27 January 2022
EMA/119741/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sprycel

dasatinib

Procedure no: EMEA/H/C/000709/P46/048

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

On 16 November 2021, the MAH submitted an addendum to a completed paediatric study for Sprycel, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study No. CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia is a stand alone study.

Please refer to the CA180372 procedure (EMEA/H/C/000709/II/0059) opinion given in February 2019 for any details for the assessment. The study was the main study in approving Sprycel for the paediatric ALL indication.

Since the Final CSR, data from follow-up visits have been collected. Subjects were followed and assessments were performed annually for maximally 7 years (2 years of treatment + 5 years after completion of treatment) for survival follow-up and bone growth/maturation exploratory endpoints.

The purpose of the CSR Addendum 01, hereby submitted, is therefore to present cumulative LTGD data for a maximum of 7 years and updated overall survival (OS) for study CA180372. The last patient last visit (LPLV) was 01-Jun-2021 and the final DBL for Addendum 01 was 21-Jul-2021.

2.2. Information on the pharmaceutical formulation used in the study

Filmcoated tablets

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted an addendum to a final report for:

- Study No. CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia.

2.3.2. Clinical study

Study No. CA180372: A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia

Description

Methods

CA180372 was a Phase 2, open-label, single-arm and historically-controlled study in which eligible children and adolescents (> 1 to < 18 years of age) with newly diagnosed Ph+ ALL were treated with dasatinib (Sprycel) added to successive blocks of standard multiagent chemotherapy (AIEOP-BFM ALL 2000 regimen) for a maximum duration of 2 years. Subjects began frontline induction chemotherapy (Block IA) prior to enrollment in this study based upon the investigator's institutional standard of care. Subjects with confirmed Ph+ ALL were enrolled in the study, and at Day 15 dasatinib treatment began and continued without planned interruption until the completion of therapy (102 weeks). Initially, at least 75 pediatric patients (> 1 year and < 18 years old) were planned to be treated with dasatinib and evaluable for the primary endpoint, including at least 20 pediatric subjects evaluable for the primary endpoint in each of the following age ranges: 1 to less than 12 years and 12 to less than 18 years.

Dasatinib was orally delivered as a tablet, as a dispersed tablet, or as a suspension from a powder (powder for oral suspension (PFOS)) at a dose of 60 mg/m2 daily.

A total of 109 subjects were enrolled and 106 subjects were treated with dasatinib (81 subjects received dasatinib in the tablet form exclusively and 25 subjects received either tablet and/or PFOS).

Please refer to the CA180372 procedure (EMEA/H/C/000709/II/0059) opinion given in February 2019 for any details for the study and the overall assessment of the data.

Results

Efficacy results

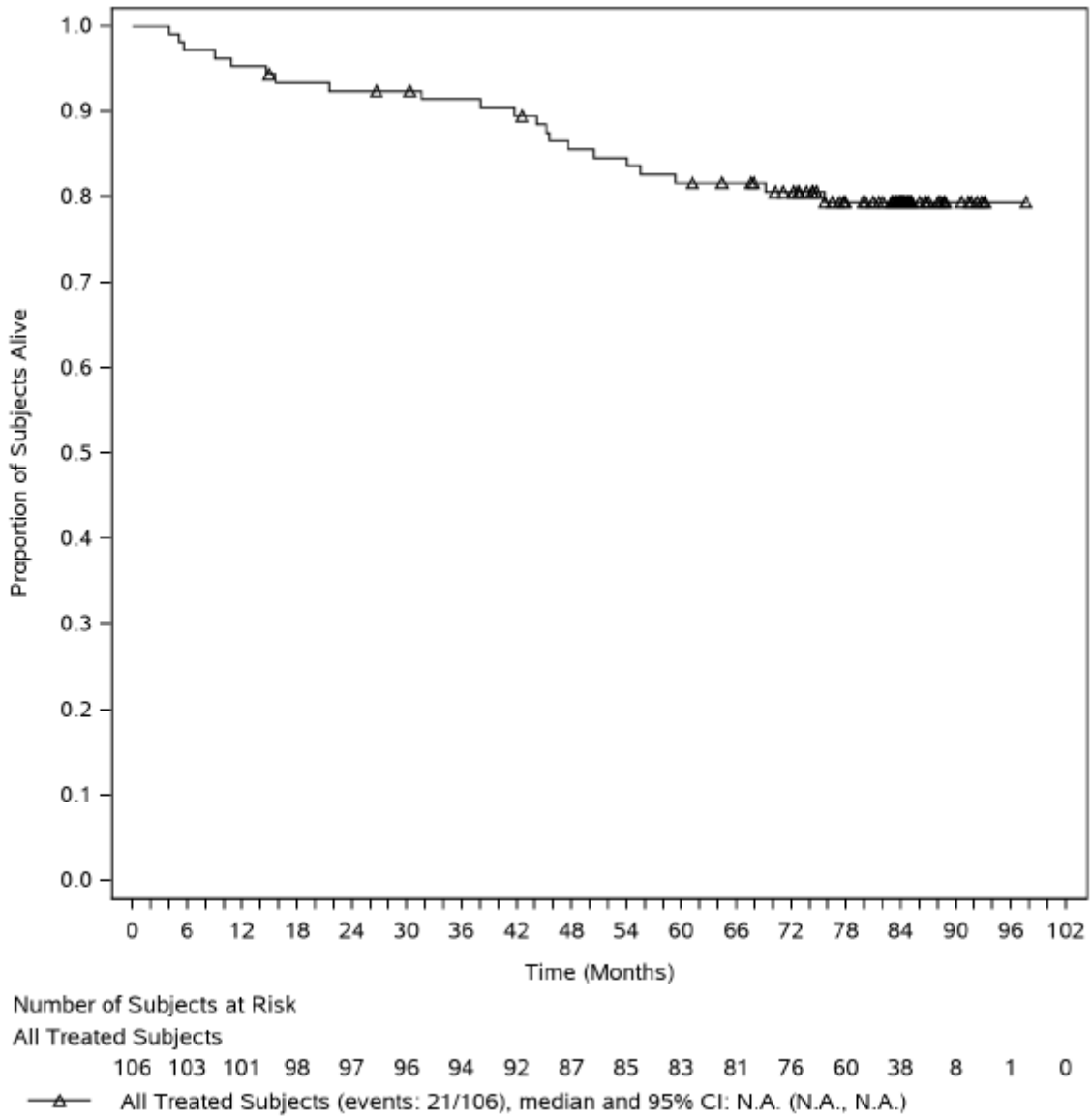
In the presented data package updated OS data, based on 5 year follow up since last dose of study medication is provided.

Overall, 21/106 (19.8%) subjects have died. Median OS was not reached. The K-M estimate of 7-year (84 month) OS in all subjects treated with dasatinib plus chemotherapy was 79.4% (95% CI: 70.1, 86.1) (Table 4). However, some subjects completed follow-up as per protocol with a total duration of less than 7 years because they completed the required 5 years of follow-up after last dose, after a treatment period shorter than 2 years. The KM estimate of 6-year (72 month) OS 80.6% (95% CI: 71.6, 87.0) and 5-year (60 month) 81.6% (72.7, 87.9) represents more robust estimates.

Table 4: Kaplan-Meier Estimates of Overall Survival-All Treated Subjects

	Tablet Only N = 81	PFOS Used N = 25	Total N = 106
# DEATHS / # SUBJECTS (%)	15/81 (18.5)	6/25 (24.0)	21/106 (19.8)
MEDIAN OS (MONTHS) (95% CI)	N.A.	N.A.	N.A.
OS RATE (95% CI)			
6-MONTH	97.5 (90.5, 99.4)	96.0 (74.8, 99.4)	97.2 (91.5, 99.1)
NO. AT RISK	79	24	103
12-MONTH	96.3 (89.0, 98.8)	92.0 (71.6, 97.9)	95.3 (89.0, 98.0)
NO. AT RISK	78	23	101
18-MONTH	95.1 (87.4, 98.1)	88.0 (67.3, 96.0)	93.4 (86.6, 96.8)
NO. AT RISK	76	22	98
24-MONTH	93.8 (85.8, 97.4)	88.0 (67.3, 96.0)	92.4 (85.4, 96.1)
NO. AT RISK	75	22	97
36-MONTH	92.5 (84.1, 96.6)	88.0 (67.3, 96.0)	91.5 (84.2, 95.5)
NO. AT RISK	72	22	94
48-MONTH	84.7 (74.7, 91.0)	88.0 (67.3, 96.0)	85.6 (77.2, 91.0)
NO. AT RISK	65	22	87
60-MONTH	82.1 (71.7, 89.0)	80.0 (58.4, 91.1)	81.6 (72.7, 87.9)
NO. AT RISK	63	20	83
72-MONTH	82.1 (71.7, 89.0)	75.8 (53.8, 88.3)	80.6 (71.6, 87.0)
NO. AT RISK	59	17	76
84-MONTH	80.6 (69.8, 87.8)	75.8 (53.8, 88.3)	79.4 (70.1, 86.1)
NO. AT RISK	30	8	38

Figure 6.1-1: Kaplan-Meier Plot of Overall Survival - All Treated Subjects



Source: Figure S.5.3.1

Safety results

The submitted addendum provides results of assessments of cumulative growth and development data collected throughout the study and during the period up to 5 years of follow-up since last dose of study medication performed annually. The majority of the data were collected while subjects were off treatment. Follow-up of subjects treated with dasatinib in combination with chemotherapy was collected after the conclusion of the study to monitor these trends.

Disposition and Baseline/Demographic Characteristics:

A total of 106 subjects were treated with dasatinib. The follow-up period has completed.

A total of 78 (73.6%) subjects completed the study treatment period and the primary reason for subjects not completing the treatment period was due to 'other' reason (such as physician decision) for 9 (8.5%) subjects. Six subjects died during the treatment or HSCT phase, leaving 100 subjects to

enter the follow-up phase. All 100 subjects who entered follow-up have discontinued the study. Seventy subjects (70.0%) completed follow-up.

Bone Growth and Development Assessments

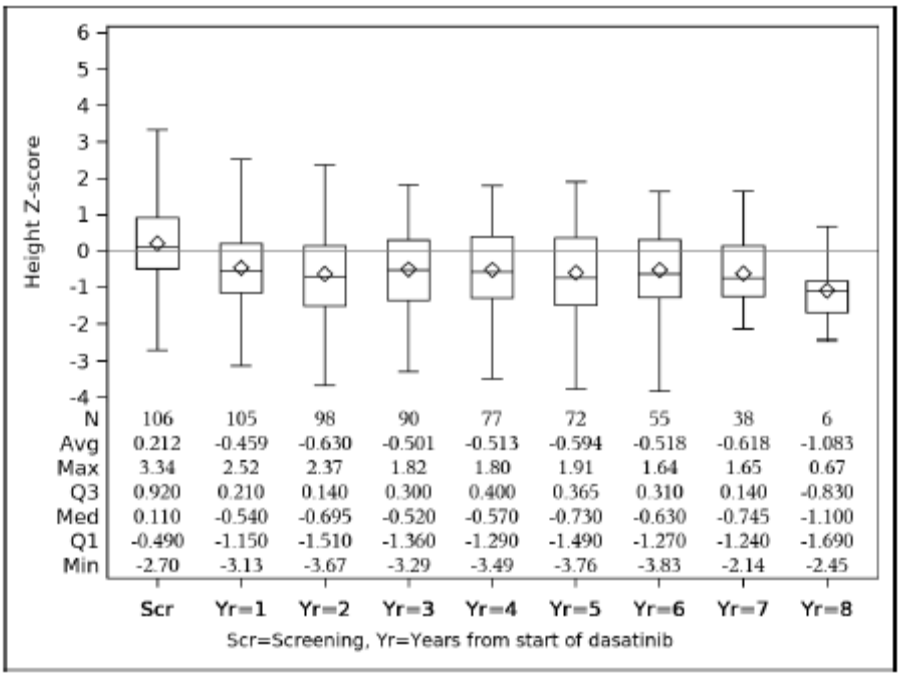
Long-term growth and development assessments were performed for up to 5 years post-treatment. Changes from baseline in height, weight, and BMI were described using standard international units, Z-scores, and percentile shift frequency.

Height

The median height remained above the 15th percentile throughout the duration of the study, but there was a downward trend over time compared to baseline in height z-score in pediatric subjects treated with dasatinib+chemotherapy. Mean (SD) and median (range) baseline z-scores for height (n=106) were 0.21 (1.158) and 0.11 (-2.7, 3.3).

The median decrease of height z-score at 1 year was -0.62 (n=105) and -0.82 at year 2 (n=98). The average z-scores remained fairly constant, varying between -0.6 and -0.5 through year 7, indicating that height values did not completely recover over time after discontinuation of therapy. However, the sample size decreased over time, leading to increased variability at the later time points. Figure 7.2.1.1-1 presents box plots of height z-scores over time, for all treated subjects.

Figure 7.2.1.1-1: Box Plots of Height Z-scores over Time-All Treated Subjects



Periods are relative to start of dasatinib.
Both on-treatment and off-treatment assessments are included.
Z-Score for height is available for participants <= 19 years old (up to age 228 completed months).
Source: Figure S.7.1.1

In 26 subjects, some alterations in height pattern have been observed:

• 7 subjects entered the study with low z-scores and had a sustained percentile <5th during treatment and follow-up.

• 8 subjects had a decrease in z-scores below <5th percentile during therapy and/or follow-up period, followed by a later catch-up to values within 10th-97th percentile.

• 11 subjects entered the study with height z-scores values within 10th-97th percentile, but an evident slow of growth was observed after initiation of therapy, with values dropping close to or below the 5th percentile. 4 of these subjects had an initial decline <5th percentile during the follow up.

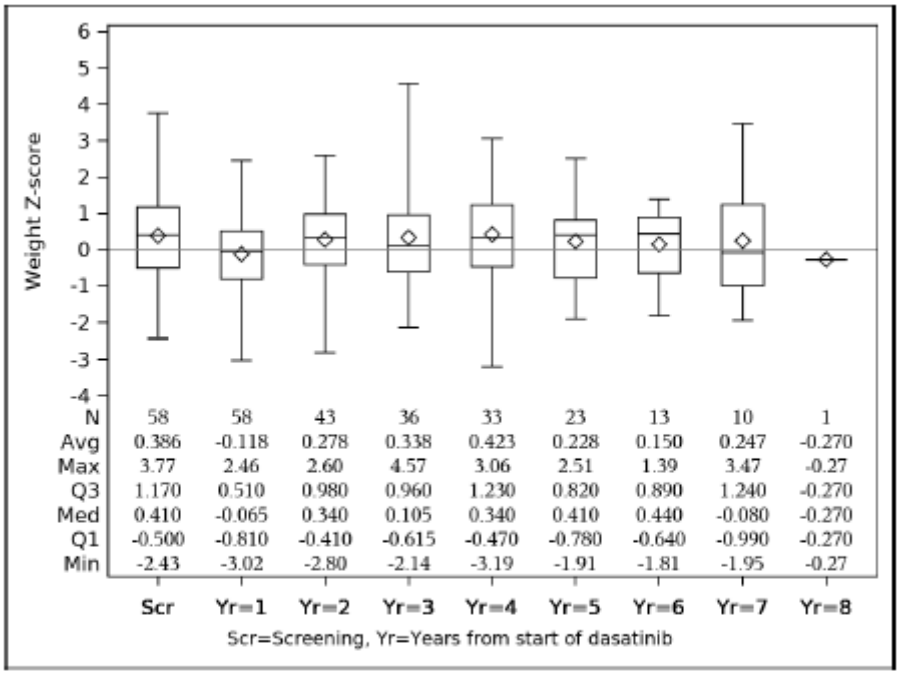
Weight

The z-score for weight was calculated up to 10 years of age only (n = 58), because this indicator may not correctly distinguish between height and body mass in subjects over 10 years old, where many children are experiencing pubertal growth and an increase of weight might incorrectly be considered excessive, when the increase in body mass may be due to an increase in height.

The weight z-scores were similar over time, as shown by little change from baseline in weight z-score and weight percentile shift from baseline. Mean (SD) and median (range) baseline z-scores for weight (n=58) were 0.39 (1.271) and 0.41 (-2.4, 3.8). Mean weight z-score was 0.4 at baseline, dropped by 0.5 in the first year, but at later time points returned to between 0 and 0.5.

Figure 7.2.1.2-1 presents box plots of weight Z-scores over time, for all treated subjects.

Figure 7.2.1.2-1: Box Plots of Weight Z-scores over Time-All Treated Subjects



Periods are relative to start of dasatinib.
Both on-treatment and off-treatment assessments are included.
Z score for weight is available for children <=10 years old (120 completed months)
Source: Figure S.7.1.4

BMI

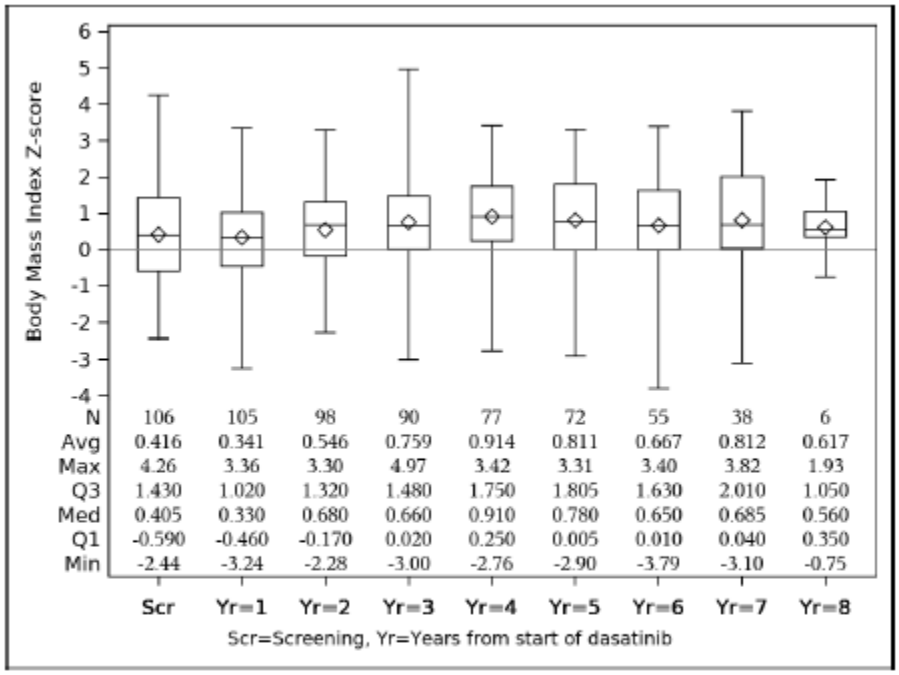
The BMI z-score is standardized by age and gender and calculated for subjects up to the age of 19 years old.

At baseline, the mean BMI for all subjects was 18.2 kg/m2 (range: 12.9 to 30.9 kg/m2). The mean BMI for all subjects gradually increased with time as expected for subjects treated with dasatinib+chemotherapy and during follow-up.

The BMI z-scores remained fairly stable over time, varying between 0.6 and 0.9 with no apparent downward or upward trend. For all treated subjects mean (SD) and median (range) baseline z-scores for BMS (n=106) were 0.42 (1.295) and 0.41 (-2.4, 4.3), respectively.

Figure 7.2.1.3-1 presents box plots of height Z-scores over time, for all treated subjects.

Figure 7.2.1.3-1: Box Plots of BMI Z-scores over Time-All Treated Subjects



Periods are relative to start of dasatinib.
Both on-treatment and off-treatment assessments are included.
Z-Score for BMI is available for participants <= 19 years old (up to age 228 completed months)
Source: Figure S.7.1.7

Subjects in the <5th-75th percentile baseline BMI category increased their BMI while on study and those with baseline >75th remained unchanged or dropped their BMI percentile. This observation was based on change from baseline in BMI z-score results and on the BMI percentile shift from baseline tabulation.

Bone Age and Pubertal Status (Tanner Stage)

Bone age, a measure of skeletal maturity, and Tanner stage, a measure of pubertal maturation, were recorded on an annual basis. The values were correlated with what is expected based on the subjects' chronologic age). Shifts over time from the baseline Tanner Stage distribution do not suggest any clinical abnormalities in pubertal development associated with dasatinib+chemotherapy.

Growth Factors

Insulin-like growth factor 1 (IGF-1) and IGF binding protein-3 (IGFB-3) subunit are required for maximal growth in children. The changes in IGF-1 and IGFB-3 levels over time were not indicative of any clinical abnormality associated with dasatinib+chemotherapy.

Declines in IGF-1 levels were reported in 25 subjects during therapy. The IGF-1 levels were low at screening for 13 subjects and baseline values were missing for 7 subjects. The values returned to within normal levels during follow up for these 20 subjects. Low IGF-1 values were reported at screening, during treatment and follow up periods in 3 subjects. The baseline IGF-1 levels were normal in 2 subjects at study entry, declined during the treatment period and returned to within normal levels during follow up.

Hormone Levels

Thyroid stimulating hormone (TSH) levels are measured to test the overall function of the thyroid, a gland that controls metabolism and hormone regulation in the body. Free thyroxine (T4) is used to

assess thyroid function. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) are produced by the pituitary gland and regulate the development, growth, pubertal maturation, and reproductive processes of the body. Overall, the changes in hormone levels over time were not indicative of any clinical abnormality associated with dasatinib+chemotherapy.

Most subjects had TSH, Free T4, FSH, and LH levels that were close to or within normal ranges for age.

Free T4 and TSH results for 7 subjects were compatible with a diagnosis of hypothyroidism, but only for 1 subject, substitutive therapy was initiated. In 3 subjects, the lab abnormalities were reported at the last follow up visit and there was no information of clinical diagnoses confirmation or whether substitutive therapy started. In 3 other subjects, the values recovered to normal levels at the next visit.

High FSH and LH values were reported for 6 subjects and these values remained elevated throughout the course of the study for 3 of these subjects. For 1 subject, the elevations were isolated occurrences that returned to within normal range and for 2 subjects, the increase levels were reported at the last study visit with no additional confirmation measurements. In addition, 4 subjects had high FSH levels with normal LH values; only in 1 out of the 4 subjects, the elevation remained throughout the study

Long-term Bone Metabolism

Urinary N-Telopeptide and Bone ALP

Long-term growth and development and bone metabolism assessments, including urinary N-terminal telopeptide of type I collagen (NTx) (marker of bone resorption and demonstrated to be useful in evaluating bone growth in children) and bone alkaline phosphatase (ALP) were collected for the subjects that continued in follow-up.

High NTx values were reported for 9 subjects during the study. For 8 of these subjects, the elevations in NTx were isolated occurrences that returned to within the normal range in subsequent visits (Table S.7.10.11). In only 1 subject, the NTx values remained elevated throughout the study after starting therapy.

Bone alkaline phosphatase levels at baseline min - max in 61 subjects ranged from 14.6 - 115.2 U/L. Generally, bone alkaline phosphatase over time increased but were the elevations were not indicative of any clinical abnormality associated with dasatinib+chemotherapy treatment.

Bone Densitometry

In addition to the other growth parameters, dual X-ray absorptiometry (DXA) scans were performed. A bone mineral content or density z-score of more than 2 standard deviations below expected (ie less than -2) should be considered 'low for age'.

There were approximately 40% of subjects that had at least 1 z-score considered to be "low for age" per the definition. 99 out of 106 subjects had at least one DXA scan assessment done post-baseline, however, most patients missed at least one data point. 35 subjects had at least 1 post-baseline z-score $\leq$ -2. In 11 subjects, the z-scores decreased below $\leq$ -2 and recovered to $\geq$ -2 values at subsequent assessments and in 24 subjects, the z-score remained $\leq$ -2 at the last study visit.

Based on bone densitometry scans of the lumbar spine L1-L4 region, total body less head, total hip, and femoral neck, the assessments did not suggest any relevant findings associated with dasatinib + chemotherapy.

Serum Electrolytes

Serum electrolytes (sodium, potassium, magnesium, chloride, and phosphorus) were assessed periodically through the treatment period and up to 5 years follow-up. The serum electrolyte results are consistent with the results presented previously in the Final CA180372 CSR.

2.3.3. Rapporteur´s Discussion and conclusion on clinical aspects

Study CA180372 which evaluated the addition of dasatinib to successive blocks of standard multiagent chemotherapy in children and adolescents with newly diagnosed Ph+ ALL have previously been assessed and led to the extension of indication for the paediatric population (Variation EMEA/H/C/000709/II/0059). This current submission provides cumulative long term growth and development data collected and updated OS.

As summarised by the MAH, subjects treated with dasatinib and chemotherapy had a trend downwards for height. For other LTGD parameters with longer follow-up, results are similar to the ones initially reported in the Final CSR. Weight and BMI mean z-scores in dasatinib-treated subjects were relatively unchanged at the end of the follow-up period compared to baseline. The laboratory parameters associated with LTGD and long-term bone metabolism also did not appear to be impacted by dasatinib+chemotherapy treatment. The decrease in growth velocity during treatment followed by a lack of catch-up has been previously described, with the same degree and pattern of changes as observed with the use of standard chemotherapy and therefore, the addition of dasatinib does not seem to exacerbate the condition. Hormones and other growth parameters measured during this study did not indicate any abnormality that could contribute to this trend in growth retardation. BMI measured showed a slight increase in subjects in this study. This observation should be interpreted in context of an apparent increase in weight for a given height for most patients and therefore, could be a result of relative height loss with normal weight gain, rather than an accelerated weight gain.

This summary and conclusion can be fully endorsed. It is noted that section 4.4 of the SmPC provides this information.

In paediatric trials of SPRYCEL in combination with chemotherapy in newly diagnosed Ph+ ALL paediatric patients after a maximum of 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 1 (0.6%) patient. This case was a Grade 1 osteopenia. Growth retardation has been observed in paediatric patients treated with SPRYCEL in clinical trials (see section 4.8). Monitoring of bone growth and development in paediatric patients is recommended.

Although the MAH has not proposed any updates of the SmPC, it may be considered to revisit this wording in section 4.4 in a future variation, based on the information provided in this dataset. The MAH has followed up on this issue and proposed an addition to the text and this is considered an acceptable proposal.

In study CA180372 Overall survival was included as an exploratory objective. It is agreed that based on the updated numbers in this submission dasatinib in combination with intensive multi-agent chemotherapy continues to show long term OS benefit in pediatric patients newly diagnosed with Ph+ ALL, with 79.4% of subjects alive with a follow-up of 5 years after last dose. The current SmPC reflects the data on the primary/secondary endpoints and is considered adequate.

3. Overall conclusion and recommendation

The submitted data do not raise any concerns as to the positive benefit risk for the use of dasatinib in the approved indications. The MAH has reconsidered the wording in section 4.4. An acceptable addition has been agreed, and section 4.4 will be updated as follow (**added text**/~~deleted text~~):

4.4 Special warnings and precautions for use

[…]

In paediatric trials of SPRYCEL in combination with chemotherapy in newly diagnosed Ph+ ALL paediatric patients after a maximum of 2 years of treatment, treatment-related adverse events associated with bone growth and development were reported in 1 (0.6%) patient. This case was a Grade 1 osteopenia.

Growth retardation has been observed in paediatric patients treated with SPRYCEL in clinical trials (see section 4.8). **After a maximum of 2 years of treatment, a downward trend in expected height has been observed, at the same degree as observed with the use of chemotherapy alone, without impacting expected weight and BMI and no association with hormones abnormalities or other laboratory parameters.** Monitoring of bone growth and development in paediatric patients is recommended.

[…]

The implementation of the above agreed wording should follow closure of this P46 procedure within the relevant regulatory variation.

PAM P46-048 is therefore considered fulfilled.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Sprycel Active substance: Dasatinib

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia.	CA180372	2 June 2021	16 November 2021