European Medicines Agency

London, 19 July 2007
Product name: **SPRYCEL**
Procedure number: EMEA/H/C/709/II/02

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

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 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 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.*'

The MAH has now applied for a type II variation to update sections 4.2, 4.4, 4.8, 4.9 and 5.1 of the SPC in line with the first results at 6 months of follow-up of the ongoing studies CA180034 and CA 180035, which are both conducted in accordance with current GCP standards.

Further, the MAH takes the opportunity to update section 4.8 of the SPC in line with the outcome of the CHMP assessment of the 1st PSUR and according to MedDRA version 8.2. The Package Leaflet has been amended accordingly. In addition, the MAH have implemented some minor editorial changes in the annexes and updated the contact details of the local representatives for Romania and Denmark in the Package Leaflet.

Clinical aspects

Clinical pharmacology

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

Clinical Efficacy

- Main studies

This application is based upon two Phase 3 studies comparing the efficacy of dasatinib administered once daily (QD) versus twice daily (BID) (current posology) in subjects with chronic phase CML (CA180034) and advanced phase CML or Ph+ ALL (CA180035) (Table 1).

Table 1: Studies Supporting the Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Study (Phase)	Population	Enrolled	Efficacy Cohort	
			Randomized	Treated
CA180034 (Phase 3)	Chronic phase CML (imatinib-resistant [IM-R] or imatinib-intolerant [IM-I])	724	670	662
CA180035 (Phase 3)	Advanced phase CML or Ph+ ALL (IM-R or imatinib-intolerant [IM-I])	638	611	609

- **Methods**

CA180034 is a randomized, open-label, Phase 3 study with a 2 by 2 design comparing 2 doses (100 mg and 140 mg) and 2 schedules (QD and BID) of dasatinib in subjects with chronic phase CML. Subjects with chronic phase CML previously treated with imatinib were enrolled in this study. The primary endpoint was the rate of major cytogenetic response (MCyR) with minimum follow-up of 6 months in subjects resistant to imatinib.

CA180035 is a randomized, open-label, Phase 3 study comparing the schedule of dasatinib treatment (i.e., 140 mg QD vs. 70 mg BID) in subjects with advanced (accelerated and blast) phase CML and Ph+ ALL. Subjects with accelerated phase CML, blast phase (myeloid and lymphoid) CML, and Ph+ ALL resistant or intolerant to imatinib were enrolled in this study. The primary endpoint was the rate of major haematologic response (MaHR) in all randomized subjects.

All endpoints for the Phase 3 studies are listed in Table 2. Enrolment is closed in these 2 studies although treatment is ongoing, and subjects are being followed for up to 2 years. (1 = primary endpoint; 2 = secondary endpoint)

Table 2: Primary and Key Secondary Endpoints – Phase 3 Studies

Objective	CA180034	CA180035
Cytogenic Parameters		
MCyR	1	2
Durability of MCyR	2	
Time to MCyR	2	
Hematologic Parameteres		
MaHR		1
Overall hematologic response (OHR)		2
Durability MaHR		2
Time MaHR		2

Unlike subjects with chronic phase CML, late-stage advanced CML subjects frequently present with fibrotic or hypocellular bone marrow. This results in inadequate baseline bone marrow data and subjects who are unevaluable for response. Similarly, bone marrow reserves in these subjects may be largely exhausted, resulting in an inability to reconstitute normal hematopoietic elements. For these reasons, response rates in advanced stage subjects are presented primarily as hematologic responses, such as MaHR and complete haematologic response (CHR) rates (normalization of all peripheral blood counts), in addition to complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR) rates, and no evidence of leukemia ([NEL]; absence of Ph+ metaphases on cytogenetic evaluation with persistent cytopenias on peripheral blood counts.

- **Results**

<u>Study CA180034</u>

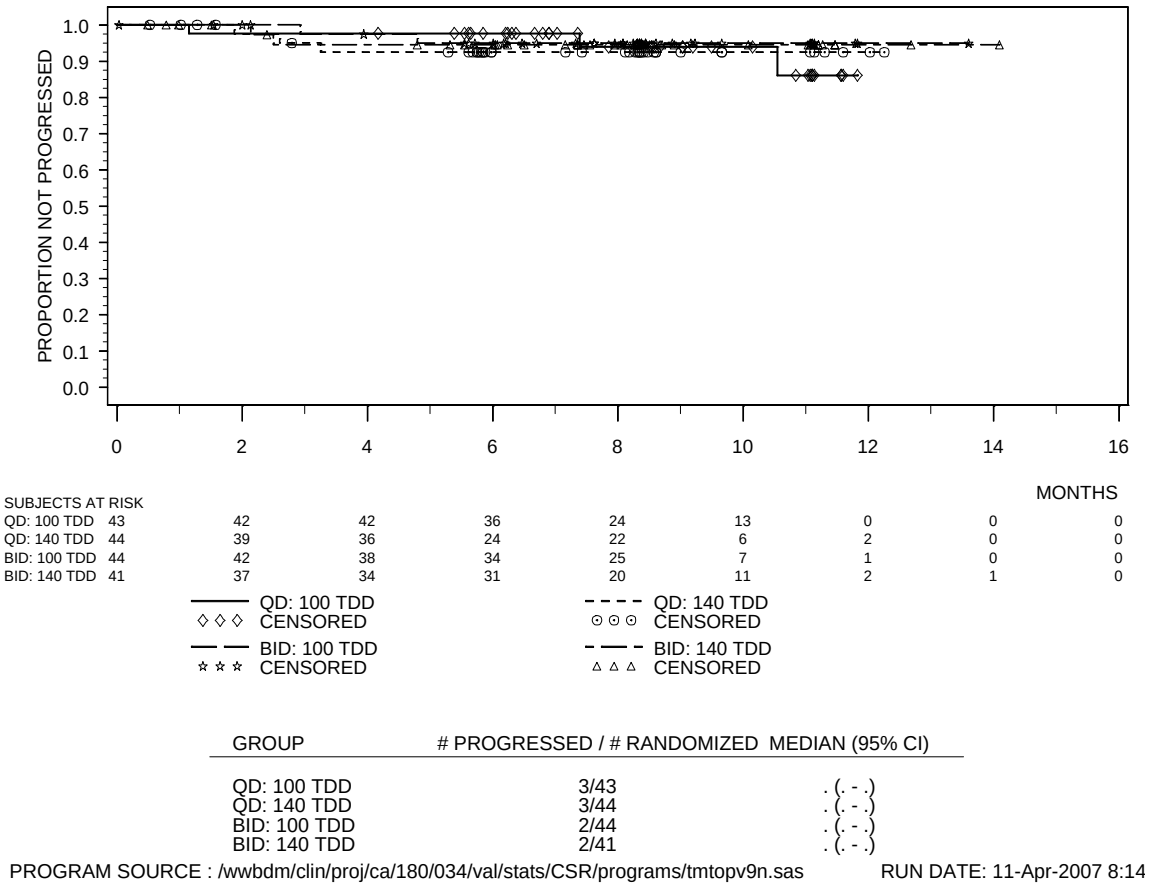
In the efficacy cohort for CA180034, 724 subjects were enrolled and 670 were randomized (498 imatinib-resistant, according to the assessment on the baseline case report form, and 172 imatinib-intolerant). Subjects had about a 4.5-year history of CML and most were treated with imatinib for more than 1 year. Pretreatment characteristics were similar between the 4 treatment groups (Table 3).

Table 3: Pretreatment Characteristics in Randomized Subjects with Chronic Phase CML (CA180034)				
	Number (%) of Subjects			
	100 mg QD N = 167	50 mg BID N = 168	140 mg QD N = 167	70 mg BID N = 168
Disease History				
Median time from initial CML diagnosis (month, [range])	55 1.6 - 251	51 4.4 - 212	56 0.9 - 227	53 1.2 - 246
Prior bone marrow transplant	10 (6)	13 (8)	5 (3)	7 (4)
Prior interferon	87 (52)	87 (52)	93 (56)	82 (49)
Prior chemotherapy	39 (23)	52 (31)	41 (25)	43 (26)
Prior Imatinib				
Highest imatinib dose				
400 - 600 mg/day	106 (64)	113 (67)	111 (67)	111 (66)
> 600 mg/day	61 (37)	55 (33)	55 (33)	56 (33)
Length of imatinib therapy				
< 1 year	36 (22)	40 (24)	39 (23)	37 (22)
1-3 years	55 (33)	68 (41)	58 (35)	60 (36)
> 3 years	76 (46)	60 (36)	68 (41)	71 (42)
Best cytogenetic response to prior imatinib (MCyR)	76 (46)	65 (39)	71 (43)	66 (39)
Best hematologic response to prior imatinib (CHR)	136 (81)	146 (87)	138 (83)	141 (84)
Baseline Imatinib-resistant Mutations	24/49 (49)	23/60 (38)	22/51 (43)	20/45 (44)

In CA180034 (Table 4), there were limited differences in efficacy between the 4 treatment groups. The MCyR ranged from 59% for the 100 mg QD dose to 54% for the 50 mg BID group. There was no difference in progression-free survival between the treatment groups (Figure 1). Overall survival was similar between the 4 treatment groups.

Table 4: Hematologic and Cytogenetic Responses in Subjects with Chronic Phase CML (CA180034); All Randomized Subjects				
	Number (%) of Subjects			
	100 mg QD N = 167	50 mg BID N = 168	140 mg QD N = 167	70 mg BID N = 168
Median Duration of Therapy (months)				
All treated subjects	8.3	8.3	8.2	7.9
Subjects still on treatment	8.3	8.3	8.3	8.3
Cytogenetic Response Rate				
MCyR				
All Subjects	98 (59)	90 (54)	93 (56)	93 (55)
Imatinib-resistant Subjects	66/124 (53)	58/124 (47)	62/123 (50)	65/127 (51)
CCyR				
All Subjects	69 (41)	70 (42)	74 (44)	75 (45)
Imatinib-resistant Subjects	42/124 (34)	43/124 (35)	44/123 (36)	50/127 (39)
Hematologic Response Rate				
CHR	150 (90)	154 (92)	143 (86)	146 (87)
Duration of Response (# Progressed / # Responders)				
MCyR	1/98 (1)	1/90 (1)	3/93 (3)	3/93 (3)
CHR	8/150 (5)	9/154 (6)	7/143 (5)	8/146 (5)
Progression-free Survival (# Progressed / # Randomized)	14/167 (8)	13/168 (8)	14/167 (8)	18/168 (11)
Overall Survival (# Death / # Randomized)	3/167 (2)	6/168 (4)	4/167 (2)	8/168 (5)

Figure 1: **Progression-free Survival: Imatinib-resistant Subjects by Treatment Group (CA180034)**



GROUP	# PROGRESSED / # RANDOMIZED	MEDIAN (95% CI)
QD: 100 TDD	3/43	. (. - .)
QD: 140 TDD	3/44	. (. - .)
BID: 100 TDD	2/44	. (. - .)
BID: 140 TDD	2/41	. (. - .)

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Source: CA180034 Clinical Study Report

The trial was powered (80%) to demonstrate that the QD MCyR rate was non-inferior to the BID MCyR rate in imatinib-resistant subjects (if the lower bound of the 2-sided 95% CI of the QD-BID difference in MCyR rates > -15%). The difference in MCyR between the QD and BID schedule in imatinib-resistant subjects was +2.8% (95% CI: -6.0%, +11.6%) (Table 5). Thus, the QD schedule demonstrated a MCyR rate that was non-inferior to the BID schedule. Within the QD group, there was no evidence of a dose response.

Table 5: Major Cytogenetic Response Rate; Imatinib-resistant Subjects by Schedule (CA180034)

	QD N = 247	BID N = 251
MCyR	128 (52%)	123 (49%)
95% exact CI	45.4% - 58.2%	42.7% - 55.4%
Difference of MCyR	2.8%	
95% CI	-6.0% - 11.6%	

The main secondary objective was achieved as imatinib-resistant subjects in the 100 mg total daily dose (TDD) group attained a MCyR rate that was non-inferior to the 140 mg TDD group. The difference in MCyR between the 100 mg TDD and 140 mg TDD in imatinib-resistant subjects was -0.8% (95% CI: -9.6% to +8.0%) (Table 6).

Table 6: Major Cytogenetic Response Rate: Imatinib-resistant Subjects by Total Daily Dose (CA180034)		
	100 mg TDD N = 248	**140 mg TDD N = 250**
MCyR	124 (50.0%)	127 (50.8%)
95% exact CI	43.6% - 56.4%	44.4% - 57.2%
Difference of MCyR	-0.8%	
95% CI	-9.6% - 8.0%	

Study CA180035

In the efficacy cohort for CA180035, 638 subjects with advanced phase CML or Ph+ ALL were enrolled and 611 were randomized (478 imatinib-resistant, according to the assessment on the baseline case report form, and 133 imatinib-intolerant). Subjects had about a 4-year history of CML and were generally treated with imatinib for more than 1 year (Table 7). Overall, there were few differences in pretreatment characteristics.

Table 7: Pretreatment Characteristics Pooled Across Disease Phase; All Randomized Subjects (CA180035)		
	Number (%) of Subjects	
	QD N = 306	**BID N = 305**
Disease History		
Median time from initial CML diagnosis (months,[range])	58 1.1 - 461	58 0.9 - 212
Prior bone marrow transplant	49 (16)	35 (12)
Prior interferon	129 (42)	125 (41)
Prior chemotherapy	176 (58)	170 (56)
Prior Imatinib		
Highest imatinib dose		
400 - 600 mg/day	178 (58)	169 (55)
> 600 mg/day	127 (42)	133 (44)
Length imatinib therapy		
< 1 year	89 (29)	86 (28)
1-3 years	104 (34)	107 (35)
> 3 years	113 (37)	111 (36)
Best hematologic response to prior imatinib (CHR)	216 (71)	218 (72)
Best cytogenetic response to prior imatinib (MCyR)	111 (36)	106 (35)
Baseline Imatinib-resistant Mutations	124/243 (51)	114/235 (49)

Efficacy analysis pooled across disease phase showed that the QD schedule was similar to the BID schedule in hematologic responses and cytogenetic responses (Table 8). Although a similar difference in overall survival was reported in the 2 groups, a greater number of subjects in the QD group than in the BID group progressed or died.

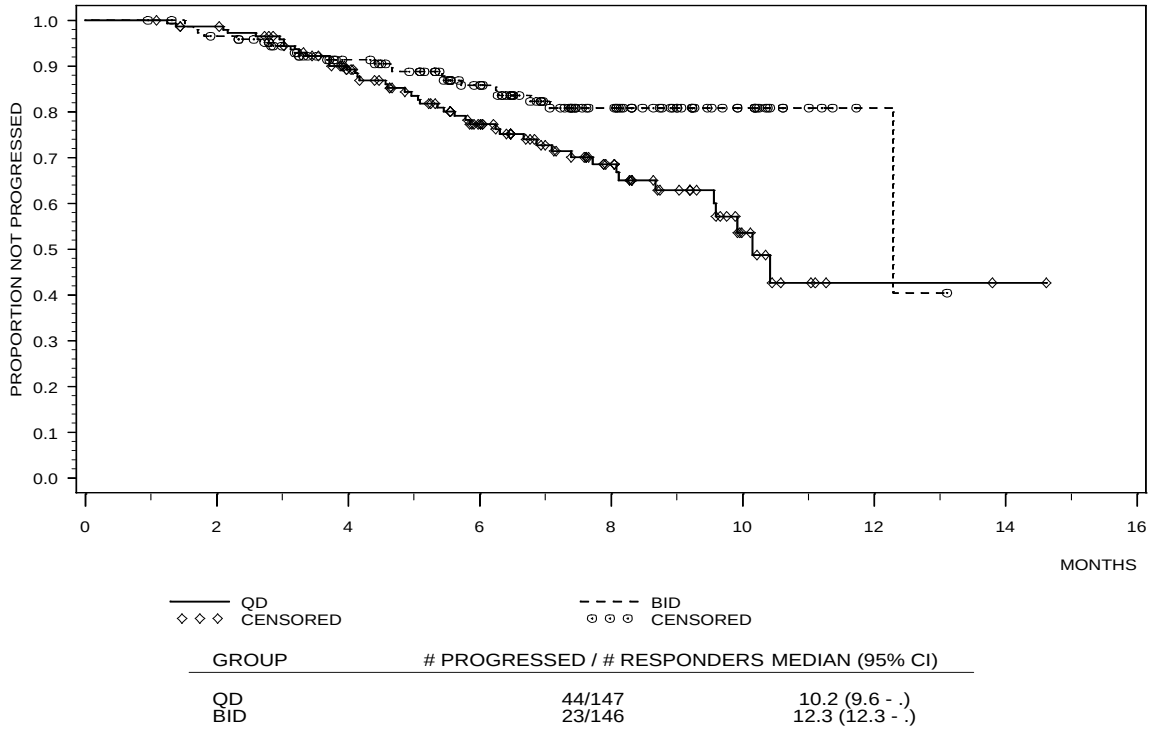
Table 8: Hematologic and Cytogenetic Responses Pooled Across Disease Phase (CA180035); All Randomized Subjects		
	Number (%) of Subjects	
	QD N = 306	**BID N = 305**
Median Duration of therapy (months)		
All treated subjects	5.6	5.5
Subjects still on treatment	8.3	8.4
Hematologic Response		
MaHR	147 (48)	146 (48)
CHR	94 (31)	96 (32)
NEL	53 (17)	50 (16)
MiHR	34 (11)	29 (10)
Median time to MaHR (months)	1.9	1.9
Cytogenetic Response		
MCyR	113 (37)	120 (39)
CCyR	89 (29)	84 (28)
Median time to MCyR (months)	1.8	1.8
Progression-free Survival (# Progressed / # Randomized)	160/306 (52)	137/305 (45)
Overall Survival (# Death / # Randomized)	108/306 (35)	92/305 (30)

The primary objective of the study was to compare the efficacy of dasatinib when administered to all randomized subjects at 140 mg QD relative to 70 mg BID. The QD schedule would be considered similar (non-inferior) to the BID schedule if the lower bound of the 2-sided 95% confidence interval of the difference in major hematologic response rates was ≥-12%. The analysis in all randomized subjects showed that the QD schedule was similar (non-inferior) to the BID schedule in major hematologic response rates (Table 9). The QD and BID groups showed little difference in MCyR (37% vs 39%, respectively) with a difference in rate of -2.4%.

Table 9: Major Hematologic Response in All Randomized Subjects with Advanced Phase CML or Ph+ ALL (CA180035)		
	QD N = 306	**BID N = 305**
MaHR	147 (48%)	146 (48%)
95% exact CI	42.3% - 53.8%	42.1% - 53.6%
Difference of MaHR	0.2%	
95% CI	-7.80% - 8.1%	

Among subjects who achieved a MaHR, durable responses were reported (Figure A).

Figure A: Duration of MaHR in Subjects who Achieved MaHR; All Randomized Subjects (CA180035)



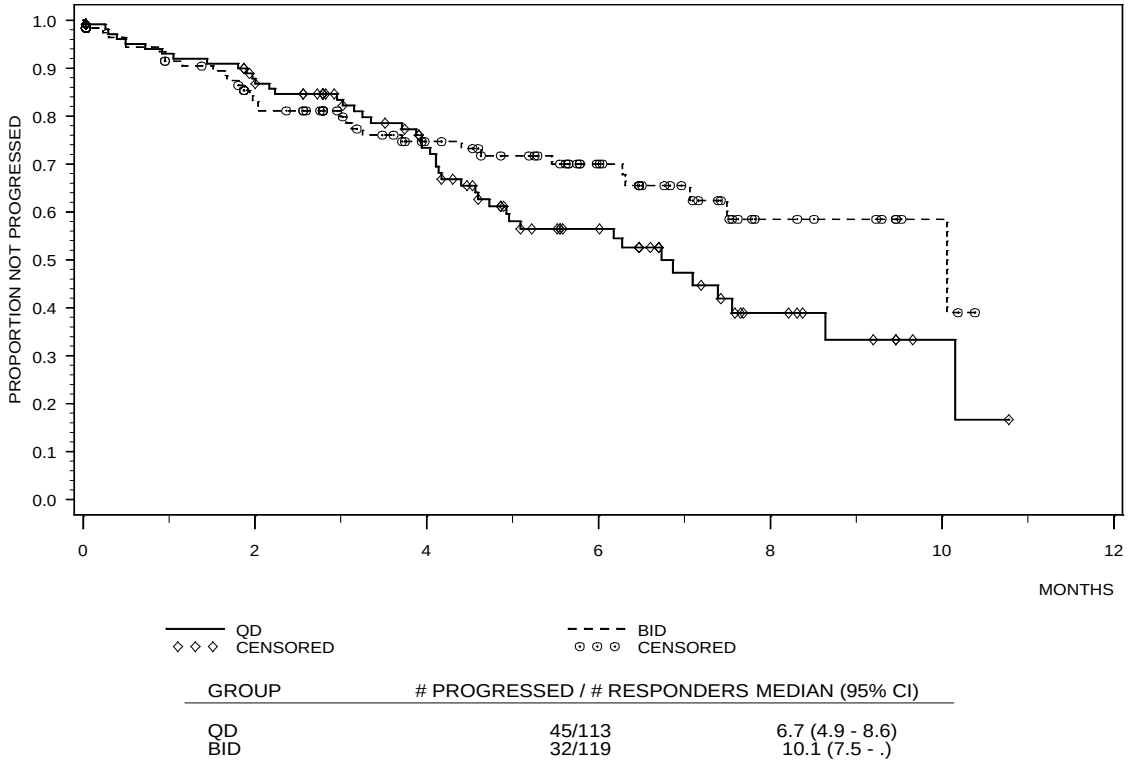
The median duration of response was shorter in the QD group vs. the BID group (10.2 months vs. 12.3 months, respectively). Overall, of the subjects with MaHR in the QD group, 30% relapsed compared with 16% in the BID group. When evaluated within each disease phase, the number of subjects who relapsed was similar between the QD and BID groups in subjects with accelerated phase CML and in subjects with myeloid blast phase CML. In subjects with lymphoid blast phase CML or Ph+ ALL, more subjects in the QD group relapsed than in the BID group, which represents 76% (16/21) of the overall difference in progression between the QD and BID groups (Table 10).

Table 10: Relapse in Subjects who Achieved MaHR by Disease Phase; Randomized Subjects (CA180035)

	Number Progressed/Number Randomized (%)		
	QD	**BID**	**Difference in Subject Number (QD - BID)**
Accelerated	13/99 (13)	10/104 (10)	3
Myeloid	8/20 (40)	6/19 (32)	2
Lymphoid	10/13 (77)	1/9 (11)	9
Ph+ ALL	13/15 (87)	6/14 (43)	7
Total	**44/147 (30)**	**23/146 (16)**	**21**

Among subjects who achieved a MCyR, durable responses were reported (Figure B).

Figure B: Duration of MCyR in Subjects who Achieved MCyR; All Randomized Subjects (CA180035)



The median duration of response was shorter in the QD group vs. the BID group (6.7 months vs. 10.1 months, respectively). Overall, of the subjects with MCyR in the QD group, 40% relapsed compared with 27% in the BID group. The increased progression in the QD group was specific to subjects with blast phase CML (myeloid and lymphoid) or Ph+ ALL (Table 11). In subjects with accelerated phase CML, fewer subjects relapsed in the QD group compared with the BID group.

Table 11: Relapse in Subjects who Achieved MCyR by Disease Phase; Randomized Subjects (CA180035)

	Number Progressed/Number Randomized (%)	
	QD	**BID**
Accelerated	1/48 (2)	6/62 (10)
Myeloid	8/20 (40)	6/21 (29)
Lymphoid	15/18 (83)	5/13 (38)
Ph+ ALL	21/27 (78)	15/23 (65)
Total	**45/113 (40)**	**32/119 (27)**

Clinical studies in special populations

These analyses include hematologic and cytogenetic endpoints based on age, race, and gender in Studies CA180034 and CA180035 in the efficacy cohort. In CA180034, no consistent response differences were observed among subpopulations of age, race, or gender. In CA180035, fewer subjects over the age of 75 years achieved a MaHR in the QD group compared with the BID group.

Discussion on Clinical Efficacy

The study design and selected endpoints are all acceptable and in accordance with the agreed FUM 010. Both studies are still ongoing and the final results due in 2009. The provision of these interim results is part of the FUM.

With reference to Study CA180034, an adequate number of patients reflecting the approved indication has been included in the study. From an efficacy point these results clearly support the proposed change in dosing recommendation for patients with chronic phase CML. The results must be considered robust as consistency is found for both primary and secondary endpoints.

In Study CA180035, although non-inferiority was demonstrated for the overall QD versus BID treatment schedule, the secondary endpoints do not unequivocally support this finding. Major differences in duration of response (median time to progression) and deaths favours the current BID dosing for patients with advanced CML or Ph+ ALL. It is agreed with the MAH, that this dose not support a change in dosing posology.

Again the CHMP considers that these data across age, race and gender support the proposed changes in posology for Chronic Phase CML but not for advanced CML or Ph+ ALL.

Clinical Safety

- **Exposure**

The median duration of exposure in subjects with chronic phase CML ranged from 7.9 to 8.3 months (Table 12). The median duration of exposure in subjects with advanced phase disease was ~5.5 months (Table 13).

Table 12: Duration of Treatment (CA180034); Chronic Phase CML				
	Number (%) of Subjects			
	100 mg QD N = 166	50 mg BID N = 166	140 mg QD N = 163	70 mg BID N = 167
Duration of Therapy (months)				
Median	8.3	8.3	8.2	7.9
Min - Max	1 - 12.9	0.2 - 14.5	0.2 -13.8	0.1 - 14.0

Table 13:Duration of Treatment (CA180035); Advanced Phase CML and Ph+ ALL		
	Number (%) of Subjects	
	QD N = 304	BID N = 305
Duration of Therapy (months)		
Median	5.6	5.5
Min – Max	0.03 - 15.6	0.03 - 14.0

- **General Safety Results**

Safety data reported in CA180034 and CA180035 were similar to results reported in the Phase 2 studies. Adverse events of myelosuppression and fluid retention identified as Adverse Events (AEs) of special interest are further described below.

In CA180034, similar safety events were reported across the 4 treatment arms. The results from this study demonstrated that treatment with dasatinib 100 mg QD provides a better overall safety profile than the other three doses/schedules. Drug-related AEs occurred less frequently in the 100 mg QD group than in the 70 mg BID group. Similarly, the rates of deaths and serious adverse events (SAEs) were lower in the 100 mg QD group than in the 70 mg BID group. Grade 3 or 4 myelosuppression was reported less frequently in subjects in the 100 mg QD group than in the 70 mg BID group. The rates of thrombocytopenia and leukocytopenia were significantly lower in the 100 mg QD group than in the other 3 groups. Subjects administered a starting dose of 100 mg QD reported significantly fewer pleural effusions than the other 3 groups.

CA180035 - The results from this study demonstrated that the QD schedule was better tolerated than the BID schedule. The most important difference between the groups was observed in the rate of fluid retention. Pleural effusion was reported in fewer subjects in the QD group than in the BID group.

Similarly, there was a substantial decrease in the incidence of other fluid retention events in the QD vs. BID group. There were small differences in other non-hematologic AEs, some favouring the QD group (nausea and anorexia) and others favouring the BID group (headache). There were minimal differences in myelosuppression, which were severe in both treatment groups. The difference in toxicity resulted in less frequent dose reductions and dose interruptions in the QD group, allowing for a more sustained drug administration.

- **Common Drug-related Adverse Events**

Overall, drug-related AEs reported in CA180034 and CA180035 were common to those reported in the Phase 2 studies. In CA180034, drug-related AEs occurred less frequently in the 100 mg QD group (81%) than in the 70 mg BID group (89%). Drug-related Grade 3 to 5 AEs also occurred less frequently in the 100 mg QD group (30%) than in the 70 mg BID group (48%). In CA180035, drug-related AEs were similar between the QD group (88%) and BID group (87%).

Of the overall (all clinical trials reported to date) population of 2182 dasatinib-treated subjects, 1864 (85%) experienced at least 1 drug-related AE over the course of the study (Table 14). The most frequently reported (≥10%) drug-related AEs (all grades combined) of clinical relevance included diarrhea (29%), pleural effusion (17%), and hemorrhage (19%).

Table 14: Adverse Drug Reactions (ADR) reported in ≥ 5% of All Subjects in Clinical Studies

	All Subjects (N= 2182) Percent (%) of Subjects	
	All Grades	Grades 3/4
Nervous system disorders		
Very common: headache	23	1
Common: neuropathy (including peripheral neuropathy)	5	<1
Respiratory, thoracic and mediastinal disorders		
Very common: pleural effusion,	17	4
Dyspnea	16	3
Common: cough	7	<1
Gastrointestinal disorders		
Very common: diarrhea,	29	3
nausea,	20	1
Vomiting	11	1
Common: abdominal pain,	9	1
mucosal inflammation (including mucositis/stomatitis)	6	<1
Skin and subcutaneous tissue disorders		
Very common: skin rash [a]	20	1
Common: pruritus	6	<1
Musculoskeletal and connective tissue disorders		
Very common: musculoskeletal pain	12	1
Common: arthralgia,	7	1
Myalgia	7	<1
Metabolism and nutrition disorders		
Common: anorexia	8	<1
Infections and infestations		
Common: infection (including bacterial, viral, fungal, nonspecific)	8	2
Vascular disorders		
Very common: haemorrhage,	19	6
of which: gastrointestinal bleeding,	7	4
and CNS bleeding	1	<1
General disorders and administration site conditions		
Very common: superficial odema [b]	18	<1

Table 14: Adverse Drug Reactions (ADR) reported in ≥ 5% of All Subjects in Clinical Studies		
	All Subjects (N= 2182) Percent (%) of Subjects	
	All Grades	Grades 3/4
fatigue,	19	2
pyrexia,	12	1
Common: pain,	6	<1
Asthenia	8	1

a Includes drug eruption, erythema, erythema multiforme, erythrosis, exanthem, exfoliative rash, generalised erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, systemic lupus erythematosus rash, toxic skin eruption and urticaria vesiculosa.
b Includes conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, gravitational oedema, localised oedema, oedema genital, oedema mouth, oedema peripheral, orbital oedema, periorbital oedema, pitting oedema, scrotal oedema and swelling face.

- **Serious Adverse Events**

Overall, SAEs reported in CA180034 and CA180035 were consistent with the Phase 2 program. In CA180034, SAEs occurred less frequently in the 100 mg QD group (24%) than in the 70 mg BID group (34%). In CA180035, SAEs were similar between the QD group (66%) and BID group (70%).

Of the overall population of 2182 dasatinib-treated subjects, 922 (42%) reported SAEs. The most frequently reported (≥2%) SAEs included pyrexia, pleural effusion, febrile neutropenia, lower gastrointestinal hemorrhage, pneumonia, infection, sepsis, dyspnea, diarrhea, and cardiac failure. Fluid retention, myelosuppression, bleeding-related events, and QT interval prolongation are further addressed below.

- **Deaths**

In CA180034, the death rate was low in subjects with chronic phase CML with fewer deaths in the 100 mg QD group (0%) than in the 70 mg BID group (2%). In CA180035, more deaths in subjects with advanced phase disease were reported in the QD group (36%) than in the BID group (30%). The main difference in deaths between the groups was due to a higher number of deaths attributed to disease in the QD group compared with the BID group.

Three hundred sixty-four of the 2,182 subjects (16.7%) included in this pooled population died; 210 deaths (9.6%) occurred within 30 days after administration of the last dose of dasatinib. The most frequent reasons for deaths were disease progression (8.3%) and infection (3.3%). Twenty-two deaths (1.0%) were due to fatal bleeding.

- **Laboratory Abnormalities**

In this heavily pretreated population of subjects, treatment with dasatinib was associated with severe (Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Myelosuppression is addressed below as an AE of special interest.

There were few clinically meaningful non-hematologic changes in laboratory parameters reported on treatment with dasatinib in CA180034 and CA180035, a result consistent with the Phase 2 program. Of the overall population of 2182 dasatinib-treated subjects, Grade 3 or Grade 4 non-hematologic laboratory abnormalities included hypophosphemia (12.0%), hypocalcemia (5.4%), elevated SGPT (2.5%), hyperbilirubinemia (1.6%), elevated serum creatinine (1.1%), and elevated SGOT (1.5%).

- **Selected Safety Events**

Safety issues of special importance in the dasatinib product label included the AEs of myelosuppression, fluid retention (pleural effusion and pericardial effusion), bleeding-related events, and QT prolongation. There are no new QT prolongation data being reported in this section.

Study CA180034

The rates of fluid retention-related events reported in CA180034 were lower in the 100 mg QD group than the 70 mg BID group (Table 15). Subjects administered a starting dose of 100 mg QD reported significantly fewer pleural effusions than the other treatment groups.

Table 15: Selected Adverse Drug Reactions - All Treated Subjects in CA180034

	Percent of Subjects (%)							
	100 mg QD (N = 166)		140 mg QD (N = 163)		50 mg BID (N = 166)		70 mg BID (N = 167)	
Preferred Term	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)	Any Grade	Severe (3-4)
Diarrhea	24	1	23	2	24	2	22	4
Fluid Retention	21	1	26	4	22	2	28	4
Superficial Edema	14	0	12	1	13	0	14	0
Pleural Effusion	7	1	15	3	11	2	16	1
Generalized edema	2	0	2	0	1	0	1	0
Congestive heart failure /cardiac dysfunction [a]	0	0	1	1	1	1	3	2
Pericardial effusion	1	0	3	1	1	1	1	1
Pulmonary edema	0	0	1	0	1	0	1	1
Pulmonary hypertension	0	0	0	0	0	0	1	1
Hemorrhage								
Gastrointestinal bleeding	1	1	1	0	4	2	4	2

a Includes ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular failure

Grade 3 or 4 myelosuppression was reported less frequently in subjects in the 100 mg QD group than in the 70 mg BID group (Table 16). The rates of thrombocytopenia and leukocytopenia were lower in the 100 mg QD treatment group than in the other treatment groups.

Subjects administered the 100 mg QD dose achieved the highest dose intensity of all the treatment groups.

The average TDD in the 100 mg QD group was close to the target of 100 mg TDD (i.e., 99.5 mg). In contrast, in the 70 mg BID group, the average daily dose was 108 mg/day, a reduction from the target of 140 mg TDD. The rates of dose interruption and reduction were lower in the 100 mg QD group than in the 70 mg BID group. The number of recurrent dose interruptions and reductions was also lowest in the 100 mg QD group, allowing for a more sustained drug administration.

Table 16: CTC Grades 3/4 Laboratory Abnormalities: All Treated Subjects in CA180034

	Percent (%) of Subjects			
	100 mg QD N = 166	140 mg QD N = 163	50 mg BID N = 166	70 mg BID N = 167
Hematolgy Parameters				
Neutropenia	33	42	44	42
Thrombocytopenia	22	39	32	37
Anemia	10	17	16	16

Study CA180035

Fewer subjects in the QD group than in the BID group reported fluid retention-related AEs of all grades, including pleural effusion, pulmonary edema, pericardial effusion, and CHF (Table 17). There were minimal differences in myelosuppression, which were severe in both treatment groups (Table 18). The difference in toxicity resulted in less frequent dose reductions and dose interruptions in the QD group, allowing for a more sustained drug administration.

Table 17: Selected Adverse Drug Reactions: All Treated Advanced Phase CML and Ph+ALL Subjects in CA180035

	Percent (%) of Subjects			
	140 mg QD N = 304		70 mg BID N = 305	
Preferred Term	**All Grades**	**Grade 3 / 4**	**All Grades**	**Grade 3 / 4**
Diarrhea	27	3	27	3
Fluid Retention	26	5	34	9
Superficial oedema	12	<1	16	1
Pleural Effusion	16	4	23	6
Generalised oedema	1	0	2	1
Congestive heart failure / cardiac dysfunction	1	0	2	1
Pericardial effusion	1	0	4	1
Pulmonary oedema	1	1	3	1
Ascites	0	0	1	0
Pulmonary hypertension	0	0	1	<1
Haemorrhage				
Gastrointestinal bleeding	7	6	12	6

Table 18:CTC Grades 3/4 Laboratory Abnormalities: All Treated Subjects in CA180035

	Percent (%) of Subjects	
	QD N = 304	**BID N = 305**
Hematology Parameters		
Neutropenia	58	64
Thrombocytopenia	47	52
Anemia	20	23

Safety in the Overall Population

In the overall population of 2182 dasatinib-treated subjects, severe (Grade 3/4) fluid retention was reported in 7% of subjects treated with dasatinib, including pleural and pericardial effusion reported in 4% and 1% of subjects, respectively. Severe ascites and generalized edema were each reported in <1%. Severe pulmonary edema was reported in 1% of subjects. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that included diuretics and/or short courses of steroids.

Myelosuppression occurred more frequently in subjects with advanced phase CML or Ph+ ALL than in chronic phase CML. The reported Grade 3 or Grade 4 hematologic abnormalities included neutropenia (57.6%), thrombocytopenia (56.3%), and anemia (35.4%). Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction.

Overall, severe central nervous system (CNS) hemorrhages, including fatalities, occurred in 1% of subjects receiving dasatinib. Severe gastrointestinal (GI) hemorrhage occurred in 6% of subjects and

generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 3% of subjects. Most bleeding events were associated with severe thrombocytopenia.

Discussion on Clinical Safety

Safety data from CA180034 supports the change in posology proposed by the MAH in this type II variation. The QD dosing in patients with chronic phase CML resulted in fewer AE's including those most frequently seen with dasatinib in the overall clinical development program.
Safety data also supported the QD dosing in patients with advanced phase CML or Ph+ ALL, although these results are not as convincing as for patients in chronic phase (study CA180034).

The data from these two phase III studies add to the overall safety database for dasatinib, and the relevant SPC sections have been amended accordingly by the MAH. Further, the MAH has forwarded an updated Risk Management Plan, which is considered acceptable.

SPC changes as a result of the CHMP assessment of the 1st PSUR

Following the Committee's assessment of the 1st Periodic Safety Update Report (PSUR) for dasatinib oral tablets (covering the period from 28 June 2006 through 27 December 2006), the MAH was requested to file a type II variation to update the SPC as follows:

- "The treatment with dasatinib is associated with the important adverse reaction Myelosuppression. In section 4.4. Special warnings and precautions for use it says "Myelosuppression: treatment with Sprycel is associated with anaemia, neutropenia and thrombocytopenia". Under section 4.8. only neutropenia is mentioned under blood and lymphatic system disorders. The SPC should be updated to also include anaemia and thrombocytopeniain in section 4.8.

- The event gastrointestinal haemorrhage is only mentioned in the SPC under the adverse reaction "Vascular disorders". Even though most bleeding related events seen in the treatment with dasatinib are associated with severe thrombocytopenia, which encourages that gastrointestinal bleeding is mentioned under this section, several reported bleeding disorders are related to gastrointestinal disorders. It is therefore recommended that gastrointestinal bleeding should be mentioned under this SOC as well. Therefore the SPC should be updated accordingly in section 4.8.

- The event cerebral haemorrhage is only mentioned in the SPC under the adverse reaction "Vascular disorders". Most bleeding related events seen in the treatment with dasatinib are associated with severe thrombocytopenia, which is already stated in the SPC. But since several reported bleeding disorders are related to the event cerebral haemorrhage the event should be specified in point 4.8 in the SPC. It is recommended that the SPC should be updated under point 4.8. to specify the event Cerebral haemorrhage under the SOC Nervous system Disorders as well. In point 4.4 and 4.8 of the SPC It states "CNS hemorrhage occurred in 1% of Patients. Three cases were fatal and 2 of them were associated with CTC grade 4 thrombocytopenia…" The MAH states that 5 fatal cases related to cerebral hemorrhage during the review period, it seems that section 4.4 of the SPC should be updated to include these fatal events. "

The MAH took the opportunity of this type II variation to update section 4.8 of the SPC in line with the outcome of the CHMP assessment of the 1st PSUR and according to MedDRA version 8.2. The Package Leaflet has been amended accordingly.

Benefit/risk assessment

Dasatinib offers a therapeutic advance for subjects with CML or Ph+ ALL who are resistant or intolerant to imatinib. Results from the dasatinib Phase 1 and Phase 2 program showed that subjects with all phases of CML or Ph+ ALL achieve durable hematologic and cytogenetic responses. Myelosuppression and fluid retention were identified as the most important toxicities in the Phase 1

and Phase 2 studies. Recovery from myelosuppression and fluid retention-related AEs were managed in most cases by dose interruptions, dose reductions, or supportive care.

Previous findings from Phase 1 assessing BID and QD dose regimens among subjects with chronic phase CML, showed similar efficacy with a suggestion of improved safety for the QD regimen; however, the study was not designed to compare dosing schedules. In an attempt to improve the safety profile of dasatinb while maintaining efficacy, Studies CA180034 and CA180035 were undertaken as a post-marketing commitment (FUM 010) to assess alternate doses and regimens to minimize the risk associated with the administration of dasatinib.

Results from the two phase III trials included in this application showed evidence of substantial and durable hematologic and cytogenetic response rates in subjects with chronic phase CML who failed imatinib because of progression or intolerance. These data demonstrate that a dose of 100 mg QD has comparable efficacy with the currently approved dose of 70 mg BID, but were associated with improved and clinically relevant less toxicity. The proposed change in posolgy for chronic phase CML recommending 100 mg QD as starting dose has a more favourable benefit/risk ratio than the current 70 mg BID and should in the opinion of the CHMP be approved.

In subjects with advanced phase CML and Ph+ ALL, despite an improvement in the safety profile of dastinib, a recommendation for alternative dosing will require further assessment of the durability of hematologic and cytogenetic responses.

The MAH has forwarded an updated Risk Management Plan, which is considered acceptable.

Both studies (CA180034 and CA180035) are still ongoing and the MAH should still provide the final (24 month) results of both studies when available (FUM 010).

In addition, the MAH took the opportunity of this type II variation to update section 4.8 of the SPC in line with the outcome of the CHMP assessment of the 1st PSUR and according to MedDRA version 8.2. The Package Leaflet has been amended accordingly. Further, the MAH have implemented some minor editorial changes in the annexes and updated the contact details of the local representatives for Romania and Denmark in the Package Leaflet.

CONCLUSION

- On 19 July 2007 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, labelling and Package Leaflet.