EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2012

EMA/273206/2012

Human Medicines Development and Evaluation

Sprycel-000709-Article 46-FUM 035
EPAR Assessment Report

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

On 22 November 2011, the MAH submitted a completed paediatric study for Sprycel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the follow up measure 035.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Sprycel and that no consequential regulatory action is required.

Scientific discussion

Information on the development program

The MAH stated that CA180018 is a phase 1 study conducted to investigate dasatinib given once daily for treatment of leukaemia in 1- 21 year old subjects. A paediatric formulation is being developed in another study (Study CA180352) for use in future phase II trials.

Information on the pharmaceutical formulation used in the study

The CA180018 study conducted in pediatric subjects, used tablet formulations of dasatinib (5, 20, and 50 mg). If necessary to permit administration in subjects who could not swallow, tablets were dispersed into 30 cc of 100% fruit juice with no preservatives. A new pediatric formulation of dasatinib powder for oral suspension is currently being tested in CA180352 for use in future Phase 2 trials.

Clinical aspects

1. Introduction

SPRYCEL® (dasatinib) is approved in 69 countries, including the United States and European Union, for the treatment of adult subjects with chronic myeloid leukemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) who are resistant or intolerant to imatinib. For the treatment of adult subjects with newly diagnosed chronic phase (CP)-CML, SPRYCEL was approved in the US (28-Oct-2010) and in the EU (6-Dec-2010). Marketing authorization approval for the indication of adult subjects with newly diagnosed CP-CML is currently under review in several other countries.

The MAH submitted a final report for study CA180018, a Phase 1 study conducted to investigate dasatinib given once daily (QD) for the treatment of leukemia in 1 to 21-year-old subjects.

2. Clinical study

Study CA180018: Phase 1 Study of SRC/ABL Tyrosine Kinase Inhibitor Dasatinib (BMS-354825) in Children and Adolescents with Relapsed or Refractory Leukemia, Protocol ITCC 005

Description:

The primary objective of this Phase 1, dose-finding study was to establish a recommended Phase 2 dose of dasatinib in children and adolescents with relapsed or refractory leukemia. In the absence of an MTD utilizing the pre-specified dose levels, efficacy, safety and PK data were reviewed to determine the recommended Phase 2 dasatinib dose. The recommended Phase 2 dose is 60 mg/m^2 QD for pediatric subjects with CP-CML (Stratum 1) and 80 mg/m^2 QD for pediatric subjects with Ph+ ALL or AP/BP-CML (Stratum 2/3). Due to the lack of efficacy, there is no plan to move forward with the development of dasatinib therapy for the Ph- leukemias in Phase 2 (Stratum 4).

Methods

- Objectives

Primary Objective:

To establish, by stratum using a dose-finding design, a recommended Phase 2 dose of dasatinib (BMS-354825) in children and adolescents with relapsed or refractory leukemia.

Secondary Objectives:

1) To determine the adverse events (AEs) and identify any dose-limiting toxicities (DLTs) of dasatinib in children and adolescents with chronic myeloid leukemia (CML) in chronic phase (CP) (Ph+;Stratum 1) or advanced leukemias (Strata 2/3 and 4 aggregated)

2) To estimate, by stratum, the rates of morphologic (major hematologic response [MaHR]), cytogenetic (major cytogenetic response [MCyR]; Strata 1 and 2/3 only), and molecular (quantitative polymerase chain reaction [qPCR]; subjects with MCyR only, Strata 1 and 2/3 only) responses to dasatinib

3) To describe, by stratum, time to response, response duration, progression-free survival (PFS), and survival of children and adolescents with relapsed or refractory leukemia treated with dasatinib

4) To estimate, as a function of dasatinib dose, plasma and (if applicable) cerebrospinal fluid (CSF) pharmacokinetic (PK) parameters of dasatinib

5) To describe the spectrum of mutations in the BCR-ABL gene (Strata 1 and 2/3) and in the FLT3 and KIT genes (Stratum 4) at baseline and at end of treatment and to explore the role of mutations as predictors of response.

In addition, protocol Amendment 5 (approved 08-Dec-2009) and United Kingdom country-specific Amendment 06 (dated 05-May-2010) added laboratory and radiographic assessments to monitor growth and development and bone mineral metabolism to be performed annually for up to 5 years of follow-up after completion of study drug.

- Study design

CA180018 is a Phase 1, open-label, dose-escalation (3+3 design, intra-subject dose escalation) study in which eligible subjects were treated with dasatinib orally QD until refractory disease progression, intolerable toxicity, or patient/physician preference. Dasatinib could be continued for as long as clinical benefit was maintained.

The target population included children and adolescents, ≥ 1 to < 21 years of age, with Ph+ CML in chronic, accelerated, or blast phase (BP) resistant or intolerant to imatinib, or in first or subsequent relapse of Ph+ ALL after prior imatinib, or in second or subsequent relapse of Ph- ALL or AML.

- Study population /Sample size

In CA180018, 58 subjects were treated with dasatinib and were evaluable for the primary endpoint (selection of the Phase 2 dose):

- 17 in Stratum 1: all Ph+ CP-CML
- 17 in Stratum 2/3
    - 1 subject with Ph+ lymphoid blast phase (LBP) CML
    - 2 subjects with Ph+ AP CML
    - 14 subjects with Ph+ ALL

- 24 in Stratum 4
    - 15 subjects with Ph- AML
    - 9 subjects with Ph- ALL

The mean age of the entire study population was 10 years. Fifty-seven of the 58 treated subjects were 1 to 18 years of age. This includes 34 subjects 1 to < 12 years and 23 subjects 12 to < 18 years. One subject with Ph- AML was 21 years and 1 month at baseline. Roughly two-thirds of the subjects in each stratum were male and 90% were white. A summary of dosing is provided in Table 4.2.

Table 4.2: Median Duration of Therapy and Median of the Average Daily Dose

Strata	**Median Duration of Therapy (months)**
Stratum 1 (CP-CML)	24.11
Stratum 2/3 (Ph+ ALL or AP/BP-CML)	3.02
Stratum 4 (Ph- AML and ALL)	1.14
Strata/Dose Cohort ($mg/m^2/day$)	**Median of the Average Daily Dose ($mg/m^2/day$)**
Stratum 1 (CP-CML)	
60	66.0
80	83.0
Stratum 2/3 (Ph+ ALL or AP/BP-CML)	
60	68.0
80	79.3
Stratum 4 (Ph- AML and ALL)	
60	62.1
80	79.4
100	101.3
120	118.9

- Treatments

Treatment courses were defined as 3 weeks (21 days plus any required delay); for subjects who stayed on treatment > 12 months, courses after 12 months were defined in quartiles of 13 weeks. Subjects were to be followed until death or up to 5 years after end-of-treatment. Dasatinib dose levels are provided in Table 4.1.

Table 4.1: Dasatinib Doses

Dose Levels	**Dose**
-1	50 mg/m^2 QD (-17%)
1	60 mg/m^2 QD * Starting dose for all strata *
2	80 mg/m^2 QD (+33%)
3	100 mg/m^2 QD (+25%)
4	120 mg/m^2 QD (+20%)

150 mg/m^2 QD was planned to be used for dose escalation; however, no subject had a dose escalation to 150 mg/m^2.

The starting dose level for all strata was 60 mg/m^2 QD. Each stratum was escalated independently, following a standard 3+3 dose escalation scheme. Intra-subject dose escalation was allowed based on tolerance and on individual response. This design ensured maximal therapeutic benefit for children and

adolescents with Ph+ disease, without a requirement to escalate to maximum tolerated dose (MTD) and incur toxicity.

- Outcomes/endpoints

Efficacy: Efficacy variables included hematologic, cytogenetic, and molecular responses to dasatinib. Time to response, response duration, progression-free survival (PFS), and overall survival with relapsed or refractory leukemia treated with dasatinib were also measured. Mutations in the BCR-ABL (for subjects with Ph+ leukemias in Strata 1 and 2/3) and mutations in FLT3 and KIT genes (for subjects with Ph - leukemias in Stratum 4) were studied.

Safety: AEs, drug-related AEs, AEs leading to discontinuation, serious adverse events (SAEs), AEs of special interest, laboratory measurements, electrocardiograms (ECG), echocardiograms, and deaths were summarized. Investigator reported AE terms were coded and grouped by system organ class (SOC) using the Medical Dictionary for Regulatory Affairs (MedDRA) dictionary Version 14. AEs and other symptoms were graded according to the NCI CTCAE Version 3.0. Specific measures for long-term follow-up of growth and development were added in protocol Amendment 5 (08-Dec-2009).

Pharmacokinetics: PK variables included: maximum observed plasma concentration (Cmax), time of maximum observed plasma concentration (Tmax), area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC[0-T]), area under the plasma concentration-time curve from time zero extrapolated to infinite time (AUC[INF]), terminal elimination half-life (T-HALF), dose normalized (DN) Cmax, DN AUC(0-T), and DN AUC(INF).

- Statistical Methods

The sample size was not based on statistical power to detect a specific response rate but on the feasibility of accrual and on the dose levels used for the escalations of the starting dose.

In Stratum 1 and in Stratum 2/3, at least 12 subjects in each stratum were to be treated to meet the primary objective (6 subjects at the 60 mg/m2 starting dose; and 6 subjects at the 80 mg/m2 starting dose, unless there was excessive toxicity at either dose, or no clinical need to escalate to 80 mg/m2). Up to additional 4 subjects were to be treated at the 60 mg/m2 dose level in Stratum 1 and at the 80 mg/m2 level in Stratum 2/3 to expand the number of subjects at the dose level selected for the Phase 2 study.

In Stratum 4, a maximum of 6 subjects were to be accrued per dose level; the highest starting dose was to be 120 mg/m2.

Dose escalation was based on the tolerability at a given dose level and the clinical efficacy at a given dose. The recommended Phase 2 dose was determined based on the aggregation of safety data for these strata, and an assessment of safety at a minimum of 2 dose levels was planned.

Best on-study hematologic, cytogenetic and molecular response rates including key efficacy endpoints were estimated using all treated subjects by stratum and by dose cohort. Ninety-five percent exact confidence intervals (CIs) using the method of Clopper and Pearson were provided for rates computed on the recommended Phase 2 dose.

Kaplan-Meier plots for PFS, overall survival (OS), duration and time to response by stratum were planned and provided. A 2-sided, 95% CI for the median was computed using the method of Brookmeyer and Crowley.

Results

- Recruitment/ Number analysed

Of the 58 treated subjects, 51 subjects were off treatment at the time of database lock (Table 3). As of the data cut off for this report, a total of 7 subjects were still on study: 6 in Stratum 1 and 1 with Ph+ ALL in Stratum 2/3.

Table 3: Subject Disposition

	Number (%) of Subjects			
	Stratum 1 CP-CML	Stratum 2/3 Ph+ ALL or AP/BP-CML	Stratum 4 Ph- ALL/AML	Overall
No. of Subjects Enrolled	18 (100.0)	20 (100.0)	25 (100.0)	63 (100.0)
No. of Subjects Treated (% of Enrolled)	17 (94.4)	17 (85.0)	24 (96.0)	58 (92.1)
Still On Treatment (% of Treated)	6 (35.3)	1 (5.9)	0	7 (12.1)
Off Treatment (% of Treated)	11 (64.7)	16 (94.1)	24 (100.0)	51 (87.9)
Resistant Disease	1 (5.9)	8 (47.1)	15 (62.5)	24 (41.4)
Refractory Disease	1 (5.9)	2 (11.8)	2 (8.3)	5 (8.6)
Decision to Undergo Stem Cell Transplant	6 (35.3)	3 (17.6)	1 (4.2)	10 (17.2)
Study Drug Toxicity	0	0	2 (8.3)	2 (3.4)
Adverse Event Unrelated to Study Drug	0	0	2 (8.3)	2 (3.4)
Subject Request	1 (5.9)	1 (5.9)	1 (4.2)	3 (5.2)
Investigator Request	0	2 (11.8)	0	2 (3.4)
Other	2 (11.8)	0	1 (4.2)	3 (5.2)

Baseline hematologic disease status for each stratum was consistent with the type of leukemia specified (Table 4).

- Baseline data

Table 4: Baseline Demographic and Disease Characteristics

	Stratum 1 CP-CML N = 17	Stratum 2/3 Ph+ ALL or AP/BP-CML N = 17	Stratum 4 Ph- ALL/AML N = 24	Overall N = 58
Age (years)				
Mean	12.4	9.7	8.6	10.0
Median	13.0	9.0	7.5	10.0
Min-Max	4.0 - 17.0	4.0 - 17.0	1.3 - 21.0	1.3 - 21.0
Age Categorization, n (%)				
< 2	0	0	2 (8.3)	2 (3.4)
2 - 6	2 (11.8)	5 (29.4)	7 (29.2)	14 (24.1)
7 - 11	6 (35.3)	5 (29.4)	7 (29.2)	18 (31.0)
12 -18	9 (52.9)	7 (41.2)	7 (29.2)	23 (39.7)
> 18	0	0	1 (4.2)	1 (1.7)
Race, n (%)				
White	16 (94.1)	15 (88.2)	21 (87.5)	52 (89.7)
Black/African American	0	0	1 (4.2)	1 (1.7)
Asian	1 (5.9)	1 (5.9)	1 (4.2)	3 (5.2)
Other	0	1 (5.9)	1 (4.2)	2 (3.4)
Extramedullary Involvement, n (%)				
Spleen	0	2 (11.8)	2 (8.3)	4 (6.9)
Liver	1 (5.9)	4 (23.5)	1 (4.2)	6 (10.3)
Median WBC (/mm^3)	8.7	6.2	3.0	5.8
Median Platelets (x $10^3/mm^3$)	294	82	41	86
Median Blasts in Bone Marrow (%)	0	39	80	52

- **Efficacy results**

Preliminary evidence of efficacy in this Phase 1 trial are displayed in Table 4.3 below and are comparable to results observed in larger adult trials with dasatinib.

Table 4.3: Summary of Efficacy Results for Strata 1 and 2/3

	Number (%) of Subjects					
	Stratum 1 CP-CML			Stratum 2/3 Ph+ ALL or AP/BP-CML		
	All Doses N=17	60 mg/m^2 N=11	80 mg/m^2 N=6	All Doses N=17	60 mg/m^2 N=8	80 mg/m^2 N=9
Cytogenetic Response						
MCyR within first 12 wks	8 (47.1)	6 (54.5)	2 (33.3)	-	-	-
MCyR within first 24 wks	14 (82.4)	9 (81.8)	5 (83.3)	-	-	-
MCyR overall	15 (88.2)	9 (81.8)	6 (100.0)	11 (64.7)	4 (50.0)	7 (77.7)[c]
CCyR overall	14 (82.4)	8 (72.7)	6 (100.0)	11 (64.7)[c]	4 (50.0)	7 (77.7)[c]
Median duration of MCyR (mos)	Not Reached	-	-	4.6	-	-

Table 4.3: Summary of Efficacy Results for Strata 1 and 2/3

	Number (%) of Subjects					
	Stratum 1 CP-CML			Stratum 2/3 Ph+ ALL or AP/BP-CML		
	All Doses N=17	60 mg/m^2 N=11	80 mg/m^2 N=6	All Doses N=17	60 mg/m^2 N=8	80 mg/m^2 N=9
Confirmed Hematologic Response						
MaHR within first 6 wks	NA	NA	NA	7 (41.2)	2 (25.0)	5 (55.6)
MaHR within first 24 wks	NA	NA	NA	8 (47.1)	2 (25.0)	6 (66.7)
MaHR overall	NA	NA	NA	8 (47.1)	2 (25.0)	6 (66.7)
Confirmed CHR overall	16 (94.1)	10 (90.9)	6 (100.0)	6 (35.3)	1 (12.5)	5 (55.6)
Median duration (mos) CHR (Stratum 1)/MaHR (Stratum 2/3)	Not Reached	-	-	4.4	-	-
Unconfirmed CHR overall	16 (94.1)	10 (90.9)	6 (100.0)	10 (58.8)	3 (37.5)	7 (77.8)
Molecular Response						
MMR	8 (47.1)	6 (54.5)	2 (33.3)	8 (47.1)	2 (25.0)	6 (66.7)
CMR	4 (23.5)	3 (27.3)	1 (16.7)	-	-	-
Median PFS Survival (mos)	Not Reached	-	-	4.9	-	-
Median OS (mos)	Not Reached	-	-	8.6	-	-

No hematologic responses were reported in subjects from Stratum 4.

Last MCyR was achieved by Week 26 in Stratum 1 and by Week 15 in the Stratum 2/3.

The MCyR and CCyR rates exclude subject (CA180018-10-10006) in the 80 mg/m^2 dose cohort, who did not have a CCyR. This subject was counted as having a CCyR due to a data entry error that was fixed after database lock for this CSR.

For Stratum 2/3 Unconfirmed CHR = unconfirmed MaHR

ALL - acute lymphoblastic leukemia, AP - accelerated phase, BP - blast phase, CHR - complete hematologic response, CML - chronic myeloid leukemia, CMR - complete molecular response, CP - chronic phase, MaHR - major hematologic response, MCyR - major cytogenetic response, MMR - major molecular response, OS - overall survival, PFS - progression free survival, Ph+ - Philadelphia chromosome positive

Assessors comment

It can be agreed that the data support 60 mg/m2 QD for paediatric subjects with CP-CML and 80 mg/m2 QD for paediatric subjects with Ph+ ALL or AP/BP-CML as the recommended Phase 2 dose (table above) as clinical activity in paediatric subjects with Ph+ leukemias with resistance or intolerance to prior imatinib was shown. Response rates in children with CP-CML at 60 mg/m2 QD and in children with AP-CML and Ph+ ALL at 80 mg/m2 QD was favourable.

The data also showed that no responses were observed in paediatric subjects with treatment-refractory Ph–ALL or AML (Stratum 4) despite escalations to the highest dose in this trial of 120 mg/m2.

- **Safety results**

Table 7: Summary of Safety Results

	Number (%) of Subjects					
	Stratum 1 CP-CML N=17		Stratum 2/3 Ph+ ALL or AP/BP-CML N=17		Stratum 4 Ph- ALL/AML N=24	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Drug-related AEs of Special Interest						
Fluid Retention	2 (11.8)	0	2 (11.8)	0	3 (12.5)	1 (4.2)
Superficial Edema	2 (11.8)	0	1 (5.9)	0	1 (4.2)	0
Pleural Effusion	0	0	1 (5.9)	0	2 (8.3)	1 (4.2)
Cardiac Disorders	1 (5.9)	0	0	0	0	0
Diarrhea	4 (23.5)	0	6 (35.3)	0	2 (8.3)	0
Nausea/Vomiting	7 (41.2)	0	5 (29.4)	0	9 (37.5)	2 (8.3)
Rash	5 (29.4)	0	5 (29.4)	0	3 (12.5)	2 (8.3)
Hemorrhage	1 (5.9)	0	3 (17.6)	1 (5.9)	1 (4.2)	1 (4.2)
Hypersensitivity	0	0	0	0	0	0
Hearing Loss	0	0	0	0	0	0
Hypocalcemia	3 (17.6)	0	6 (35.3)	0	9 (37.5)	1 (4.2)
Drug-related AEs	**15 (88.2)**	**6 (35.3)**	**16 (94.1)**	**6 (35.3)**	**19 (79.2)**	**10 (41.7)**
Drug-related SAEs	**2 (11.8)**	**1 (5.9)**	**5 (29.4)**	**4 (23.5)**	**8 (33.3)**	**1 (4.2)**
Drug-related AEs Leading to Discontinuation	**0**	**0**	**0**	**0**	**2 (8.3)**	**1 (4.2)**
Drug-related Deaths	**0**	**0**	**0**	**0**	**0**	**0**
On-study Grade 3-4 Laboratory Abnormalities						
Neutrophils	4/17 (23.5)		9/17 (52.9)		21/23 (87.5)	
Hemoglobin	0/17		6/17 (35.3)		11/23 (45.8)	
Platelets	2/17 (11.8)		12/17 (70.6)		22/23 (91.7)	
ALT	0/17		3/17 (17.6)		4/22 (18.2)	
AST	0/17		3/17 (17.6)		2/20 (10.0)	
Total Bilirubin	1/17 (5.9)		0/15		0/21	

AEs - adverse events, ALL - acute lymphoblastic leukemia, ALT - alanine aminotransferase, AML - acute myeloid leukemia, AP - accelerated phase, AST - aspartate aminotransferase, BP - blast phase, CML - chronic myeloid leukemia, CP - chronic phase, Ph+ - Philadelphia chromosome positive, Ph- - Philadelphia chromosome negative, SAEs - serious adverse events

Two subjects (both in Stratum 4) with other co-morbidities, had dose-limiting toxicities. One subject developed Grade 4 anaphylaxis 5 hours after the first dose of study drug (60 mg/m^2) and the event resolved the same day. This resulted in discontinuation of dasatinib therapy and discontinuation from study. The other subject (120 mg/m^2 dose cohort), who had a platelet count of 16 x 10^9/L developed an upper GI hemorrhage (Grade 3) on Day 6 that resolved on Day 11 of the study. This event led to interruption of dasatinib dosing. A maximum tolerated dose was not established for any strata on this study.

Rates of Adverse Events, Serious Adverse Events and discontinuation from Therapy

A total of 38 subjects died: 3 (18%), 12 (71%), and 23 (96%) in Strata 1, 2/3, and 4, respectively; however, none of the deaths were considered by the investigator to be related to study therapy. Most were related to disease progression and infections.

Drug-related SAEs were reported in 12%, 29% and 33% of subjects in Strata 1, 2/3, and 4, respectively. With the exception of thrombocytopenia, which was reported in 2 subjects (12%) in Stratum 2/3, all other drug-related SAEs were reported by 1 subject each per stratum.

There were no drug-related AEs leading to discontinuation of dasatinib reported in Strata 1 and 2/3. Two (8%) subjects in Stratum 4 had drug-related AEs leading to discontinuation of dasatinib. One subject (previously mentioned in Section 5) in the 60 mg/m^2 dose cohort (with a history of allergies) had Grade 4 anaphylaxis 5 hours after the first dose of dasatinib (60 mg/m^2). The other subject in the 100 mg/m^2 dose cohort (with no reported medical history of allergies) had an SAE of urticaria (Grade 2).

Drug-related non-hematologic AEs reported by ≥ 10% of subjects in any treatment group include the following: headache, nausea, diarrhea, rash, pain in extremity, mouth ulceration, vomiting, arthralgia, back pain, fatigue, malaise, peripheral edema, pyrexia, pruritus, and urticaria in Stratum 1, diarrhea, nausea, vomiting, rash, headache, fatigue, and epistaxis in Stratum 2/3, and nausea, vomiting, headache, and arthralgia in Stratum 4.

Laboratory Assessments, Vital Signs, ECGs

Most subjects had some degree of cytopenia on study; however, no subject had cytopenia/myelosuppression that led to permanent discontinuation of study drug. No other laboratory abnormalities led to discontinuation of dasatinib therapy.

ECG results were similar among the strata; most subjects had a decline in QTc(F) from baseline in the -60 to 0 msec range (median 7.5 msec for the overall population). No subject had a QTc (F) > 500 msec. Abnormal echocardiogram results were reported for 1 subject with a normal result at baseline; this subject had no associated cardiac AEs associated with the abnormal results and subsequently had normal echocardiogram results. Two subjects with abnormal echocardiogram results at baseline also had abnormal results on study. There were no discontinuations of dasatinib therapy because of abnormal ECG or echocardiogram results.

Adverse Events and Laboratory Measurements of Special Interest

Adverse events (AEs) of special interest in the dasatinib program were examined either because of their association with dasatinib in the currently approved indications, because they are recognized events in other agents within this drug class, or because safety data from nonclinical and clinical studies warranted careful evaluation. AEs of special interest include fluid retention, cardiac disorders, diarrhea, nausea/vomiting, rash, bleeding events, hypersensitivity, and hearing loss.

Drug-related severe (Grade 3, none were Grade 4) AEs of special interest, were uncommon, manageable, and generally did not lead to discontinuation of dasatinib. In this study, 7 subjects had drug-related Grade 3 AEs of special interest; this includes

- Stratum 2/3:
  - bleeding event (n = 1), Grade 3 epistaxis on Day 57 that resolved in 2 days. The subject was thrombocytopenic with a platelet count of 20 x 10^9 c/L on Day 58.
- 6 subjects in Stratum 4:
  - rash (n = 2)
  - bleeding event (n = 1), Grade 3 upper GI hemorrhage on Day 6 that resolved on Day 12. A platelet count was not available on Day 6; the platelet count on Day 8 was 52 x 10^9 c/L. This subject also had Grade 3 drug-related nausea.
  - pleural effusion (n = 1)
  - vomiting (n = 1)
  - hypocalcemia (n = 1)

Importantly, no pediatric subjects experienced pulmonary arterial hypertension during this trial, including none of the 13 subjects treated for more than one year with dasatinib.

Tests to monitor growth and development and bone metabolism were added to the study as mandatory protocol procedures; however, at the time these tests were added, only 18 of the 58 subjects were either on treatment or in follow-up. Because of the limited amount of data available at the time of database lock for the CA180018 clinical study report and the limited follow-up, no definitive conclusions can made on the effect of dasatinib therapy on growth in pediatric subjects, however, preliminary data do not demonstrate a negative impact on growth and bone mineral metabolism. In CA180018, data for long-term growth assessment continues to be collected.

Assessors comment

The data presented showed a safety profile that was manageable in pediatric subjects with leukemia.

No unexpected adverse events were observed.

Pharmacokinetics

Plasma PK data were available for 53 subjects. Each subject could have 1, 2 or 3 plasma PK profiles sampled, depending on the number of times the dose of dasatinib was escalated. CSF PK data were available for 9 subjects.

Pharmacokinetic Parameters of Dasatinib in Plasma - Effect of Age and Dasatinib Dose

Dasatinib was rapidly absorbed in pediatric subjects with relapsed or refractory leukemia. Mean Tmax was observed between 0.5 and 6 hours. Mean T-HALF ranged from 2 to 5 hours across all dose levels and age groups. High inter-subject variability was observed in the PK parameters of pediatric subjects.

The geometric means of dose-normalized (DN) dasatinib Cmax, AUC(0-T), and AUC(INF) appeared to be similar between children and adolescents. At both the 100 and 120 mg/m2 dose levels, PK parameters were available from one subject in the infants and toddler age group. It is difficult to compare the PK of dasatinib in the infant and toddler age group with children and adolescents due to insufficient sample size in the infant and toddler age group.

In post hoc analyses, the geometric means of dose-normalized dasatinib Cmax, AUC(0-T) and AUC(INF) appeared not to be statistically different between children and adolescents at the different dose levels.

Pharmacokinetic Parameters of Dasatinib by Formulation

There were two dosage forms administered to subjects in this study: tablets and dispersed tablets. Subjects received their dasatinib dose as tablets (supplied as 5, 20, and 50 mg strengths) if they were able to swallow tablets. To permit administration in young children who were unable to swallow tablets, the dasatinib tablets were dispersed into 30 mL lemonade or orange juice or apple juice prior to dose administration. The overall median Tmax was 0.5 hour shorter for the dispersed tablet compared with the tablet formulation. PK parameters were available from only one adolescent who received the dispersed tablet; hence dasatinib exposure from the two dosage forms was compared in children group only. In a post-hoc statistical analysis comparing the exposure of dasatinib in children given tablets or dispersed tablets, no evidence of a difference between formulations could be seen in the children group. However, the relatively wide confidence intervals of the slope for the power models were obtained for all PK parameters.

Pharmacokinetic Results in Cerebral Spinal Fluid

The mean 4 hour post-dose CSF concentration of dasatinib in children and adolescents ranged from 1.0 to 3.8 ng/mL, whereas the mean dasatinib plasma concentrations at the same time point ranged from

38 to 88 ng/mL in the same groups of subjects. Hence, in pediatric subjects, the concentrations of dasatinib in CSF at 4 hours post-dose are 1% - 5% of the concentration in plasma. Of the 32 CSF samples analyzed from 9 subjects, 21 samples had measurable concentrations of dasatinib, none had detectable concentrations of BMS-582691, and 2 samples had detectable concentrations of BMS-606181.

Assessors comment

The pharmacokinetic data submitted showed that dasatinib was rapidly absorbed in paediatric subjects with relapsed or refractory leukemia and that administration of dasatinib resulted in systemic exposures in terms of Cmax, AUC(0-T), and AUC(INF) that were consistent with dose proportionality in the dose range of 60 to 120 mg/m2. Also, the median Tmax was slightly shorter for the dispersed tablet compared with the tablet formulation. No statistical difference in Cmax, AUC(0-T), and AUC(INF) was observed between the tablet and the dispersed tablet.

Rapporteur's overall conclusion and recommendation

Data for efficacy, safety and PK testing dasatinib 60 and 80 mg/m^2 QD in a paediatric population with Ph+ leukemias showed a favorable benefit risk profile. But additional studies will be conducted to further support a once daily dosing in pediatric Ph+ CML and ALL.

It can be agreed that based on the data submitted the recommended dasatinib dose for future Phase 2 studies in paediatric subjects with Ph+ leukemias will be 60 mg/m^2 QD for subjects with CP-CML and 80 mg/m^2 QD for subjects with Ph+ ALL or AP/BP-CML.

Recommendation

X **Fulfilled** – No further action required

Additional clarifications requested

Not applicable