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 in September 2006, the Marketing Authorisation Holder (MAH) made commitments to provide the final clinical study reports for a number of studies which were ongoing at the time (see below). The data submitted refer to Follow-Up Measures 008, 008.1, 009 and 011. As these updates provide further information relevant for prescribers, the MAH has submitted the data as a part of a variation application to amend the currently approved SPC.

The variation is based on 24 months of follow-up data from five phase 2 studies in subjects with chronic, accelerated, myeloid blast and lymphoid blast phases CML and Ph+ ALL resistant or intolerant to imatinib. The variation aims to update the safety and efficacy sections in the product information (i.e. section 4.4, 4.8 and 5.1) with the results of these five studies. The Package Leaflet has been amended accordingly.

The studies for which updated data have been received:

- CA18005 – A open label Phase 2 study, ongoing in 80 centers worldwide, enrollment closed. Testing 70 mg BID dasatinib in subjects with accelerated phase CML resistant or intolerant to imatinib;

- CA18006 – A open label Phase 2 study, ongoing in 47 centers worldwide, enrollment closed. Testing 70 mg BID dasatinib in subjects with myeloid blast phase CML resistant or intolerant to imatinib;

- CA180013 – A open label Phase 2 study, ongoing in 90 centers worldwide, enrollment closed. Testing 70 mg BID dasatinib in subjects with chronic phase CML resistant or intolerant to imatinib;

- CA180015 – A open label Phase 2 study, ongoing in 28 centers worldwide, enrollment closed. Testing 70 mg BID dasatinib in subjects with lymphoid blast phase CML resistant or intolerant to imatinib. And; also in Ph+ ALL subjects ongoing in 25 centers worldwide;

- CA180017 - A Randomised open label Phase 2 study, ongoing in 107 centers worldwide, enrollment closed. Testing 70 mg BID dasatinib vs. imatinib 400 mg BID in subjects with chronic phase CML resistant to imatinib 400 mg to 600 mg daily.

In this variation application the data are presented separately by phase of disease as each phase represents a different patient population with different baseline characteristics and prognosis.

Further, the MAH has updated annex IIB to include a reference to the Pharmacovigilance system (version 2.5) and the Risk Management Plan (version 3.0) agreed with the CHMP. In addition, the MAH have implemented some minor editorial changes in the SPC and annex II and took the opportunity to update the contact details of the local representative for Romania in the Package Leaflet.

3.2. Clinical aspects

Clinical Efficacy

As part of the initial Marketing Authorisation Application (MAA), the MAH provided efficacy data on 467 patients from four studies covering 6 months of treatment and one study covering 3 months of treatment. In this updated analysis the MAH presents 2 years of follow-up of the full population enrolled in the five phase 2 studies (N=865) mentioned above (Table 1A).

Table 1A: Studies Supporting the Efficacy of Sprycel (dasatinib)

			Treated	
Study	**Population**	**Total Enrolled**	**Initial Submission**	**2-Year Follow-Up**
CA180017 Randomized	Chronic phase CML (imatinib-resistant [IM-R] only)	166	36 (22 dasatinib)	150 (101 dasatinib)
CA180013 Single Arm	Chronic phase CML (IM-R or imatinib-intolerant [IM-I])	424	186	387
CA180005 Single Arm	Accelerated phase CML (IM-R or IM-I)	197	107	174
CA180006 Single Arm	Myeloid blast phase CML (IM-R or IM-I)	124	74	109
CA180015 Single Arm	Lymphoid blast CML (IM-R or IM-I)	52	42	48
CA180015 Single Arm	Ph+ ALL (IM-R or IM-I)	51	36	46

The following results were presented as part of the initial MAA:

Phase 2 Studies in Initial Submission; Dasatinib-treated Subjects

	CA180017 Chronic (N = 22)	**CA180013 Chronic (N = 186)**	**CA180005 Accelerated (N = 107)**	**CA180006 Myeloid Blast (N = 74)**	**CA180015 Lymphoid Blast (N = 42)**	**CA180015 Ph+ ALL (N = 36)**
Hematologic Response (%)						
OHR (95% CI)	NA[a]	NA	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	95[b]	90	33	24	26	31
Cytogenetic Response (%)						
MCyR (95% CI)	45[b] (24 - 68)	45 (37 - 52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	32[b]	33	21	27	43	58

Note: Shaded fields indicate primary endpoints
a NA: not applicable
b Imatinib-intolerant and imatinib-resistant subjects were enrolled in all studies except CA180017, which randomized imatinib-resistant subjects, only

Methodology

In the Phase 2 studies, dasatinib was administered in line with the 70 mg (administered twice daily) BID regimen. In all 5 studies, investigators were allowed to escalate doses to achieve better efficacy or to reduce 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 received at least a single dose of dasatinib. Response rates were estimated along with their 95% exact confidence intervals (CIs) based on the Clopper-Pearson method. Kaplan-Meier estimates of median time to and duration of response were provided along with their 95% CIs. Duration of 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 enrolled in the studies. In addition, duration of response is presented for both imatinib-resistant and imatinib-intolerant subjects enrolled in the studies.

Progression-free survival (PFS) was defined as the first date of dosing 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. Overall survival (OS) time was defined as the first date of dosing until the time of death. Subjects who had not died or who were lost to follow-up were censored on the last date on which the subject was known to be alive.

Major molecular responses (MMR) were assessed in studies CA180017 and CA180013 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. In brief, the standardized baseline or 100% correspond to the baseline established in the IRIS trial. The 3-log reduction or 0.1% on the international scale corresponds to a MMR.

Molecular data were measured at 3 laboratories in the EU, USA and Australia. Each of these laboratories obtained a conversion factor as described in the application for standardization purpose. All results were subsequently converted and expressed according to the “international scale”.

Molecular data for studies CA180005, CA180006, and CA180015 were not yet available for analysis at the time of this submission. The MAH has made a commitment in this regard to provide the molecular data for Studies CA180005, CA180006, and CA180015 within agreed timeframes.

Results

Randomised Phase 2 Study

Study CA180017 (chronic phase CML)

The major cytogenetic response (MCyR) at 12 weeks was the primary endpoint in this randomized, open-label study in subjects with chronic phase CML treated with dasatinib 70 mg BID or imatinib 400 mg BID. Secondary endpoints were durability and time to MCyR, in addition to; rate, duration and time to complete haematological response (CHR).

	Dasatinib (N = 101)	**Imatinib (N = 49)**
Baseline Characteristics		
Median time from CML diagnosis (months, [range])	64.1 (5.6 - 166.2)	51.8 (13.8 - 132.6)
Prior dose of imatinib 600 mg per day (n)	62 (61)	34 (69)
Prior imatinib therapy > 3 years (n [%])	45 (45)	15 (31)
Prior interferon therapy (n [%])	74 (73)	33 (67)
Median Duration of Therapy (months)	22.5	3.1
Cytogenetic Response Rate (at any time prior to crossover)		
MCyR (n [%])	54 (53)	16 (33)
CCyR (n [%])	44 (44)	9 (18)
Hematologic Response Rate (prior to crossover)		
CHR (n [%])	94 (93)	40 (82)
Duration of MCyR		
#Progressed / # MCyR	5/54 (9)	3/16 (19)
Imatinib-resistant mutations at baseline		
MCyR (n [%])	19/41 (46)	3/11 (27)
Treatment Cross-over (n [%])	20 (20)	39 (80)

Based on the Kaplan-Meier estimates, the proportion of subjects who maintained MCyR for 1 year was 92% for dasatinib-treated subjects and 74% for imatinib-treated subjects. The proportion of patients who maintained MCyR for 18 months was 90% for dasatinib and 74% for imatinib. The MMR rate at any time prior to crossover was higher for the dasatinib group (29%) compared with the imatinib group (12%). Subjects remained on dasatinib longer than those who were treated with imatinib.

The design of this study permitted cross-over to the alternate study drug in the case of disease progression, lack of response, or adverse events that prevented continuation of the randomized study drug. As of the data cut-off, 59 crossed over (39 of 40 from imatinib to dasatinib, and 20 of 50 from dasatinib to imatinib). Reasons for crossover from imatinib to dasatinib were: intolerance to imatinib (9 subjects), disease progression (8 subjects), lack of response (20 subjects), lack of response/disease progression (1 subject), and intolerance/lack of response/disease progression (1 subject). Reasons for crossover from dasatinib to imatinib included: intolerance to dasatinib (11 subjects), disease progression (4 subjects), lack of response (4 subjects), and intolerance/disease progression (1 subject).

Open-label Phase 2 Studies

Study CA180013 (chronic phase CML)

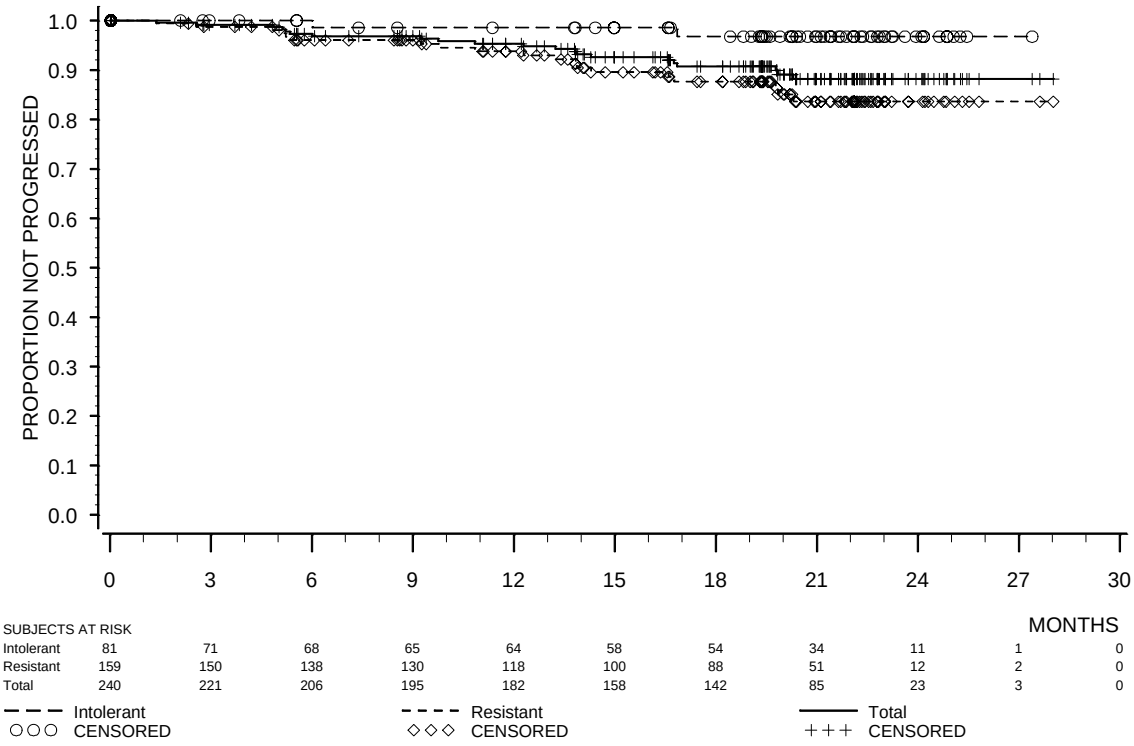
In this open label phase 2 study, in subjects with chronic phase CML resistant or intolerant to imatinib, the primary endpoint was MCyR. The secondary endpoints were durability and time to MCyR, and time to CHR.

Baseline Characteristics	Intolerant N = 99	Resistant N = 288	Total N = 387
Median time from CML diagnosis (months, [range])	26.3 (3.2 - 144.5)	74.4 (2.8 - 250.5)	60.7 (2.8 - 250.5)
Prior dose of imatinib > 600 mg per day (n [%])	8 (8)	206 (72)	214 (55)
Prior imatinib therapy > 3 years (n [%])	12 (12)	194 (67)	206 (53)
Prior interferon therapy (n [%])	46 (47)	206 (72)	252 (65)
Median Duration of Therapy (months)	24.8	23.6	24.2
Cytogenetic Response Rate			
MCyR (n [%])	81 (82)	159 (55)	240 (62)
CCyR (n [%])	77 (78)	130 (45)	207 (54)
Hematologic Response Rate			
CHR (n [%])	93 (94)	259 (90)	352 (91)
Major Molecular Response (n [%])	73/99 (74)	102/288 (35)	175/387 (45)
Duration of MCyR			
# Progressed / # MCyR	2/81 (2)	19/159 (12)	21/240 (9)
Imatinib-resistant mutations at baseline			
MCyR (n [%])	13/14 (93)	79/133 (59)	92/147 (63)

Among the 387 subjects treated, MCyR was achieved in 62% and CHR was achieved in 91%. Nearly half of the subjects who achieved MCyR did so within the first 6 months with most subjects achieving MCyR by 1 year. Projected rates of MCyR at 12 and 24 months were 95% and 88%, respectively. A higher proportion of imatinib-intolerant subjects (74%) compared with imatinib-resistant subjects (35%) achieved a MMR. In subjects with imatinib resistant mutations, 63% achieved a MCyR to dasatinib and 93% achieved a haematologic response to dasatinib. Responses to dasatinib were durable; only 21 of the 240 subjects with MCyR progressed or died.

In the current analysis in chronic phase CML with durations of dasatinib exposure up to 30 months, response rates continued to improve compared with the initial analysis (e.g., from 45% to 62% for MCyR and from 33% to 54% for CCyR in study CA180013). Although most cytogenetic responses were reported within the first 6 months, responses were achieved subsequently and up to the 2 years of follow-up in this analysis. Cytogenetic responses were reported in all subsets of imatinib-resistant and imatinib-intolerant subjects including those who never responded to imatinib. Durable major molecular response was reported with imatinib-intolerant subjects achieving higher rates than in imatinib-resistant subjects. Cytogenetic responses were also reported in subjects with most types of BCR/ABL mutations. And finally, these responses were durable with less than 10% of subjects with a MCyR losing their response thereby translating into survival benefit (Figure 4.4A). Altogether, third-line dasatinib generated results superior to second-line imatinib.

Figure 4.4A: Duration of MCyR in Resistant and Intolerant Subjects with Chronic Phase CML (CA180013)



GROUP	# PROGRESSED / # TREATED	MEDIAN (95% CI)
Intolerant	2/81	. (. - .)
Resistant	19/159	. (. - .)
Total	21/240	. (. - .)

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Study CA180005 (Accelerated CML)

The overall haematologic response (OHR) and major haematologic response (MaHR) were the primary endpoints in this study in subjects with accelerated CML who are resistant to or intolerant of imatinib.

	Intolerant N = 13	**Resistant N = 161**	**Total N = 174**
Baseline Characteristics			
Median time from CML diagnosis (months, [range])	91.0 (4.3 - 205.5)	81.7 (4.1 - 358.8)	82.4 (4.1 - 358.8)
Prior dose of imatinib > 600 mg per day (n [%])	3 (23)	88 (55)	91 (52)
Prior imatinib therapy > 3 years (n [%])	2 (15)	101 (63)	103 (59)
Prior interferon therapy (n [%])	9 (69)	117 (73)	126 (72)
Median Duration of Therapy (months)	10.4	14.6	13.5
Hematologic Response Rate			
OHR (n [%])	12 (92)	127 (79)	139 (80)
MaHR (n [%])	9 (69)	103 (64)	112 (64)
Cytogenetic Response Rate			
MCyR (n [%])	5 (39)	65 (40)	70 (40)
CCyR (n [%])	5 (39)	53 (33)	58 (33)
Duration of MaHR			
# Progressed / # MaHR	4/9 (44)	35/103 (34)	39/112 (35)
Imatinib-resistant mutations at baseline			
MaHR (n [%])	1/1 (100)	65/89 (73)	66/90 (73)

Among the 174 subjects treated, OHR was achieved in 80% and MaHR was achieved in 64%. MCyR was achieved in 40% of subjects. Most subjects who achieved MaHR did so within the first 6 months of treatment. In subjects with imatinib-resistant mutations, 73% achieved a MaHR and 40% achieved a MCyR to dasatinib. Responses to dasatinib were durable; of the 112 subjects with MaHR, 39 had progressed or died.

In subjects with accelerated phase CML, haematologic and cytogenetic responses continued to improve over time. CHR, MCyR, and CCyR rates among imatinib-resistant subjects (50%, 40%, and 33%, respectively) approximated those achieved with imatinib in similar, generally less heavily pretreated subjects. Responses were durable, improving patient's disease to chronic phase. The 2-year survival rate in subjects who failed imatinib was 72%, which exceeds the expected survival in accelerated phase CML subjects treated with cytotoxic chemotherapy. Overall, this high clinical efficacy confirms evidence of clinical benefit in this population.

Study CA180006 (Myeloid blast phase CML)

The OHR and MaHR were the primary endpoints in this study in subjects with myeloid blast phase CML who are resistant to or intolerant of imatinib.

	Intolerant N = 10	**Resistant N = 99**	**Total N = 109**
Baseline Characteristics			
Median time from CML diagnosis (months, [range])	74.2 (22.1 - 129.5)	45.7 (3.3 - 215.5)	48.3 (3.3 - 215.5)
Prior dose of imatinib > 600 mg per day (n [%])	2 (20)	52 (53)	54 (50)
Prior imatinib therapy > 3 years (n [%])	5 (50)	40 (40)	45 (41)
Prior interferon therapy (n [%])	7 (70)	46 (47)	53 (49)
Median Duration of Therapy (months)	3.2	3.6	3.5
Hematologic Response Rate			
OHR (n [%])	4 (40)	50 (50)	54 (50)
MaHR (n [%])	2 (20)	34 (34)	36 (33)
Cytogenetic Response Rate			
MCyR (n [%])	2 (20)	35 (35)	37 (34)
CCyR (n [%])	2 (20)	27 (27)	29 (27)
Duration of MaHR			
# Progressed / # MaHR	1/2 (50)	15/34 (44)	16/36 (44)
Imatinib-resistant mutations at baseline			
MaHR (n [%])	1/3 (33)	12/39 (31)	13/42 (31)

Among the 109 subjects treated, OHR was achieved in 50% and MaHR was achieved in 33%. MCyR was achieved in 34% of subjects. Most subjects who achieved MaHR did so within the first 4 months of treatment. In subjects with imatinib-resistant mutations, 31% achieved a MaHR and 29% achieved a MCyR to dasatinib. Responses to dasatinib were durable; of the 36 subjects who achieved MaHR, 16 had progressed or died.

Study CA180015 (Lymphoid blast phase CML)

The OHR and MaHR were the primary endpoints in this study in subjects with lymphoid blast phase CML who are resistant to or intolerant of imatinib.

Baseline Characteristics	Intolerant N = 6	Resistant N = 42	Total N = 48
Median time from CML diagnosis (months, [range])	63.5 (7.7 - 144.3)	19.7 (1.7 - 193.6)	27.6 (1.7 - 193.6)
Prior dose of imatinib > 600 mg per day (n [%])	2 (33)	23 (55)	25 (52)
Prior imatinib therapy > 3 years (n [%])	2 (33)	9 (21)	11 (23)
Prior interferon therapy (n [%])	5 (83)	18 (43)	23 (48)
Median Duration of Therapy (months)	3.1	2.6	2.9
Hematologic Response Rate			
OHR (n [%])	2 (33)	17 (41)	19 (40)
MaHR (n [%])	2 (33)	15 (36)	17 (35)
Cytogenetic Response Rate			
MCyR (n [%])	4 (67)	21 (50)	25 (52)
CCyR (n [%])	4 (67)	18 (43)	22 (46)
Duration of MaHR			
# Progressed / # MaHR	0/2	12/15 (80)	12/17 (71)
Imatinib-resistant mutations at baseline			
MaHR (n [%])	1/2 (50)	8/27 (30)	9/29 (31)

Among the 48 subjects treated, OHR was achieved in 40% and MaHR was achieved in 35%. MCyR was achieved in 52% of subjects. Most subjects who achieved MaHR did so within the first 2 months of treatment. In subjects with imatinib-resistant mutations, 31% achieved a MaHR and 48% achieved a MCyR to dasatinib. Of the 17 subjects who achieved MaHR, 12 subjects had progressed or died.

Study CA180015 (Ph+ ALL)

The OHR and MaHR were the primary endpoints in this study in subjects with Ph+ ALL who are resistant to or intolerant of imatinib.

Baseline Characteristics	Intolerant N = 2	Resistant N = 44	Total N = 46
Median time from Ph+ ALL diagnosis (months, [range])	17.5 (11.6 - 23.5)	18.0 (3.2 - 163.0)	18.0 (3.2 - 163.0)
Prior dose of imatinib > 600 mg per day (n [%])	1 (50)	20 (46)	21 (46)
Prior imatinib therapy > 3 years (n [%])	0	1 (2)	1 (2)
Prior interferon therapy (n [%])	0	4 (9)	4 (9)
Median Duration of Therapy (months)	9.7	2.5	3.0
Hematologic Response Rate			
OHR (n [%])	2 (100)	20 (46)	22 (48)
MaHR (n [%])	2 (100)	17 (39)	19 (41)
Cytogenetic Response Rate			
MCyR (n [%])	2 (100)	24 (55)	26 (57)
CCyR (n [%])	2 (100)	23 (52)	25 (54)
Duration of MaHR			
# Progressed / # MaHR	1/2 (50)	11/17 (65)	12/19 (63)
Imatinib-resistant mutations at baseline			
MaHR (n [%])	1/1 (100)	13/30 (43)	14/31 (45)

Among the 46 subjects treated, OHR was achieved in 48% and MaHR was achieved in 41%. MCyR was achieved in 57% of subjects. Most subjects who achieved MaHR did so within the first 2 months of treatment. Of these 19 subjects who achieved MaHR, 12 had progressed or died.

Subjects with blast phase CML or Ph+ ALL with 2 years of follow-up continued to demonstrate benefit from dasatinib. Haematologic and cytogenetic response rates were achieved by one-third or more of the subjects and most subjects who achieved a response did so rapidly. Durations of response were shorter providing a limited long-term impact on survival. Twelve subjects with myeloid blast phase CML were receiving dasatinib at the time of this 2 year analysis, suggesting that dasatinib

monotherapy can lead to long-term survival. In addition, subjects who responded to dasatinib became candidates for bone marrow transplant.

MAH's Summary of Efficacy

With 2 years of follow-up, subjects treated with dasatinib achieved haematologic and cytogenetic responses in the open-label Phase 2 studies. Dasatinib was active in subjects across all phases of CML or Ph+ ALL. Subjects with 1 or more detectable imatinib-resistant mutations achieved haematologic and cytogenetic responses upon treatment with dasatinib. Table 4.3.2B summarises key efficacy findings in the efficacy cohort; data are pooled across imatinib-resistant and imatinib-intolerant subjects.

Table 4.3.2B: Efficacy in Phase 2 Non-randomized Clinical Studies

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

a Numbers in bold font are the results of primary endpoints.

b Haematologic response criteria (all responses confirmed after 4 weeks): Major haematologic response: (MaHR) = complete haematologic response (CHR) + no evidence of leukemia (NEL).

CHR (chronic CML): WBC ≤ institutional ULN, platelets <450,000/mm3, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

CHR (advanced CML/Ph+ ALL): WBC ≤ institutional ULN, ANC ≥1000/mm3, platelets ≥100,000/mm3, no blasts or promyelocytes in peripheral blood, bone marrow blasts ≤5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

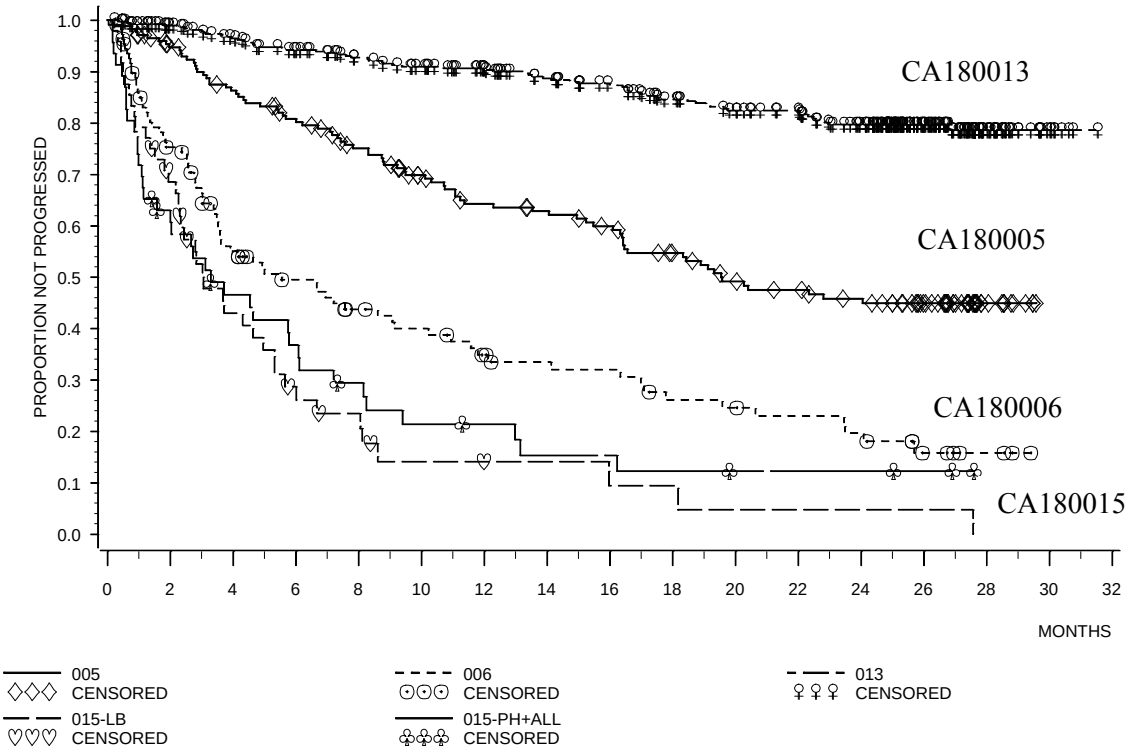
NEL: same criteria as for CHR but ANC ≥500/mm3 and <1000/mm3, or platelets ≥20,000/mm3 and ≤100,000/mm3.

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

n/a = not applicable CI = confidence interval ULN = upper limit normal range.

Dasatinib continued to be effective in all phases of CML and Ph+ ALL and in all subpopulations (e.g., imatinib intolerant, imatinib resistant, genetic resistance, response to prior chemotherapies, etc.). Robust response rates, durable responses, and long-term survival were reported with 2 years of follow-up on dasatinib in subjects resistant or intolerant to imatinib (Figure 4.4B; Figure 4.4C).

Figure 4.4B: Progression-free Survival with 2 Years of Follow-up in Subjects with CML or Ph+ ALL



005 CENSORED
006 CENSORED
013 CENSORED
015-LB CENSORED
015-PH+ALL CENSORED

GROUP	# PROGRESSED / # TREATED	MEDIAN (95% CI)
005	82/174	19.5 (16.4 - .)
006	75/109	5.6 (3.5 - 9.1)
013	65/387	. (. - .)
015-LB	40/48	3.1 (2.3 - 5.3)
015-PH+ALL	37/46	3.3 (1.6 - 6.1)

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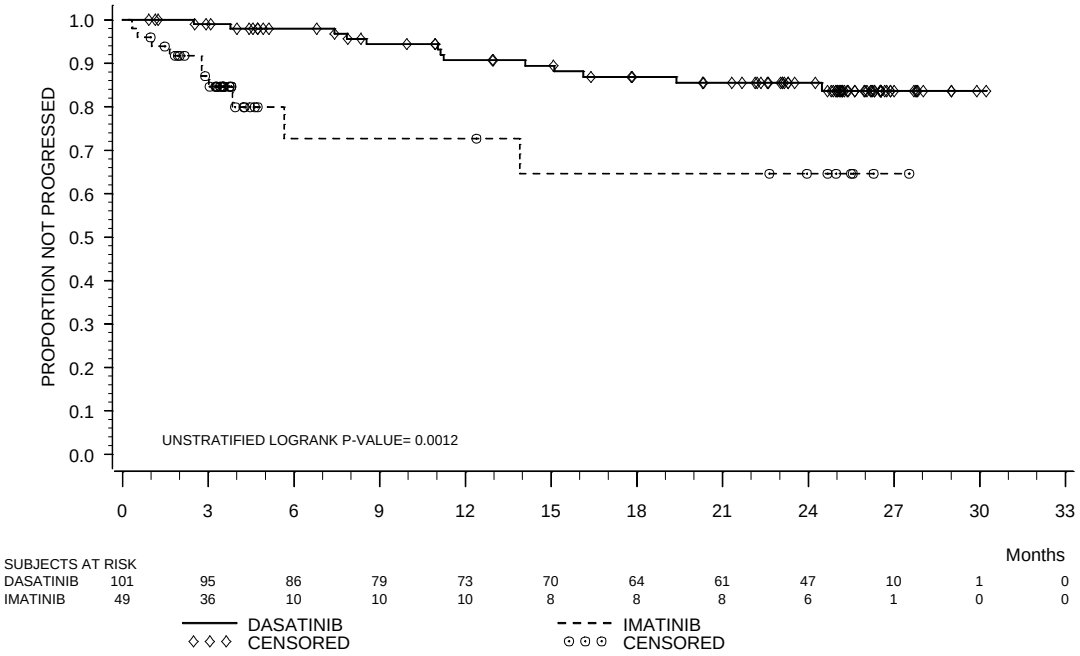
Figure 4.4C: Progression-Free Survival Prior to Crossover (CA180017)



GROUP	# PROGRESSED / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95% CI)
DASATINIB	13/101	. (. - .)	
IMATINIB	10/49	. (13.9 - .)	
DASATINIB OVER IMATINIB			0.26 (0.11 - 0.62)

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Discussion on Clinical Efficacy

The overall efficacy database has increased considerably since the submission of the initial MAA. The data on dasatinib presented above represent the two year follow-up of treating subjects with CML in all phases who were intolerant of or resistant to imatinib. The group of patients were heavily pre-treated with other chemotherapeutic agents and also received stem cell reconstitution beside the imatinib treatment.

Overall, it can be agreed that considering the fact that haematological and cytogenetic responses are commonly accepted as a surrogate endpoint in the treatment of CML, these updated analyses with longer follow-up provide further evidence that early haematological and cytogenetic responses correlate with a long-term favourable outcome. Dasatinib has shown substantial activity in all subsets of patients with CML.

Dasatinib induces durable MCyR in patients with chronic phase CML who are imatinib-resistant and imatinib-intolerant. So far less than 10% have lost their MCyR. As expected the MCyR rate is higher in imatinib-intolerant patients than in patients with true imatinib resistance.

The results in accelerated phase CML patients with imatinib-resistance are impressive.

Study CA180006 showed that even in late stage CML dasatinib induces haematological and cytogenetic responses in patients with prolonged prior exposure to imatinib. High doses of imatinib were used in about 50% of the patients before the switch to dasatinib. As expected the duration of response is quite short.

The MAH has made a commitment to provide the molecular data for Studies CA180005, CA180006, and CA180015 when available for review by the CHMP.

Clinical Safety

Background

In the initial MAA, safety data (with a minimum of 3 months of follow-up) were collected from 511 subjects with leukaemia from one Phase 1 (CA180002) and five Phase 2 studies (CA180005, CA180006, CA180013, CA180015, and CA180017). In the Phase 1 and Phase 2 clinical programme, myelosuppression and fluid retention were the most important toxicities identified in subjects treated with dasatinb 70 mg BID. In subjects with chronic phase CML (CA180013 and CA180002), 49% of subjects reported Grade 3/4 neutropenia and thrombocytopenia and 17% reported pleural effusion (Grade 3/4 in 3%). In subjects with advanced phase disease (CA180005, CA180006, and CA180015), approximately 80% of subjects reported Grade 3/4 neutropenia and thrombocytopenia and 28% reported pleural effusion (Grade 3/4 in 7%). Dose interruptions and reductions were common in all studies.

Whereas this submission is based largely on the results from 2 years of follow-up in the Phase 2 studies with 865 subjects, pooled safety data are also presented in this document from the overall population of 2,182 dasatinib-treated subjects. Data were pooled by disease phase. Limited pooling of data was determined to be the best way to assess drug-producing adverse events (AEs) because of difficulties in distinguishing disease-related toxicities from drug-related toxicities in advanced phases of CML.

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. For study CA180017, safety data prior to crossover were included in the safety cohort.

In all studies, investigators were allowed to escalate subjects' doses to achieve better efficacy or to reduce subjects' doses to manage adverse events. Since none of the studies conducted used a fixed-dose design (i.e., dose adjustments up and down were permitted) data are not analyzed by dose. Data collected from any subject who received at least a single dose of dasatinib are presented. Safety and tolerability were assessed through collection of spontaneously reported AEs, measurement of vital signs, and routine laboratory testing. Severity of on-study AEs was graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3 grading system. The investigator's adverse event terms were coded and grouped by preferred term and system organ class using the MedDRA dictionary (version 10.0) and were summarized by any grade, Grade 3 to 4, and Grade 5 (i.e., death).

Among the 865 subjects with CML or Ph+ ALL from the Phase 2 studies, the median duration of exposure was 15.67 months (range 0.03 - 30.62 months). The majority of subjects (71%) were administered dasatinib for more than 6 months (Table 5.3A); 313 (36%) subjects were treated in excess of 24 months.

Table 5.3A: Total Duration of Dasatinib Treatment; Phase 2 Studies

Duration	Number (%) of Subjects
N	865
Median	15.67
Min - Max	0.03 - 30.62
≤ 3 months	161 (18.61)
3 - < 6 months	94 (10.87)
6 - <12 months	129 (14.91)
12 - < 24 months	168 (19.42)
> 24 months	313 (36.18)

The median duration of exposure in the 2,182 dasatinib-treated subjects with CML or Ph+ ALL was 11.04 months; 39% of the subjects were administered dasatinib for more than 12 months (Table 5.3B).

Table 5.3B: Total Duration of Dasatinib Treatment; Overall Population	
Duration	**Number (%) of Subjects**
N	2182
Median	11.04
Min - Max	0.03 - 30.62
≤ 3 months	423 (19.39)
3 - < 6 months	250 (11.46)
6 - <12 months	666 (30.52)
12 - < 24 months	530 (24.29)
> 24 months	313 (14.34)

Results

Results from the five Phase 2 studies of dasatinib treatment with 2 years of follow-up at a dose of 70 mg twice daily (BID) were consistent with the safety profile reported in the initial submission with 3 months of follow-up and in the updated safety analysis with 8 months of follow-up in 911 subjects with CML or Ph+ ALL. Adverse events of myelosuppression and fluid retention identified as AEs of special interest are further described below.

Common Drug-related Adverse Events

Of the overall population of 2,182 dasatinib-treated subjects, the most frequently reported drug-related AEs (≥ 20%) included diarrhoea, pleural effusion, headache, rash, nausea, superficial oedema, fatigue, and dyspnoea. While the safety profile of dasatinib in the geriatric population (≥ 65 years of age; 25%) was similar to that in the younger population (< 65 years of age; 75%), patients aged 65 years and older reported a higher incidence of some drug-related AEs associated with dasatinib use. Pleural effusion (38% vs. 20%), congestive heart failure (6% vs. 2%), gastrointestinal bleeding (12% vs. 7%), fatigue (26% vs. 20%), and dyspnoea (34% vs. 17%) were all greater in subjects > 65 years of age compared with subjects < 65 years old, respectively. However, the elderly generally report more co-morbidities than the younger group, which should be taken into consideration before drawing conclusions.

Comparison of Adverse Events by Length of Follow-up

Overall, the drug-related AEs initially reported with 8 months of follow-up were consistent with those reported after 2 years of follow-up in subjects from the 4 non-randomized Phase 2 studies. Most drug-related AEs showed minimal increases with longer follow-up. Fluid-retention AEs and dyspnoea were exceptions. With longer follow-up, higher incidence of drug-related pleural effusion, pericardial effusion, and cardiac congestive failure/cardiac dysfunction was reported compared with shorter (8 month) follow-up. Drug-related dyspnoea increased from 18% to 29% with longer follow-up.

Drug-related Adverse Events that led to Discontinuation

Drug-related AEs leading to discontinuation occurring up to 30 days after the last dose were reported in 122 (14%) of the 865 subjects in the Phase 2 studies. Most of these discontinuations were reported as AEs related to disease progression. Pleural effusion accounted for discontinuation in 40 subjects with 12 subjects reporting severe (Grade 3-4) pleural effusion. More pleural effusions were reported in subjects with chronic phase CML (N = 27) and myeloid blast CML (N = 7) than in the accelerated phase (N = 3), lymphoid blast phase (N = 1), and Ph+ ALL (N = 2).
Of the overall population of 2,182 dasatinib-treated subjects, drug-related AEs leading to discontinuation were mostly mild to moderate in severity and occurred at a rate of < 1% in any one category. Exceptions included pleural effusion (3%; N = 68), congestive heart failure (1%; N = 13), dyspnoea (1%; N = 23), and headache (1%; N = 12).

Serious Adverse Events

Overall, SAEs reported with 2 years of follow-up were consistent with the initial submission of the Phase 2 programme. Drug-related SAEs occurring up to 30 days after the last dose were reported in 341 (39%) dasatinib-treated subjects. Pleural effusion, thrombocytopenia, and dyspnoea were the most common drug-related SAEs. Of the overall population of 2,182 dasatinib-treated subjects, the most frequently reported drug-related SAEs (> 2%) included pleural effusion (10%), GI haemorrhage (4%), febrile neutropenia (4%), dyspnoea (3%), pyrexia (3%), and pneumonia (3%).The majority of GI haemorrhage, febrile neutropenia, and pneumonia events were considered severe. Fluid retention, myelosuppression, bleeding-related events, and QT interval prolongation are discussed below.

Deaths

A total of 175 (22%) subjects died. Of these 175 deaths, 104 occurred within 30 days of the last dose of dasatinib. Nearly half of the deaths were due to disease progression with the majority in subjects in advanced phases of CML or Ph+ ALL. Infection was the cause of death is 36 (4%) subjects. The rate of death due to infection increased with advancing disease phase with Ph+ ALL reporting the highest rate. Cardiovascular disease was the reason for death in 4 subjects (acute heart failure [2 subjects], arrhythmia/cardiovascular arrest [1 subject], cardiopulmonary arrest [1 subject]). Fatal bleeding occurred in 12 subjects (8 due to cerebral, 2 due to pulmonary, 1 due to gastrointestinal, and 1 listed as haemorrhage). Of these 12 subjects, gastrointestinal bleeding (CA180013-30-13257) was considered possibly related and central nervous system (CNS) bleeding (CA180013-47-13061) was considered probably related to study treatment. Death due to study drug toxicity occurred in 4 subjects. Reasons for study drug toxicity in these subjects were (1 subject each) bone marrow failure, intracranial hypertension, global cardiac insufficiency, and moderate pleural effusion.

Four hundred seventy-four of the 2,182 subjects (21.7%) included in this pooled population died; 239 deaths (11%) occurred within 30 days after administration of the last dose of dasatinib. More than half (247 subjects) of the deaths were due to disease. Infection was the cause of death is 94 (4%) subjects. Death due to fatal bleeding occurred in 33 (2%) subjects. Death due to study drug toxicity occurred in 10 (< 1%) subjects.

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 Phase 2 submission. Of the overall population of 2,182 dasatinib-treated subjects, Grade 3 or Grade 4 non-haematologic laboratory abnormalities included hypophosphaemia (13%), hypocalcaemia (6%), elevated SGPT (3%), elevated SGOT (2%), hyperbilirubinaemia (2%), and elevated serum creatinine (1%).

Selected Safety Events

Safety issues of particular interest addressed in the dasatinib product information included the AEs myelosuppression, fluid retention (pleural effusion and pericardial effusion), bleeding-related events and QT prolongation.

<u>Haematology</u>

In the Phase 2 studies with 2 years of follow-up, the occurrence of severe leucopoenia, 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 the overall population of 2,182 dasatinib-treated subjects, myelosuppression occurred more frequently in subjects with advanced phase CML or Ph+ ALL than in chronic phase CML (Table

5.5.1). The reported Grade 3 or Grade 4 haematologic abnormalities included neutropenia (57.6%), thrombocytopenia (56.3%), and anaemia (35.4%). Myelosuppression was generally reversible and was usually managed by withholding dasatinib temporarily or dose reduction.

Table 5.5.1: CTC Grades 3/4 Haematological Laboratory Abnormalities in Clinical Studies; Overall Population

	Chronic Phasea (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	Percent (%) of Patients			
Haematology Parameters				
Neutropenia	46	68	80	76
Thrombocytopenia	41	71	81	77
Anaemia	19	55	75	45

a The chronic phase data include subjects treated with any dose of dasatinib.
CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 109/L, Grade 4 <0.5 × 109/L); thrombocytopenia (Grade 3 ≥10–50 × 109/L, Grade 4 <10 × 109/L); anaemia (hemoglobin ≥65–80 g/L, Grade 4 <65 g/L).

Fluid Retention

In the Phase 2 studies with 2 years of follow-up, drug-related fluid retention was reported in 441 (51%) subjects, including pleural effusion in 32% of these subjects. Severe pleural effusion was reported in 9% of subjects with CML or Ph+ ALL. Subjects with lymphoid blast phase CML reported fewer events than in the other disease phases; however, subjects with lymphoid blast phase CML had the lowest median duration of therapy compared with the other disease phases. Congestive heart failure, generalized oedema, and pericardial effusion accounted for a total of 16% of the events. Congestive heart failure was highest in subjects with chronic phase CML.

In the overall population of 2,182 dasatinib-treated subjects, drug-related fluid retention was reported in 855 (39%) subjects, including pleural effusion in 25% of these subjects. Severe pleural effusion was reported in 6% of subjects with CML or Ph+ ALL. There was little difference in pleural effusion between the disease phases. Congestive heart failure, generalized oedema, and pericardial effusion accounted for a total of 10% of the events.

Bleeding-related Events

In the Phase 2 studies with 2 years of follow-up, drug-related CNS haemorrhages occurred in 1% of subjects receiving dasatinib. Drug-related GI haemorrhage occurred in 10% of subjects. Other cases of haemorrhage occurred in 20% of subjects.
In the overall population of 2,182 dasatinib-treated subjects, drug-related CNS haemorrhages occurred in 1% of subjects receiving dasatinib. Drug-related GI haemorrhage occurred in 8% of subjects. Other cases of haemorrhage occurred in 15% of subjects.

Cardiovascular Events

A comprehensive evaluation of data from Phase 2 studies identified treatment-emergent cardiac or vascular AEs. In the Phase 2 studies with 2 years of follow-up, drug-related cardiac disorders were reported in 141 (16%) subjects. The majority of cardiac events included arrhythmia (5%), congestive heart failure/cardiac dysfunction (5%), and pericardial effusion (6%). Most drug-related events were mild to moderate with the exception of severe congestive heart failure/cardiac dysfunction, which was reported in 24 of the 39 subjects.
In the overall population of 2,182 dasatinib-treated subjects, drug-related cardiac disorders were reported in 250 (11%) subjects. The majority of cardiac events included arrhythmia (3%), congestive heart failure/cardiac dysfunction (3%), and pericardial effusion (4%). Most drug-related events were

mild to moderate with the exception of severe congestive heart failure/cardiac dysfunction, which was reported in 31 of the 59 subjects.

QT Prolongation

In the five Phase 2 clinical trials, repeated baseline and on-treatment ECGs were obtained at pre-specified time points and read centrally for 865 subjects receiving dasatinib 70 mg BID. 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. Of the 2,182 subjects who received dasatinib in clinical trials, 18 had QTc prolongation reported as an adverse event. Seventeen subjects (< 1%) reported a QTcF > 500 msec.

Pharmacovigilance

The CHMP considered that the Pharmacovigilance system (version 2.5) as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH has submitted an updated risk management plan (version 3.0), which included a risk minimisation plan, based on the new safety data from the studies addressed above. All updates have been consequential to the 2 year follow-up data submitted. No major changes have been introduced.

Summary of the Risk Management Plan for Sprycel

Safety Concerns, Proposed PV Actions, and Proposed Risk Minimisation Activities

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
Myelosuppression	Routine pharmacovigilance 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 once daily (QD) 2) Warning in section 4.4. of the SPC 3) Dose adjustment guidelines in section 4.2. of the SPC 4) Presented as ADRs (e.g., myelosuppression, pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anemia) in section 4.8 of SPC
Fluid retention	Routine pharmacovigilance as listed in the current RMP Additional information from	1) The revised recommended starting dosage for chronic phase CML is 100

Safety Concerns, Proposed PV Actions, and Proposed Risk Minimisation Activities

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	ongoing clinical trials	mg once daily 2) Warning in section 4.4. of the SPC 3) Presented as ADRs (e.g., pleural effusion, ascites, pulmonary edema, pericardial effusion, superficial edema) in section 4.8 of SPC
Bleeding-related events	Routine pharmacovigilance 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 once daily 2) Warning in section 4.4. of the SPC 3) Presented as ADRs (e.g., hemorrhage, petechiae, epistaxis, gastrointestinal hemorrhage, CNS bleeding) in section 4.8 of SPC, and (iv) nonclinical findings in section 5.3 of SPC
QT prolongation	Routine pharmacovigilance as listed in the current RMP Additional information from ongoing clinical trials	1) Warning in section 4.4. of the SPC, 2) Presented as laboratory test abnormalities in section 4.8 of SPC 3) Nonclinical findings in section 5.3 of SPC
Important Potential Risks		
Severe hepatotoxicities	Routine pharmacovigilance 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 SPC to warn physicians of the risks of potential severe hepatotoxicities
Direct cardiotoxic effects (e.g., cardiomyopathy)	Routine pharmacovigilance Additional information from ongoing clinical trials	1) The revised recommended starting dosage for chronic phase CML is 100 mg once daily

Safety Concerns, Proposed PV Actions, and Proposed Risk Minimisation Activities

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		2) Events of cardiac dysfunction and congestive heart failure listed as ADRs in section 4.8 of SPC
Important Missing Information		
Patients with moderate to severe hepatic impairment	Routine pharmacovigilance Additional information from ongoing clinical trials A commitment to submit the results of the ongoing hepatic impairment study by Jan 2009 is included in the letter of undertaking (FUM, Clinical 2).	1) Warning in section 4.4. of the SPC 2) Drug use in impaired liver function in section 4.2 of SPC 3) Presented as ADRs (e.g., hepatitis, cholestasis) and Laboratory test abnormalities (e.g., elevation of transaminases and bilirubin) in section 4.8 of SPC 4) Information related to impaired liver function in section 5.2 of SPC
Reproductive and developmental toxicology	Routine pharmacovigilance An oral fertility and early embryonic development (Segment 1) study will be initiated in 2Q2007 and a pre- and postnatal development (Segment 3) study in rats will be initiated during 3Q2007. The results from these studies will be submitted by Dec 2008 (Segment 1) and Mar 2009 (Segment 3), as stated in the letter of undertaking (FUM Module 4 - 1)	1) Potential risk information related to pregnancy in section 4.6 of SPC 2) Nonclinical findings in section 5.3 of SPC.
Carcinogenicity	Routine pharmacovigilance Additional information from ongoing clinical trials A rat carcinogenicity study will be initiated during 2Q2007. The results from these studies 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 SPC
Other Potential		

Safety Concerns, Proposed PV Actions, and Proposed Risk Minimisation Activities

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Concerns		
Drug interactions: dasatinib and potent CYP3A4 inhibitors or CYP3A4 substrates	Routine pharmacovigilance as listed in the current RMP Additional information from ongoing clinical trials	1) Warning in section 4.4. of the SPC 2) Drug interaction information in section 4.5 of the SPC
Drug interactions: dasatinib and other highly protein-bound medicinal products	Routine pharmacovigilance as listed in the current RMP Additional information from ongoing clinical trials	Drug interaction information in section 4.5 of the SPC
Phototoxicity	Routine pharmacovigilance Additional information from ongoing clinical trials An in vivo phototoxicity study in mice will be initiated, and a commitment to submit study reports on this potential risk and update the SPC accordingly by Dec 2008 is included in the letter of undertaking (FUM Module 4 -2)	Listed as ADR in section 4.8 of SPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Discussion on Clinical Safety

The data provided represent the safety results after having treated 875 subjects with 70 mg dasatinib BID for 2 years. In the Phase 2 studies, most subjects (> 90%) with CML or Ph+ ALL treated with dasatinib reported at least 1 drug-related AE regardless of relationship to study drug. The pattern of drug-related AEs was similar across studies. In general, the most common drug-related AEs (> 20%) were diarrhoea, pleural effusion, dyspnoea, fatigue, headache, nausea, and rash. Severe (Grade 3-4) drug-related AEs were reported in 511 (59%) subjects with CML or Ph+ ALL. Overall, diarrhoea, pleural effusion, and dyspnoea were the most common severe drug-related AEs.

The data following 2 years of follow-up are consistent with the safety profile reported in the initial MAA based on 511 subjects and in the updated safety analysis at 8 months on 911 subjects with CML or Ph+ ALL. The most frequent AEs were tolerable, and SAEs were managed by dose interruptions or dose reductions. Non-haematologic AEs were mild to moderate. Incidence rates of fluid retention-related events (including pleural effusion, congestive heart failure, pericardial effusion, pulmonary oedema) and of myelosuppression (including neutropenia, thrombocytopenia, and anaemia) continue to be of special interest. No new safety issues were identified.

Pharmacovigilance

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Changes to the Product Information

The MAH has revised sections 4.4, 4.8 and 5.1 of the SPC in the light of the 2-year data discussed above.

With reference to section 4.4, the main change relates to extended information regarding fluid retention in elderly and a corresponding recommendation of close monitoring. Additional information detailing the use of anticoagulants, ASA and NSAIDs in some trials has also been included.

Section 4.8 has undergone a major update as a consequence of the 2 year safety follow-up. Overall, no new safety signals occurred during the two years, although as a result of the exposure, some events have been observed more frequently, i.e. infection, vomiting, cough and abdominal pain. Table 3 in section 4.8 (ADR reported ≥ 5% in clinical trials) has thus been updated accordingly. Further, the sections addressing ADRs at a frequency of < 5% have been amended but no new events have been added; the existing ADRs have just been re-categorised.
A new table 4 has been introduced in section 4.8 replacing the previous text in order to provide clearer information about the haematological abnormalities observed in the clinical studies.

In section 5.1 the description of the trials have been updated and also table 5 (former table 4) as a consequence.

As for the Package Leaflet relevant changes have been inserted. The MAH has submitted a justification for not having performed another consultation with target groups when amending the Package Leaflet. Their main justifications are that the initial Package Leaflet was tested in 2006, and the update aims at amending the efficacy and safety sections only. Also, in their view, the changes to the Package Leaflet are not of a major character, which can be agreed. Thus, no new readability testing is considered necessary.

Further, the MAH has updated annex IIB to include a reference to the Pharmacovigilance system (version 2.5) and the Risk Management Plan (version 3.0) agreed with the CHMP. In addition, the MAH have implemented some minor editorial changes in the SPC and annex II and took the opportunity to update the contact details of the local representative for Romania in the Package Leaflet. All these changes are acceptable.

Benefit/risk assessment

Dasatinib is a therapeutic advance for subjects with CML or Ph+ ALL who are resistant or intolerant to imatinib. Updated results from the finalised dasatinib Phase 2 programme showed that subjects with all phases of CML or Ph+ ALL achieve durable haematologic and cytogenetic responses. Myelosuppression and fluid retention were identified as the most important toxicities in the Phase 1 and Phase 2 studies and are still considered as events of major interest.

The MAH has forwarded an updated Risk Management Plan which is considered acceptable. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.

- no additional risk minimisation activities were required beyond those included in the product information.

The MAH has updated annex IIB to reflect the latest Pharmacovigilance system (version 2.5) and Risk Management Plan (version 3.0) approved by the CHMP, which is acceptable.

The proposed update of the SPC and Package Leaflet is agreed based on the submitted 2 year follow up data from the five phase II studies performed in subjects with various forms of leukaemia, confirming the results seen in the initial MAA which the current approval is based on.

IV. CONCLUSION

- On 30 May 2008 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