EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2025
EMADOC-1700519818-2348379
Human Medicines Division

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

Sprycel

Dasatinib

Procedure no: EMA/PAM/0000291073

Note

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

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned Date**	**Actual Date**
☐	CHMP Rapporteur AR	20 October 2025	16 October 2025
☐	CHMP comments	3 November 2025	N/A
☐	Updated CHMP Rapporteur AR	6 November 2025	N/A
☐	Request for Supplementary Information	13 November 2025	13 November 2025
☐	Submission deadline	18 November 2025	18 November 2025
☐	Start date	19 November 2025	19 November 2025
☐	CHMP Rapporteur AR	26 November 2025	28 November 2025
☐	CHMP comments (extended)	3 December 2025	3 December 2025
☐	Updated CHMP Rapporteur AR	4 December 2025	4 December 2025
☒	CHMP Opinion	11 December 2025	11 December 2025

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1. Introduction

On 28 July 2025, the MAH submitted 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 CA180226 is a stand-alone study.

Dasatinib is approved in the EU (and US) for the treatment of paediatric patients with Ph+ CML in CP and newly diagnosed Ph+ ALL in combination with chemotherapy.

As part of the approval, long-term safety post marketing commitments in paediatric subjects were included in the dasatinib EU-RMP3 to monitor growth, development, and bone mineral metabolism disorders through:

- Five-years post-treatment follow-up in CML and Ph+ ALL paediatric studies (CA180018, CA180204, CA180226, and CA180372)
- Growth and development assessments in Study CA180226, specifically for subjects on treatment in Cohort 3, that enrolled subjects < 11 years old, continuing until 18 years of age

Long-term follow-up (FU) data for studies CA180018, CA180204, and CA180372 for clinical evaluation of disorders of growth and development and of bone mineral metabolism in paediatric subjects were submitted and assessed by the EMA, fulfilling the commitment for these 3 studies.

Therefore, the first part of the commitment was removed from the dasatinib RMP.

Long-term FU data for Phase 2 study CA180226 (EudraCT number 2008-002260-33) assessing dasatinib treatment in children and adolescents with CML or with Ph+ leukaemias resistant or intolerant to imatinib, was collected from Cohort 3 (included subjects < 11 years old, continuing through 18 years old). At the time of ad hoc analysis (cutoff date: 14-Oct-2022), 5 of the 130 total subjects were still on the study, and the additional long-term safety data to be collected until the last of these subjects reached 18 years of age was not expected to impact the current safety profile. Therefore, the EMA agreed to the MAH proposal to satisfy the RMP commitment and close the study by the first quarter of 2025 with a closeout CSR, as sufficient data on the safety profile of dasatinib had been gathered. The study was completed (LPLV: 27-Jan-2025) 5 years earlier than planned based on the revised commitment in the RMP.

2.2. Information on the pharmaceutical formulation used in the study

The formulation used is the authorised presentation of film-coated tablets and powder for oral suspension and thus suitable for the paediatric population.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Cohort 3 of:

Study CA180226 A PHASE II STUDY OF DASATINIB THERAPY IN CHILDREN AND ADOLESCENTS WITH NEWLY DIAGNOSED CHRONIC PHASE CHRONIC MYELOGENOUS LEUKEMIA OR WITH PH+ LEUKEMIAS RESISTANT OR INTOLERANT TO IMATINIB

2.3.2. Clinical study

CA180226 is a phase II study of dasitinib therapy in children and adolescents with newly diagnosed cronic phase chronic myelogenous leukemia or with PH+ leukemias resistant or intolerant to imatinib

This CA180226 open-label, multi-center, Phase 2 study was designed to help establish the safety and efficacy of dasatinib in children and adolescents with CML who are treatment-naive and in subjects with Ph+ leukaemias who were resistant or intolerant to imatinib. It consisted of 3 cohorts.

Enrolment in Cohort 2 was permanently closed due to poor treatment response rate based on interim analysis and recommendation from DSMB. The primary objectives for Cohort 1 (MCyR rate > 30%) and for Cohort 3 (CCyR rate > 55%) were met. Results from PK sub-study of dasatinib PFOS (90 mg/m2) neither showed clinically relevant safety concerns nor new safety signals reported in paediatric subjects. The exposures were similar to the previous model -predicted PPK exposures in paediatric subjects, providing supporting evidence for the dasatinib PFOS 90 mg/m2 dose justification in paediatric subjects.

Long-term FU until subjects are 18 years old was requested by EU HA, particularly for Cohort 3 (N = 40) in which subjects were < 11 years old when enrolled. In Cohort 3, at the time of an ad hoc analysis (data cutoff: 14-Oct-2022), 10 subjects were still on the study: 8 ongoing on study treatment and 2 in follow up. The MAH submitted a Clinical Overview to the EMA to propose the completion of the study; at the time of CO submission, 2 subjects turned 18 years old and discontinued the study, 3 subjects discontinued study therapy and entered FU, and 5 subjects remained on study drug. The MAH believed that the currently available long-term safety findings were adequately robust to support the safe use of dasatinib in the paediatric population. Therefore, the EMA agreed to the BMS proposal to satisfy the PMR commitment and close the study by quarter 1 of 2025 in view of sufficient data on the safety profile of dasatinib, contingent upon the submission of a final closeout CSR.

The purpose of this closeout abbreviated CSR is to provide the final update on safety and efficacy of dasatinib in Cohort 3 based on the final analysis (LPLV:27-Jan-2025), which will be submitted to the EMA.

Methods

The study consisted of the following periods: screening (within 2 weeks), treatment, safety FU and survival FU (yearly up to 5 years).

Three cohorts of subjects received dasatinib in the following doses and schedules:

- Cohort 1 (N=29): Children and adolescents with CP-CML who were resistant or intolerant to imatinib received dasatinib tablets at 60 mg/m2 QD on a continuous oral regimen.
- Cohort 2 (N=17): Children and adolescents with Ph+ ALL, AP-CML or BP-CML who were resistant or intolerant to, or relapsed after imatinib therapy, received dasatinib tablets at a dose schedule of 80 mg/m2 QD on a continuous oral regimen.
- Cohort 3 (N=84): Children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or PFOS at 72 mg/m2 QD on a continuous oral regimen.

Study CA180226 was initially designed for subjects resistant or intolerant to imatinib and was subsequently amended in December 2009 to add a cohort (Cohort 3) in the treatment-naïve population. Cohort 3 was comprised of 2 sub-cohorts:

- Cohort 3A: tablet at 60 mg/m2 (maximum dose of 100 mg for subjects with higher BSA)
- Cohort 3B: PFOS at 72/90 mg/m2 (maximum dose of 120/150 mg for subjects with higher BSA) for a minimum of 12 months post which subjects continuing in the study were allowed to switch to take dasatinib tablet formulation if they chose. Previous pharmacokinetic studies showed lower bioavailability of dasatinib in PFOS formulation than tablet formulation. Hence, a higher dose of dasatinib was considered for PFOS formulation than for tablet formulation.

Subjects were treated for a minimum of 24 months. A single dose escalation was allowed for subjects who were tolerating their therapy but did not achieve an acceptable response. Dose reductions were to be performed for excess toxicity.

Objective(s)

Outcomes/endpoints

Table 2-1: Cohort 3 Objectives and Endpoints

Objective	Endpoint	Endpoint Description	Analysis
Primary			
To estimate CCyR rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment-naive	proportion of all treated subjects who achieve a CCyR on study	CyR criteria was based on the percentage of Ph+ metaphases among ≥ 20 analyzed metaphases in BMA. CyR category - % Ph+ metaphases in BMA: CCyR 0%, PCyR > 0 to 35%, Minor > 35 to 65%, Minimal > 65 to 95%, and None > 95 to 100%. - MCyR was defined as CCyR or PCyR	Section 7.5.2 of SAP
Secondary			
To assess the safety and tolerability of dasatinib in children and adolescents with newly diagnosed Ph+ CP-CML who were treatment-naive.	Incidence, severity, and relationship of death, AEs, SAEs, AE leading to discontinuation, AESI, late toxicities	AEs were graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Frequencies were calculated for the on-study and post-treatment period. Late toxicities were defined as dasatinib-related AEs with an onset date > 30 days of the last dose. Long-term safety assessment evaluated the effects of dasatinib therapy on growth and development and bone metabolism.	Section 7.6 of SAP
To evaluate additional measures of efficacy in children and adolescents with newly diagnosed CP-CML or subjects with relapsed or refractory Ph+ leukaemias treated on a given regimen of dasatinib including:			
Duration and time to MCyR	Proportion of all treated subjects who achieve a complete or partial CyR on study	For details see above	Section 7.5.2 of SAP
Duration and time to CHR	Proportion of all treated subjects who achieve a confirmed CHR on study	Cohorts 3 (NCP): WBC < 10,000/mm³, Platelet count < 450,000/mm³, Peripheral blood basophils < 5%, no blasts or promyelocytes (myelocytes + meta-myelocytes) < 5% in peripheral blood, and no evidence of extramedullary leukaemia, including no splenomegaly or hepatomegaly	Section 7.5.1 of SAP
PFS	Proportion of achieving PFS	PFS was defined as time from the first dosing date until the time progressive disease was first documented by the investigator or death. Assessed using KM technique	Section 7.5.4 of SAP

Table 2-1: Cohort 3 Objectives and Endpoints

Objective	Endpoint	Endpoint Description	Analysis
DFS	Proportion of achieving DFS	DFS defined as time from CCyR until the time progression is first documented by the investigator or death from any cause. Assessed using KM technique	Section 7.5.5 of SAP
OS	Duration of OS	OS was defined as time from the first dosing date until the time of death. Assessed using KM technique	Section 7.5.6 of SAP
Rates of MCyR	Proportion of subjects with MCyR	The rate MCyR at any time was defined as the proportion of all treated subjects who achieve a complete or partial cytogenetic response on study.	Section 7.5 of SAP
Best cytogenetic response	Proportion of subjects with CyR	For details see above	Section 7.5 of SAP
Rates of CHR	Proportion of subjects with CHR	The CHR rate was defined as the proportion of all treated subjects who achieve a confirmed CHR on study.	Section 7.5 of SAP
Rates of MR (assessed by quantitative PCR)	Proportion of subjects with MR	The MR rate was defined as the proportion of all treated subjects who met criteria for MR on study.	Section 7.5 of SAP
To describe the spectrum of the BCR-ABL mutations at baseline, at progression, treatment failure, or end of treatment, and to explore the role of mutations as predictors of response.	Number of subjects with mutation	Treatment failure was defined as progression, death or lack of response	Section 7.7 of SAP
Exploratory			
To describe growth and development and bone mineral content	Assessment of weight, height, BMI, hormones, and bone metabolism suggesting clinical abnormality	Long-term safety assessment was evaluated for the effects of dasatinib therapy on growth and development and bone metabolism.	Section 7.7 of SAP

This CSR presents only Cohort 3 objectives/endpoints. Results from Cohorts 1 and 2 were presented in previous CSRs.[1,2,3]
Source: Protocol (Appendix 16.1.1) and SAP (Appendix 16.1.9)

Efficacy was assessed by cohort and sub-cohort for all treated subjects. Safety of dasatinib was reported for all treated subjects. The effects of dasatinib on growth and development and bone metabolism were assessed annually until age 18. Subjects were followed yearly for survival up to 5 years after treatment discontinuation. LTGD parameters were assessed annually for up to 5 years for subjects discontinuing from study treatment.

Sample size

In Cohort 3, 84 subjects enrolled in the study. The all-treated population set included subjects who received at least one dose of dasatinib.

In Cohort 3 (84 subjects), 51 subjects from Cohort 3A and 33 subjects from Cohort 3B were included in the all treated population set.

Randomisation and blinding (masking)

N/A for an open-label study

Results

Participant flow

Of the 145 subjects enrolled in the study, 84 treatment-naive subjects with CP-CML were treated in Cohort 3. At the time of LPLV (27-Jan-2025), all subjects were off study treatment and off study. Half of the subjects were off study treatment, primarily because they reached the age of 18 years. Around half of the subjects (56%) entered the FU period and 29.8% subjects completed the FU period. The most common reason for not completing FU period was due to other reason: SAE due to drug, reached 18 years of age, PI decision, toxicity FU complete, and progression.

Table 4.1-1: Subject Status Summary for Cohort 3 - All Treated Subjects

	CHRONIC CML		
	NCP-3A	NCP-3B	Total NCP
SUBJECTS TREATED	51	33	84
ON TREATMENT (%)	1 (2.0)[a]	0	1 (1.2)[a]
OFF TREATMENT (%)			
DISEASE PROGRESSION	5 (9.8)	2 (6.1)	7 (8.3)
STUDY DRUG TOXICITY	2 (3.9)	2 (6.1)	4 (4.8)
DEATH	0	0	0
SUBJECT REQUEST TO DISCONTINUE			
STUDY TREATMENT	3 (5.9)	3 (9.1)	6 (7.1)
SUBJECT WITHDREW CONSENT	1 (2.0)	1 (3.0)	2 (2.4)
MAXIMUM CLINICAL BENEFIT	2 (3.9)	3 (9.1)	5 (6.0)
POOR/NON-COMPLIANCE	1 (2.0)	0	1 (1.2)
PREGNANCY	1 (2.0)	0	1 (1.2)
SUBJECT NO LONGER MEETS STUDY			
CRITERIA	3 (5.9)	1 (3.0)	4 (4.8)
ADMINISTRATIVE REASON BY			
SPONSOR	6 (11.8)	3 (9.1)	9 (10.7)
OTHER[bc]	24 (47.1)	18 (54.5)	42 (50.0)
NOT REPORTED	2 (3.9)	0	2 (2.4)
ENTERED FOLLOW-UP	27 (52.9)	20 (60.6)	47 (56.0)
REASON FOR END OF FOLLOW-UP			
COMPLETED	14 (27.5)	11 (33.3)	25 (29.8)
SUBJECT WITHDREW CONSENT	3 (5.9)	2 (6.1)	5 (6.0)
DEATH	0	0	0
LOST TO FOLLOW-UP	0	0	0
OTHER	3 (5.9)	4 (12.1)	7 (8.3)
MISSING - ADMINISTRATIVE			
REASONS IN RUSSIA	3 (5.9)	1 (3.0)	4 (4.8)
NOT REPORTED	4 (7.8)	2 (6.1)	6 (7.1)

[a] This subject was discontinued from the treatment. The data could not be corrected in the database as the site was closed.

[b] In 2019, sites were instructed to stop collecting long-term FU data for subjects who reached 18 years of age. The majority of discontinuations in this cohort were due to subjects reaching the age of 18 years and being transitioned to commercial drug.

[c] Other reasons for discontinuing study treatment were: transitioned to commercially available drug, transitioned to post study drug access, reached 18 years of age, sponsor decision, loss of efficacy /PI decision, suboptimal response, completed the study, closure of country level activity, administer HSCT, 2nd malignancy, poor compliance, and T315I mutation

Source: Table 14.1.1.1

Efficacy results

The primary endpoint of CCyR rate (> 55%) was achieved by 6 months.

The OS was 100% as there was no death.

The PFS rate was 87.7% (77.5%, 93.4%) at 72 months.

The DFS rate was 91.0% (81.1%, 95.9%) at 66 months.

Table 6-1: Cumulative Response Rate in Cohort 3 - All Treated Subjects

Parameters	Cohort 3A (N=51)		Cohort 3B (N=33)		Cohort 3 (N=84)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
By 15 months	49 (96.1)	86.5 - 99.5	30 (90.9)	75.7 - 98.1	79 (94.0)	86.7 - 98.0
By 24 months	49 (96.1)	86.5 - 99.5	30 (90.9)	75.7 - 98.1	79 (94.0)	86.7 - 98.0
At any time	49 (96.1)	86.5 - 99.5	30 (90.9)	75.7 - 98.1	79 (94.0)	86.7 - 98.0
Secondary Objective: MMR Rate						
By 12 months	29 (56.9)	42.2 - 70.7	15 (45.5)	28.1 - 63.6	44 (52.4)	41.2 - 63.4
By 24 months	38 (74.5)	60.4 - 85.7	21 (63.6)	45.1 - 79.6	59 (70.2)	59.3 - 79.7
By 90 months/At any time	46 (90.2)	78.6 - 96.7	25 (75.8)	57.7 - 88.9	71 (84.5)	75.0 - 91.5
MR4 rate						
By 24 months	22 (43.1)	29.3 - 57.8	10 (30.3)	15.6 - 48.7	32 (38.1)	27.7 - 49.3
At any time	32 (62.7)	48.1 - 75.9	17 (51.5)	33.5 - 69.2	49 (58.3)	47.1 - 69.0
CMR Rate						
By 24 months	17 (33.3)	20.8 - 47.9	4 (12.1)	3.4 - 28.2	21 (25.0)	16.2 - 35.6
At any time	25 (49.0)	34.8 - 63.4	11 (33.3)	18.0 - 51.8	36 (42.9)	32.1 - 54.1

Source: Table 14.2.1.1, Table 14.2.1.3, Table 14.2.1.4, and Table 14.2.1.5.

Cytogenetic Response (Primary endpoint)

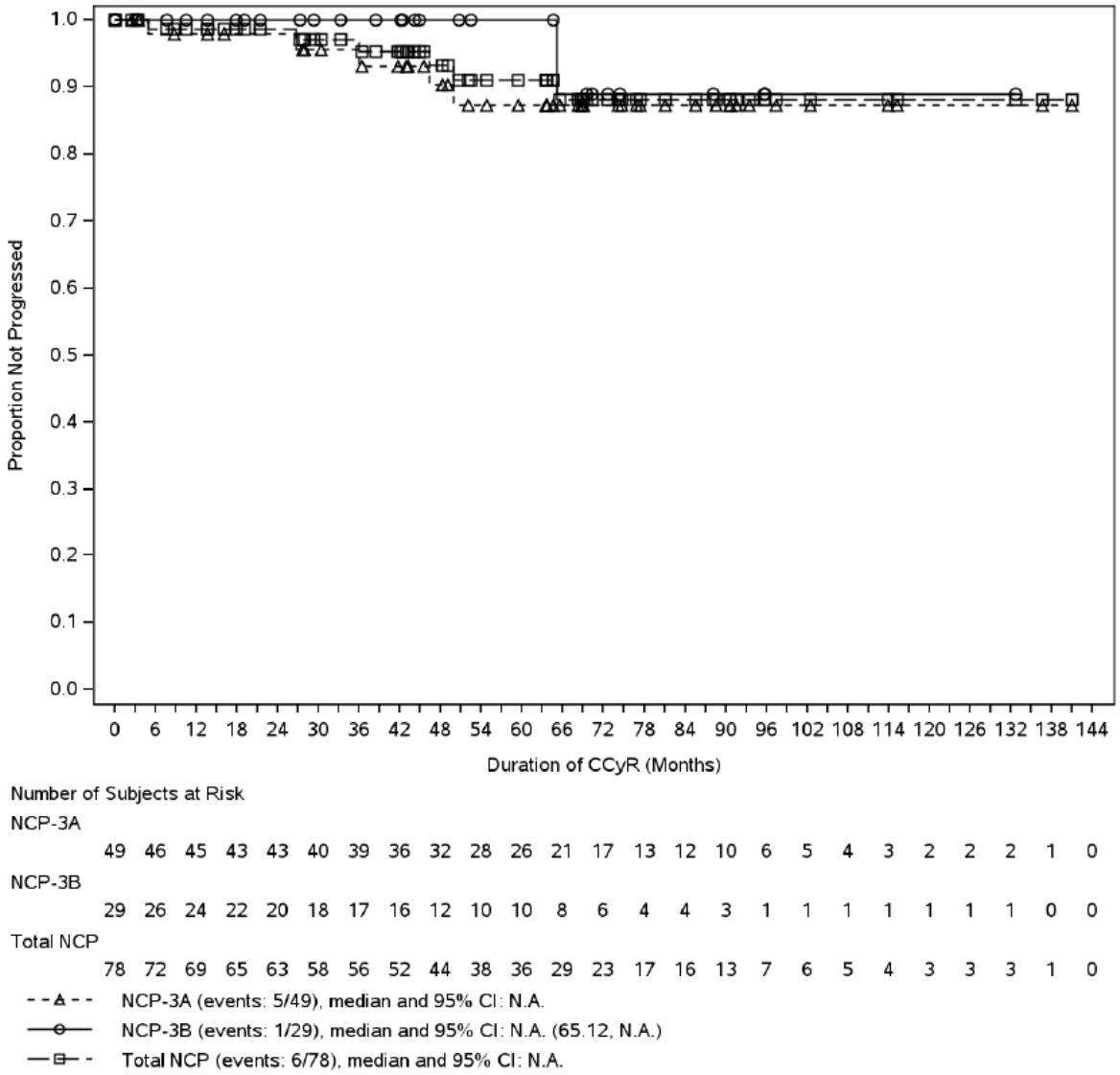
In Cohort 3, the majority (67.9%) of subjects achieved CCyR rate by 6 months (Table 6-1). Most of the subjects achieved CCyR rate by ≥ 12 months which was maintained up to 24 months:

- Cohort 3A: 96.1% subjects by 12 months
- Cohort 3B: 90.9% subjects by 15 months

Cytogenetic testing was not mandated per protocol after Month 24 and was only performed at investigator's discretion.

Progression (defined as transformation, increase of WBC, loss of CHR or loss of MCyR or death) was reported in 6/78 subjects in Cohort 3 with a CCyR at any time (Figure 6.1-1).

Figure 6.1-1: Kaplan-Meier Plot of Duration of CCyR in Cohort 3 (Any Number of Metaphases) - All Treated Subjects who Achieved CCyR by Month 12



Molecular Response (Secondary endpoint)

The majority of subjects in Cohort 3 overall had the MMR p210 BCR-ABL transcript.

Molecular response rate gradually increased over time in Cohort 3. Majority of the subjects achieved MR rate by 72 months which sustained for up to 90 months (Table 6-1):

- Cohort 3A: 64.7% (95% CI: 50.1, 77.6) at 15 months which increased to 90.2% at 51 months
- Cohort 3B: 63.6% (95% CI: 45.1, 79.6) at 21 months which increased to 75.8% at 72 months

MR4 rate gradually increased over time from 6 months in Cohort 3:

- Cohort 3A: 51.0% (95% CI: 36.6, 65.2) by 39 months; majority of the subjects (62.7%) achieved MR4 rate by 114 months
- Cohort 3B: 51.5% (95% CI: 33.5, 69.2) by 72 months

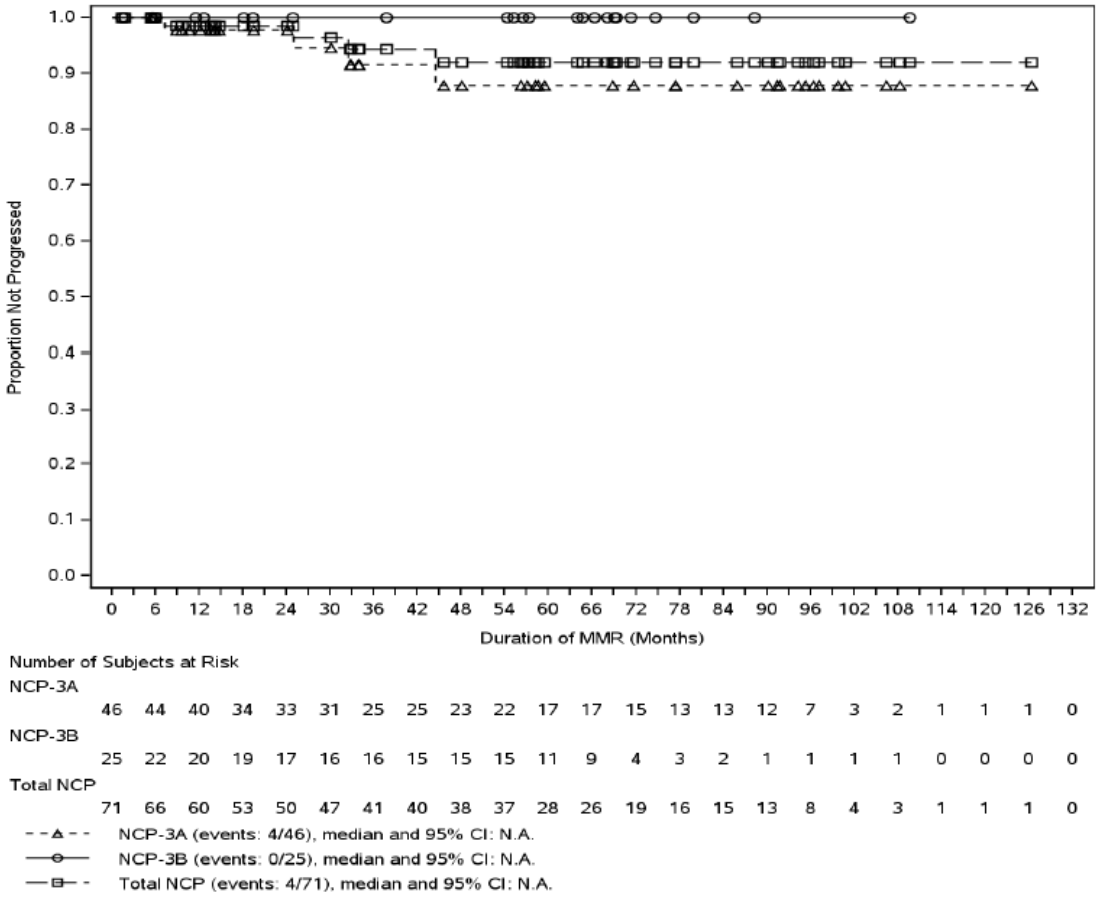
CMR rate gradually increased over time from ≥ 6 months in Cohort 3 which sustained until 90 months (Table 6-1):

- Cohort 3A: 49.0% by 72 months
- Cohort 3B: 33.3% by 78 months

Of the subjects who achieved MMR in Cohort 3 (Figure 6.2-1):

- Cohort 3A: 4 subjects reported loss of response by 42 to 45 months (MMR rate: 87.9% [95% CI: 70.4, 95.3])
- Cohort 3B: No subject reported loss of response

Figure 6.2-1: Kaplan-Meier Plot for Duration of MMR in Cohort 3 - All Treated Subjects who Achieved MMR

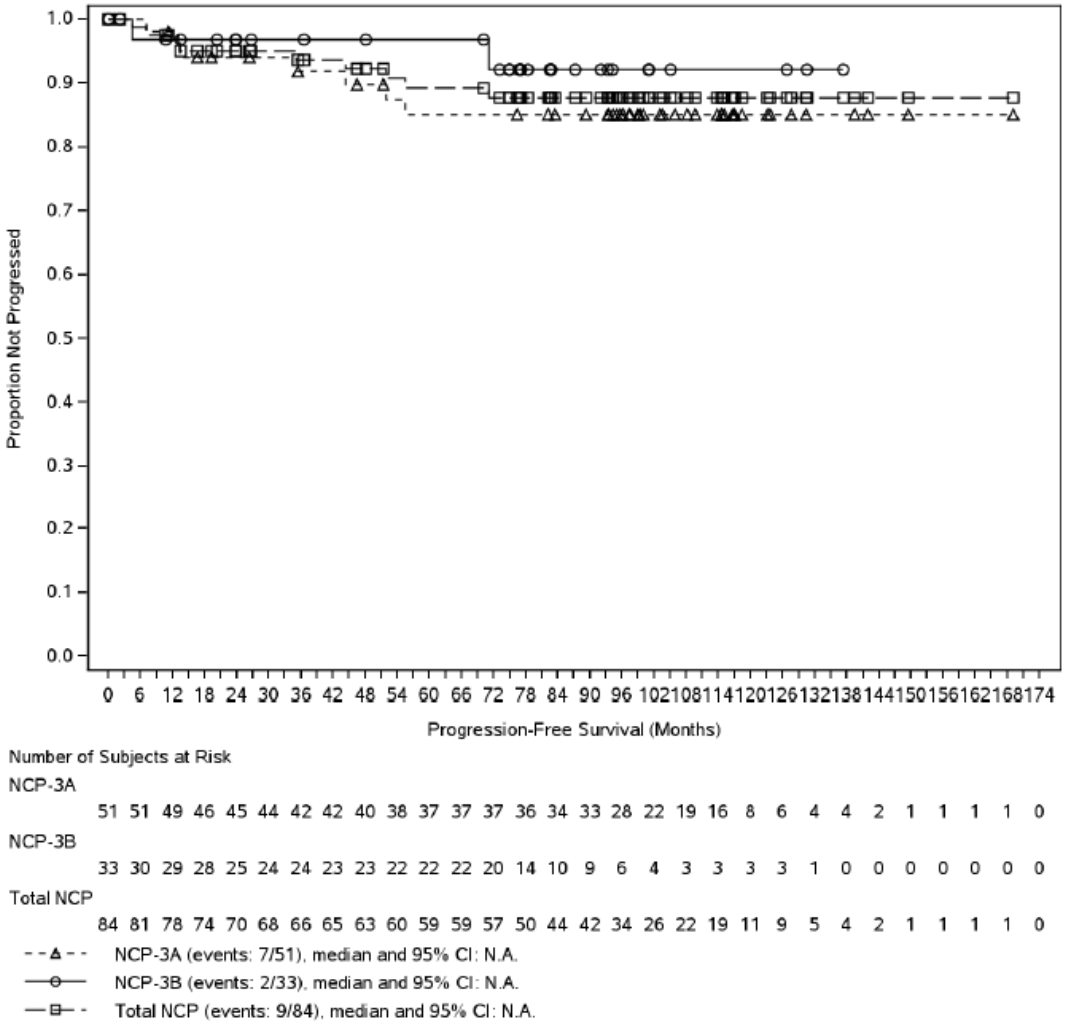


Progression-free Survival (Secondary endpoint)

The KM estimates of PFS rate in Cohort 3 was 87.7% (77.5%, 93.4%) at 72 months (Figure 6.3-1):

- Cohort 3A: 85.1% (95% CI: 71.2%, 92.6%) at 57 months
- Cohort 3B: 92.2% (95% CI: 71.5%, 98.0%) at 72 months

Figure 6.3-1: Kaplan-Meier Plot for Progression-Free Survival (PFS) in Cohort 3 - All Treated Subjects

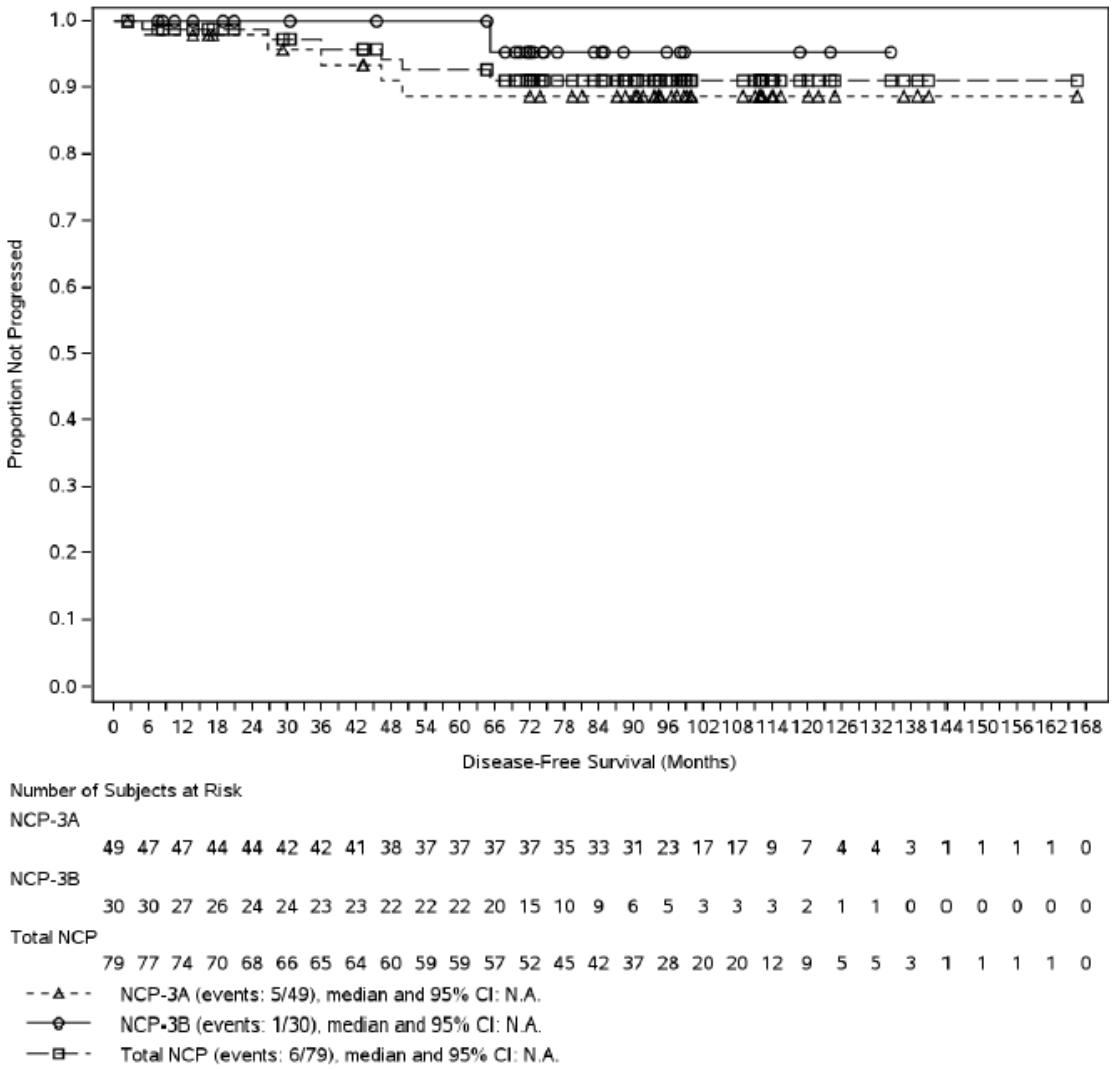


Disease-free Survival (Secondary endpoint)

The KM estimates of DFS rate in Cohort 3 was 91.0% (81.1%, 95.9%) at 66 months (Figure 6.4-1):

- Cohort 3A: 88.6% (95% CI: 74.7%, 95.1%) at 51 months
- Cohort 3B: 95.2% (95% CI: 70.7%, 99.3%) at 66 months

Figure 6.4-1: Kaplan-Meier Plot for Disease-Free Survival (DFS) - All Treated Subjects who Responded (CCyR) in Cohort 3



Overall Survival (Secondary endpoint)

The OS rate was 100% in Cohort 3 as there was no event or death achieved. Therefore, the median OS couldn't be obtained.

Safety results

In Cohort 3 (overall), the median (min, max) duration of exposure to dasatinib in tablet form was 81.0 (0, 169) months and in PFOS form was 12.3 (0, 130) months. The majority (85.7%) of subjects received > 24 months of dasatinib (tablet) therapy. The median (min, max) daily dose of dasatinib in tablet form was 58.5 (35, 79) mg/m2/day and dasatinib in PFOS form was 71.5 (34, 97) mg/m2/day.

The dose was either interrupted or reduced primarily due to hematologic toxicity and escalated for subjects showing resistance to treatment (Table 5-1). There were few additional subjects who had a dose modification since the primary CSR,2 indicating that most of adjustments occurred during the initial months of therapy.

In Cohort 3B, 26 (78.8%) subjects switched to dasatinib tablet formulation with a median (min, max) time to formulation modification of 369.0 (3, 1255) days.

Table 5-1: Summary of Dose Modification in Cohort 3 - All Treated Subjects

	CHRONIC CML		
	NCP-3A N = 51	NCP-3B N = 33	Total NCP N = 84
N OF SUBJECTS (%) WITH AT LEAST 1 DOSE INTERRUPTION	34 (66.7)	15 (45.5)	49 (58.3)
REASON:			
HEMATOLOGIC TOXICITY	13 (25.5)	6 (18.2)	19 (22.6)
NON-HEMATOLOGIC TOXICITY	9 (17.6)	5 (15.2)	14 (16.7)
DOSING ERROR	8 (15.7)	3 (9.1)	11 (13.1)
OTHER	4 (7.8)	1 (3.0)	5 (6.0)
N OF SUBJECTS (%) WITH AT LEAST 1 DOSE REDUCTION	8 (15.7)	5 (15.2)	13 (15.5)
REASON FOR FIRST DOSE REDUCTION:			
HEMATOLOGIC TOXICITY	5 (9.8)	2 (6.1)	7 (8.3)
NON-HEMATOLOGIC TOXICITY	2 (3.9)	1 (3.0)	3 (3.6)
DOSING ERROR	0	0	0
OTHER	1 (2.0)	1 (3.0)	2 (2.4)
NOT REPORTED	0	1 (3.0)	1 (1.2)
N OF SUBJECTS (%) WITH AT LEAST 1 DOSE ESCALATION	16 (31.4)	9 (27.3)	25 (29.8)
REASON FOR FIRST DOSE ESCALATION:			
HEMATOLOGIC TOXICITY	1 (2.0)	0	1 (1.2)
RESISTANCE	8 (15.7)	3 (9.1)	11 (13.1)
DOSING ERROR	0	1 (3.0)	1 (1.2)
OTHER	4 (7.8)	1 (3.0)	5 (6.0)
NOT REPORTED	3 (5.9)	4 (12.1)	7 (8.3)
N OF SUBJECTS (%) WITH PFOS TO TABLET CHANGE[a]	0	26 (78.8)	26 (31.0)
REASON FOR DOSE/FORMULATION MODIFICATION:			
NON-HEMATOLOGIC TOXICITY	0	1 (3.0)	1 (1.2)
RESISTANCE	0	1 (3.0)	1 (1.2)
DOSING ERROR	0	1 (3.0)	1 (1.2)
OTHER	0	4 (12.1)	4 (4.8)
NOT REPORTED	0	19 (57.6)	19 (22.6)
TIME TO FIRST REDUCTION/ INTERRUPTION DUE TO TOXICITY (DAYS)[b]			
N (%)	24 (47.1)	11 (33.3)	35 (41.7)
MEDIAN (MIN - MAX)	82.0 (8 - 1603)	43.0 (4 - 1366)	72.0 (4 - 1603)
LENGTH OF FIRST INTERRUPTION DUE TO TOXICITY (DAYS)[b]			
N (%)	24 (47.1)	11 (33.3)	35 (41.7)
MEDIAN (MIN - MAX)	12.0 (2 - 35)	13.0 (4 - 45)	13.0 (2 - 45)
TIME TO FIRST REDUCTION/ INTERRUPTION DUE TO HEMATOLOGIC TOXICITY (DAYS)			
N (%)	17 (33.3)	7 (21.2)	24 (28.6)
MEDIAN (MIN - MAX)	72.0 (8 - 2607)	52.0 (23 - 243)	66.5 (8 - 2607)
LENGTH OF FIRST INTERRUPTION DUE TO HEMATOLOGIC TOXICITY (DAYS)			
N (%)	17 (33.3)	7 (21.2)	24 (28.6)

Table 5-1: Summary of Dose Modification in Cohort 3 - All Treated Subjects

	CHRONIC CML		
	NCP-3A N = 51	NCP-3B N = 33	Total NCP N = 84
MEDIAN (MIN - MAX) TIME TO FORMULATION MODIFICATION (DAYS)[a]	14.0 (4 - 28)	9.0 (2 - 16)	13.0 (2 - 28)
N (%)	0	26 (78.8)	26 (31.0)
MEDIAN (MIN - MAX)	0	369.0 (3 - 1255)	369.0 (3 - 1255)

[a] Applicable to cohort NCP-3B only.

[b] Toxicity: hematologic or non-hematologic.

Source: Table 14.1.5.2

Overall Safety Summary (Secondary endpoint) is shown in Table 7.1-1

Table 7.1-1: Summary of Safety Results for Cohort 3 - All Treated Subjects

Number (%) of Subjects	Cohort 3A (N = 51), n(%)			Cohort 3B (N = 33), n(%)			Cohort 3 (N = 84), n(%)		
	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Any SAE	21 (41.2)	11 (21.6)	6 (11.8)	12 (36.4)	8 (24.2)	1 (3.0)	33 (39.3)	19 (22.6)	7 (8.3)
Drug-related SAE	7 (13.7)	4 (7.8)	2 (3.9)	4 (12.1)	3 (9.1)	0	11 (13.1)	7 (8.3)	2 (2.4)
AE leading to discontinuation (DC)	2 (3.9)	1 (2.0)	0	4 (12.1)	2 (6.1)	1 (3.0)	6 (7.1)	3 (3.6)	1 (1.2)
Drug-related AE leading to DC	2 (3.9)	1 (2.0)	0	2 (6.1)	1 (3.0)	0	4 (4.8)	2 (2.4)	0
Any AE	50 (98.0)	18 (35.3)	14 (27.5)	33 (100.0)	21 (63.6)	3 (9.1)	83 (98.8)	39 (46.4)	17 (20.2)
Drug-related Any AE	42 (82.4)	13 (25.5)	8 (15.7)	28 (84.8)	11 (33.3)	1 (3.0)	70 (83.3)	24 (28.6)	9 (10.7)
Drug-related late toxicity	0	0	0	1 (3.0)	0	0	1 (1.2)	0	0
	All Grade	Grade ≥ 3		All Grade	Grade ≥ 3		All Grade	Grade ≥ 3	
AESI	7 (13.7)	2 (3.9)		5 (15.2)	1 (3.0)		12 (14.3)	3 (3.6)	
Drug-related AESI	2 (3.9)	0		2 (6.1)	0		4 (4.8)	0	

Source: Table 14.3.2.2.1 (SAE), Table 14.3.2.2.2 (drug-related SAE), Table 14.3.2.3.1 (AE leading to DC), Table 14.3.2.3.2 (drug-related AE leading to DC), Table 14.3.1.1.1 (all AE), Table 14.3.1.1.2 (drug-related AE), Table 14.3.1.1.4 (drug-related AE- late toxicity), Table 14.3.2.4.1 (AESI), and Table 14.3.2.4.2 (drug-related AESI).

Adverse Events

Most of the subjects (98.0%) in Cohort 3A and all subjects in Cohort 3B experienced at least 1 AE (all causality) (Table 7.1-1).

The most frequently reported AEs in ≥ 40% subjects were (Table 7.2-1):

- Cohort 3A: diarrhoea (29 [56.9%]), headache (25 [49.0%]), pyrexia (23 [45.1%]), nausea (22 [43.1%]), and vomiting (22 [43.1%])
- Cohort 3B: diarrhoea (18 [54.5%]), headache (16 [48.5%]), pyrexia (15 [45.5%]) pain in extremity (15 [45.5%]), vomiting (14 [42.4%]), upper respiratory tract infection (14 [42.4%]), and rash (14 [42.4%])

Table 7.2-1: Adverse Events by Worst CTC Grade with Frequencies ≥ 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown (1)	Total
Cohort: NCP-3A (N = 51)							
TOTAL SUBJECTS WITH AN EVENT	4 (7.8)	14 (27.5)	18 (35.3)	14 (27.5)	0	0	50 (98.0)
Infections and infestations							
Upper respiratory tract infection	11 (21.6)	8 (15.7)	0	0	0	0	19 (37.3)
Gastrointestinal disorders							
Diarrhoea	19 (37.3)	10 (19.6)	0	0	0	0	29 (56.9)
Nausea	17 (33.3)	5 (9.8)	0	0	0	0	22 (43.1)
Vomiting	13 (25.5)	8 (15.7)	1 (2.0)	0	0	0	22 (43.1)
Abdominal pain	14 (27.5)	5 (9.8)	0	0	0	0	19 (37.3)
Abdominal pain upper	6 (11.8)	5 (9.8)	1 (2.0)	0	0	0	12 (23.5)
Constipation	10 (19.6)	1 (2.0)	0	0	0	0	11 (21.6)
Respiratory, thoracic and mediastinal disorders							
Cough	17 (33.3)	1 (2.0)	1 (2.0)	0	0	0	19 (37.3)
Oropharyngeal pain	10 (19.6)	1 (2.0)	1 (2.0)	0	0	0	12 (23.5)
Rhinorrhoea	9 (17.6)	3 (5.9)	0	0	0	0	12 (23.5)
Skin and subcutaneous tissue disorders							
Rash	14 (27.5)	5 (9.8)	0	0	0	0	19 (37.3)
General disorders and administration site conditions							
Pyrexia	13 (25.5)	7 (13.7)	3 (5.9)	0	0	0	23 (45.1)
Fatigue	8 (15.7)	2 (3.9)	1 (2.0)	0	0	0	11 (21.6)
Nervous system disorders							
Headache	16 (31.4)	8 (15.7)	1 (2.0)	0	0	0	25 (49.0)
Dizziness	9 (17.6)	3 (5.9)	0	0	0	0	12 (23.5)
Blood and lymphatic system disorders							
Neutropenia	1 (2.0)	2 (3.9)	10 (19.6)	4 (7.8)	0	0	17 (33.3)
Thrombocytopenia	3 (5.9)	3 (5.9)	4 (7.8)	3 (5.9)	0	0	13 (25.5)

Table 7.2-1: Adverse Events by Worst CTC Grade with Frequencies ≥ 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown (1)	Total
Anaemia	0	5 (9.8)	3 (5.9)	3 (5.9)	0	0	11 (21.6)
Musculoskeletal and connective tissue disorders							
Arthralgia	8 (15.7)	4 (7.8)	1 (2.0)	0	0	0	13 (25.5)
Back pain	7 (13.7)	5 (9.8)	0	0	0	0	12 (23.5)
Pain in extremity	7 (13.7)	4 (7.8)	0	0	0	0	11 (21.6)
Cohort: NCP-3B (N = 33)							
TOTAL SUBJECTS WITH AN EVENT	2 (6.1)	7 (21.2)	21 (63.6)	3 (9.1)	0	0	33 (100.0)
Gastrointestinal disorders							
Diarrhoea	10 (30.3)	7 (21.2)	1 (3.0)	0	0	0	18 (54.5)
Vomiting	3 (9.1)	10 (30.3)	1 (3.0)	0	0	0	14 (42.4)
Abdominal pain	8 (24.2)	5 (15.2)	0	0	0	0	13 (39.4)
Nausea	6 (18.2)	7 (21.2)	0	0	0	0	13 (39.4)
Infections and infestations							
Upper respiratory tract infection	7 (21.2)	6 (18.2)	1 (3.0)	0	0	0	14 (42.4)
General disorders and administration conditions							
Pyrexia	7 (21.2)	5 (15.2)	2 (6.1)	0	0	1 (3.0)[a]	15 (45.5)
Fatigue	6 (18.2)	2 (6.1)	0	0	0	0	8 (24.2)
Musculoskeletal and connective tissue disorders							
Pain in extremity	12 (36.4)	2 (6.1)	1 (3.0)	0	0	0	15 (45.5)
Arthralgia	7 (21.2)	2 (6.1)	0	0	0	0	9 (27.3)
Back pain	7 (21.2)	1 (3.0)	0	0	0	0	8 (24.2)
Skin and subcutaneous tissue disorders							
Rash	8 (24.2)	6 (18.2)	0	0	0	0	14 (42.4)
Acne	1 (3.0)	6 (18.2)	0	0	0	0	7 (21.2)
Blood and lymphatic system disorders							
Neutropenia	0	1 (3.0)	6 (18.2)	1 (3.0)	0	0	8 (24.2)

Table 7.2-1: Adverse Events by Worst CTC Grade with Frequencies ≥ 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown (1)	Total
Thrombocytopenia	3 (9.1)	1 (3.0)	4 (12.1)	0	0	0	8 (24.2)
Anaemia	3 (9.1)	4 (12.1)	0	0	0	0	7 (21.2)
Respiratory, thoracic and mediastinal disorders							
Cough	9 (27.3)	3 (9.1)	0	0	0	0	12 (36.4)
Oropharyngeal pain	8 (24.2)	3 (9.1)	0	0	0	0	11 (33.3)
Investigations							
Platelet count decreased	6 (18.2)	3 (9.1)	2 (6.1)	1 (3.0)	0	0	12 (36.4)
Neutrophil count decreased	5 (15.2)	2 (6.1)	1 (3.0)	0	0	0	8 (24.2)
Nervous system disorders							
Headache	10 (30.3)	6 (18.2)	0	0	0	0	16 (48.5)
Cohort: Total NCP (N = 84)							
TOTAL SUBJECTS WITH AN EVENT	6 (7.1)	21 (25.0)	39 (46.4)	17 (20.2)	0	0	83 (98.8)
Infections and infestations							
Upper respiratory tract infection	18 (21.4)	14 (16.7)	1 (1.2)	0	0	0	33 (39.3)
Gastrointestinal disorders							
Diarrhoea	29 (34.5)	17 (20.2)	1 (1.2)	0	0	0	47 (56.0)
Vomiting	16 (19.0)	18 (21.4)	2 (2.4)	0	0	0	36 (42.9)
Nausea	23 (27.4)	12 (14.3)	0	0	0	0	35 (41.7)
Abdominal pain	22 (26.2)	10 (11.9)	0	0	0	0	32 (38.1)
Abdominal pain upper	7 (8.3)	10 (11.9)	1 (1.2)	0	0	0	18 (21.4)
Respiratory, thoracic and mediastinal disorders							
Cough	26 (31.0)	4 (4.8)	1 (1.2)	0	0	0	31 (36.9)
Oropharyngeal pain	18 (21.4)	4 (4.8)	1 (1.2)	0	0	0	23 (27.4)
Skin and subcutaneous tissue disorders							
Rash	22 (26.2)	11 (13.1)	0	0	0	0	33 (39.3)

Table 7.2-1: Adverse Events by Worst CTC Grade with Frequencies ≥ 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown (1)	Total
General disorders and administration site conditions							
Pyrexia	20 (23.8)	12 (14.3)	5 (6.0)	0	0	1 (1.2)	38 (45.2)
Fatigue	14 (16.7)	4 (4.8)	1 (1.2)	0	0	0	19 (22.6)
Musculoskeletal and connective tissue disorders							
Pain in extremity	19 (22.6)	6 (7.1)	1 (1.2)	0	0	0	26 (31.0)
Arthralgia	15 (17.9)	6 (7.1)	1 (1.2)	0	0	0	22 (26.2)
Back pain	14 (16.7)	6 (7.1)	0	0	0	0	20 (23.8)
Blood and lymphatic system disorders							
Neutropenia	1 (1.2)	3 (3.6)	16 (19.0)	5 (6.0)	0	0	25 (29.8)
Thrombocytopenia	6 (7.1)	4 (4.8)	8 (9.5)	3 (3.6)	0	0	21 (25.0)
Anaemia	3 (3.6)	9 (10.7)	3 (3.6)	3 (3.6)	0	0	18 (21.4)
Nervous system disorders							
Headache	26 (31.0)	14 (16.7)	1 (1.2)	0	0	0	41 (48.8)

Subjects may have more than one event within a class.
MedDRA Version: 27.1; CTC Version: 3.0

[a] Toxicity reported but not graded.
Source: Table 14.3.1.1.1

Adverse Events by Severity

In Cohort 3, at least 1 Grade 3 AE was reported in 46.4% subjects and at least 1 Grade 4 AE was reported in 20.2% subjects (Table 7.1-1). Neutropenia was the most frequently reported Grade ≥ 3 AE (Table 7.2-1):

- Cohort 3A: Grade 3: 19.6%; Grade 4: 7.8%

- Cohort 3B: Grade 3: 18.2%; Grade 4: 3.0%

In Cohort 3, none of the AEs were of Grade 5 severity.

Drug-related Emergent Adverse Events

The majority of subjects (83.3%) experienced at least 1 drug-related AE (any-grade) in Cohort 3

(Table 7.1-1). The most frequently reported drug-related AEs in ≥ 20% subjects were:

- Cohort 3A: neutropenia (17 [33.3%] subjects), headache (12 [23.5%] subjects), thrombocytopenia (11 [21.6%] subjects), and diarrhoea (11 [21.6%] subjects)
- Cohort 3B: platelet count decreased (8 [24.2%] subjects), nausea, vomiting, neutropenia, neutrophil count decreased, fatigue, and headache, each reported in 7 (21.2%) subjects

In Cohort 3, at least 1 drug-related Grade 3 AE was reported in 28.6% subjects and at least 1 drug-related Grade 4 AE was reported in 10.7% subjects (Table 7.1-1). The most frequently reported Grade ≥ 3 AEs in > 5% subjects were (Table 7.2.2-1).

- Cohort 3A: neutropenia (Grade 3: 10 [19.6%]; Grade 4: 4 [7.8%]) and thrombocytopenia (Grade 3: 4 [7.8%]; Grade 4: 3 [5.9%])
- Cohort 3B: neutropenia (Grade 3: 5 [15.2%]; Grade 4: 1 [3.0%]) and platelet count decreased (Grade 3: 2 [6.1%]; Grade 4: 0)

Three subjects experienced drug-related pleural and/or pericardial effusion:

- Cohort 3A: 1 subject experienced Grade 2 AE of pleural effusion which resolved in 22 days and the subject was discontinued from the study treatment.
- Cohort 3B: 1 subject experienced an SAE of Grade 2 pleural effusion and concurrently, an SAE of Grade 3 pericardial effusion, which led to treatment interruption (37 days). These SAEs got resolved in 8 days with treatment and the subject resumed on study treatment with reduction of dose to 60 mg. The subject completed the study treatment and FU period. Another subject experienced Grade 1 AE of pericardial effusion. The AE resolved in 358 days however, no action was taken on the study treatment.

Three drug-related late toxicities (all in Cohort 3B) reported in 1 subject each were (Table 7.1-1): anaemia (Grade 2), neutropenia (Grade 1), and AST increased (Grade 1).

Table 7.2.2-1: Drug-Related Adverse Event by Worst CTC Grade with Frequencies > 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Cohort: NCP-3A (N = 51)							
TOTAL SUBJECTS WITH AN EVENT	11 (21.6)	10 (19.6)	13 (25.5)	8 (15.7)	0	0	42 (82.4)
Blood and lymphatic system disorders							
Neutropenia	1 (2.0)	2 (3.9)	10 (19.6)	4 (7.8)	0	0	17 (33.3)
Thrombocytopenia	1 (2.0)	3 (5.9)	4 (7.8)	3 (5.9)	0	0	11 (21.6)
Gastrointestinal disorders							
Diarrhoea	6 (11.8)	5 (9.8)	0	0	0	0	11 (21.6)
Nervous system disorders							
Headache	9 (17.6)	2 (3.9)	1 (2.0)	0	0	0	12 (23.5)
Cohort: NCP-3B (N = 33)							
TOTAL SUBJECTS WITH AN EVENT	5 (15.2)	11 (33.3)	11 (33.3)	1 (3.0)	0	0	28 (84.8)
Gastrointestinal disorders							
Nausea	4 (12.1)	3 (9.1)	0	0	0	0	7 (21.2)
Vomiting	4 (12.1)	3 (9.1)	0	0	0	0	7 (21.2)
Blood and lymphatic system disorders							
Neutropenia	0	1 (3.0)	5 (15.2)	1 (3.0)	0	0	7 (21.2)
Investigations							
Platelet count decreased	4 (12.1)	2 (6.1)	2 (6.1)	0	0	0	8 (24.2)
Neutrophil count decreased	5 (15.2)	2 (6.1)	0	0	0	0	7 (21.2)
General disorders and administration site conditions							
Fatigue	5 (15.2)	2 (6.1)	0	0	0	0	7 (21.2)
Nervous system disorders							
Headache	5 (15.2)	2 (6.1)	0	0	0	0	7 (21.2)
Cohort: Total NCP (N = 84)							
TOTAL SUBJECTS WITH AN EVENT	16 (19.0)	21 (25.0)	24 (28.6)	9 (10.7)	0	0	70 (83.3)

Table 7.2.2-1: Drug-Related Adverse Event by Worst CTC Grade with Frequencies > 20% of Total by Preferred Term in Cohort 3 - All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Blood and lymphatic system disorders							
Neutropenia	1 (1.2)	3 (3.6)	15 (17.9)	5 (6.0)	0	0	24 (28.6)
Thrombocytopenia	3 (3.6)	3 (3.6)	8 (9.5)	3 (3.6)	0	0	17 (20.2)
Nervous system disorders							
Headache	14 (16.7)	4 (4.8)	1 (1.2)	0	0	0	19 (22.6)

Subjects may have more than one event within a class
MedDRA Version: 27.1; CTC Version: 3.0
Source: Table 14.3.1.1.2

Serious adverse events

There were no death reported.

In Cohort 3, at least 1 SAE of any causality was reported in 39.3% of the subjects (Table 7.1-1). The most frequently reported SAE in > 5% subjects was pyrexia (6.0%).

Drug-related SAEs were reported in 11 (13.1%) subjects in Cohort 3, of which the SAEs reported in 9 subjects were of Grade ≥ 3 severity (Grade 3: 8.3%; Grade 4: 2.4%) (Table 7.4-1).

Table 7.4-1: Drug-Related Serious Adverse Event by Worst CTC with Frequency ≥ 1 Subjects of Total by Preferred Term in Cohort 3 -All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Cohort: NCP-3A (N = 51)							
TOTAL SUBJECTS WITH AN EVENT	0	1 (2.0)	4 (7.8)	2 (3.9)	0	0	7 (13.7)
Blood and lymphatic system disorders	0	0	1 (2.0)	2 (3.9)	0	0	3 (5.9)
Anaemia	0	0	0	2 (3.9)	0	0	2 (3.9)
Febrile neutropenia	0	0	1 (2.0)	0	0	0	1 (2.0)
Gastrointestinal disorders	0	0	1 (2.0)	0	0	0	1 (2.0)
Haematochezia	0	0	1 (2.0)	0	0	0	1 (2.0)
General disorders and administration site conditions	0	1 (2.0)	0	0	0	0	1 (2.0)
Oedema peripheral	0	1 (2.0)	0	0	0	0	1 (2.0)
Infections and infestations	0	0	1 (2.0)	0	0	0	1 (2.0)
Periorbital cellulitis	0	0	1 (2.0)	0	0	0	1 (2.0)
Investigations	0	1 (2.0)	0	0	0	0	1 (2.0)
White blood cell count decreased	0	1 (2.0)	0	0	0	0	1 (2.0)
Reproductive system and breast disorders	0	1 (2.0)	0	0	0	0	1 (2.0)
Uterine haemorrhage	0	1 (2.0)	0	0	0	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	0	0	1 (2.0)	0	0	0	1 (2.0)
Chylothorax	0	0	1 (2.0)	0	0	0	1 (2.0)
Cohort: NCP-3B (N = 33)							
TOTAL SUBJECTS WITH AN EVENT	0	1 (3.0)	3 (9.1)	0	0	0	4 (12.1)
Cardiac disorders	0	0	1 (3.0)	0	0	0	1 (3.0)
Pericardial effusion	0	0	1 (3.0)	0	0	0	1 (3.0)
Immune system disorders	0	0	1 (3.0)	0	0	0	1 (3.0)
Drug hypersensitivity	0	0	1 (3.0)	0	0	0	1 (3.0)

Table 7.4-1: Drug-Related Serious Adverse Event by Worst CTC with Frequency ≥ 1 Subjects of Total by Preferred Term in Cohort 3 -All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
Infections and infestations	0	0	1 (3.0)	0	0	0	1 (3.0)
Cellulitis	0	0	1 (3.0)	0	0	0	1 (3.0)
Infection	0	0	1 (3.0)	0	0	0	1 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (3.0)	0	0	0	0	1 (3.0)
Leukaemia recurrent	0	1 (3.0)	0	0	0	0	1 (3.0)
Respiratory, thoracic and mediastinal disorders	0	1 (3.0)	0	0	0	0	1 (3.0)
Pleural effusion	0	1 (3.0)	0	0	0	0	1 (3.0)
Cohort: Total NCP (N = 84)							
TOTAL SUBJECTS WITH AN EVENT	0	2 (2.4)	7 (8.3)	2 (2.4)	0	0	11 (13.1)
Blood and lymphatic system disorders	0	0	1 (1.2)	2 (2.4)	0	0	3 (3.6)
Anaemia	0	0	0	2 (2.4)	0	0	2 (2.4)
Febrile neutropenia	0	0	1 (1.2)	0	0	0	1 (1.2)
Infections and infestations	0	0	2 (2.4)	0	0	0	2 (2.4)
Cellulitis	0	0	1 (1.2)	0	0	0	1 (1.2)
Infection	0	0	1 (1.2)	0	0	0	1 (1.2)
Periorbital cellulitis	0	0	1 (1.2)	0	0	0	1 (1.2)
Respiratory, thoracic and mediastinal disorders	0	1 (1.2)	1 (1.2)	0	0	0	2 (2.4)
Chylothorax	0	0	1 (1.2)	0	0	0	1 (1.2)
Pleural effusion	0	1 (1.2)	0	0	0	0	1 (1.2)
Cardiac disorders	0	0	1 (1.2)	0	0	0	1 (1.2)
Pericardial effusion	0	0	1 (1.2)	0	0	0	1 (1.2)
Gastrointestinal disorders	0	0	1 (1.2)	0	0	0	1 (1.2)
Haematochezia	0	0	1 (1.2)	0	0	0	1 (1.2)

Table 7.4-1: Drug-Related Serious Adverse Event by Worst CTC with Frequency ≥ 1 Subjects of Total by Preferred Term in Cohort 3 -All Treated Subjects

System Organ Class (%) Preferred Term (%)	I	II	III	IV	V	Unknown	Total
General disorders and administration site conditions	0	1 (1.2)	0	0	0	0	1 (1.2)
Oedema peripheral	0	1 (1.2)	0	0	0	0	1 (1.2)
Immune system disorders	0	0	1 (1.2)	0	0	0	1 (1.2)
Drug hypersensitivity	0	0	1 (1.2)	0	0	0	1 (1.2)
Investigations	0	1 (1.2)	0	0	0	0	1 (1.2)
White blood cell count decreased	0	1 (1.2)	0	0	0	0	1 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2)	0	0	0	0	1 (1.2)
Leukaemia recurrent	0	1 (1.2)	0	0	0	0	1 (1.2)
Reproductive system and breast disorders	0	1 (1.2)	0	0	0	0	1 (1.2)
Uterine haemorrhage	0	1 (1.2)	0	0	0	0	1 (1.2)

Subjects may have more than one event within a class
MedDRA Version: 27.1; CTC Version: 3.0
Source: Table 14.3.2.2.2

Adverse Events Leading to Discontinuation of Study Drug

AEs reported in 7.1% of subjects in Cohort 3 led to discontinuation of the study drug, of which the AEs reported in 4 subjects were of Grade ≥ 3 severity (Grade 3: 3.6%; Grade 4: 1.2%; Table 7.1-1). The Grade ≥ 3 AEs leading to discontinuation of study drug were:

- Cohort 3A: chylothorax (Grade 3) reported in 1 subject
- Cohort 3B: leukaemia (Grade 3), drug hypersensitivity (Grade 3), and leukaemia recurrent (Grade 4) reported in 1 subject each

Of the AEs leading to discontinuation of study drug, chylothorax and drug hypersensitivity of Grade ≥ 3 severity were assessed as drug-related.

Adverse Events of special interest

AESI discussed in this section included fluid retention, respiratory disorders, cardiac disorders, bleeding events, pediatric bone growth and development, respiratory disorders, pulmonary arterial hypertension, diarrhea, nausea/vomiting, fatigue, myalgias/arthralgias, and rash.

AESIs (all causality, any grade) reported in ≥ 10% of subjects from Cohort 3 consisted of rash (53 [63.1%]), diarrhea (48 [57.1%]), vomiting (36 [42.9%]), nausea (35 [41.7%]), non-productive cough (31 [36.9%]), other hemorrhage (29 [34.5%]), arthralgia (22 [26.2%]), superficial edema (21 [25.0%]), fatigue (21 [25.0%]), chest pain (18 [21.4%]), generalized edema (14 [16.7%]), pediatric bone growth and development (12 [14.3%]), cardiac disorders (11 [13.1%]), and myalgia (11 [13.1%]).

Except for rash (5 [6.0%]) and vomiting (2 [2.4%]), no Grade 3-4 AESI (any causality) was reported in > 1 subject.

Of the drug-related AESIs reported in Cohort 3, Grade ≥ 3 AESIs were reported in 1 subject each (Table 7.6-1):

- Cohort 3A: pleural effusion, rash, GI bleeding, and other haemorrhage
- Cohort 3B: pericardial effusion

Table 7.6-1: Drug-Related Adverse Event of Special Interest by Worst CTC in Cohort 3 -All Treated Subjects

AE Special Interest	Number of Subjects (%)					
	NCP-3A (N=51)		NCP-3B (N=33)		Total NCP (N=84)	
	Any Grade	Severe (3-5)	Any Grade	Severe (3-5)	Any Grade	Severe (3-5)
PEDIATRIC BONE GROWTH AND DEVELOPMENT	2 (3.9)	0	2 (6.1)	0	4 (4.8)	0
FLUID RETENTION	9 (17.6)	1 (2.0)	8 (24.2)	1 (3.0)	17 (20.2)	2 (2.4)
SUPERFICIAL EDEMA	5 (9.8)	0	5 (15.2)	0	10 (11.9)	0
PLEURAL EFFUSION	2 (3.9)	1 (2.0)	1 (3.0)	0	3 (3.6)	1 (1.2)
OTHER FLUID RELATED	6 (11.8)	0	4 (12.1)	1 (3.0)	10 (11.9)	1 (1.2)
GENERALIZED EDEMA	4 (7.8)	0	3 (9.1)	0	7 (8.3)	0
ASCITES	0	0	0	0	0	0
PERICARDIAL EFFUSION	0	0	2 (6.1)	1 (3.0)	2 (2.4)	1 (1.2)
CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION	2 (3.9)	0	1 (3.0)	0	3 (3.6)	0
PULMONARY EDEMA	0	0	0	0	0	0
PULMONARY HYPERTENSION	0	0	0	0	0	0
RESPIRATORY DISORDERS	1 (2.0)	0	3 (9.1)	0	4 (4.8)	0
CHEST PAIN	0	0	2 (6.1)	0	2 (2.4)	0
NON-PRODUCTIVE COUGH	0	0	0	0	0	0
SHORTNESS OF BREATH	1 (2.0)	0	1 (3.0)	0	2 (2.4)	0
CARDIAC DISORDERS	1 (2.0)	0	2 (6.1)	0	3 (3.6)	0
PULMONARY ARTERIAL HYPERTENSION	0	0	1 (3.0)	0	1 (1.2)	0
DIARRHEA	12 (23.5)	0	4 (12.1)	0	16 (19.0)	0
NAUSEA/VOMITTING	9 (17.6)	0	10 (30.3)	0	19 (22.6)	0
NAUSEA	7 (13.7)	0	7 (21.2)	0	14 (16.7)	0
VOMITTING	5 (9.8)	0	7 (21.2)	0	12 (14.3)	0
FATIGUE	5 (9.8)	0	7 (21.2)	0	12 (14.3)	0

Table 7.6-1: Drug-Related Adverse Event of Special Interest by Worst CTC in Cohort 3 -All Treated Subjects

AE Special Interest	Number of Subjects (%)					
	NCP-3A (N=51)		NCP-3B (N=33)		Total NCP (N=84)	
	Any Grade	Severe (3-5)	Any Grade	Severe (3-5)	Any Grade	Severe (3-5)
MYALGIAS/ARTHRALGIAS	3 (5.9)	0	6 (18.2)	0	9 (10.7)	0
MYALGIA	0	0	3 (9.1)	0	3 (3.6)	0
ARTHRALGIA	3 (5.9)	0	4 (12.1)	0	7 (8.3)	0
RASH	11 (21.6)	1 (2.0)	7 (21.2)	0	18 (21.4)	1 (1.2)
HEMORRHAGE	8 (15.7)	1 (2.0)	2 (6.1)	0	10 (11.9)	1 (1.2)
GI BLEEDING	3 (5.9)	1 (2.0)	0	0	3 (3.6)	1 (1.2)
CNS BLEEDING	0	0	0	0	0	0
OTHER HEMORRHAGE	8 (15.7)	1 (2.0)	2 (6.1)	0	10 (11.9)	1 (1.2)

MedDRA Version: 27.1; CTC Version: 3.0
Source: Table 14.3.2.4.2

Haematology

The decrease in number of subjects from primary CSR was noted for few parameters. This was due to additional data cleaning activities.

The hematological laboratory values from baseline to worst CTC grade during study in Cohort 3 were:

- From baseline Grade 0 to Grade 3-4: leucocytes (12 [14.3%]), absolute neutrophil count (5 [6.0%]), and platelet count (9 [10.7%])
- From baseline Grade 1-2 to Grade 3-4: platelet count (1 [1.2%]) and hemoglobin (13 [15.5%])

Similar to the primary CSR, most subjects had some degree of cytopenia(s) during the study; however, the majority were Grade 1 or 2. Cytopenias tended to occur within the first 8 weeks of starting dasatinib, and most of them were short in duration. There were few new events with onset during the long-term FU period of the study.

Serum Chemistry

The chemistry parameters from baseline to worst CTC grade during study in Cohort 3 were:

- From baseline Grade 0 to Grade 3-4: AST (1 [1.2%]), ALT (2 [2.4%]), and hypophosphatemia (3 [3.6%])
- From baseline Grade 1-2 to Grade 3-4: total bilirubin (1 [1.2%])

There were no additional liver toxicities with longer FU as compared with primary results.

Electrocardiograms and Echocardiograms

The median QTc(F) change from baseline in Cohort 3 was 15.65 msec and none of the subjects had a maximal QTc(F) > 500 msec:

- Cohort 3A: 17.0 msec in, and
- Cohort 3B: 11.0 msec in.

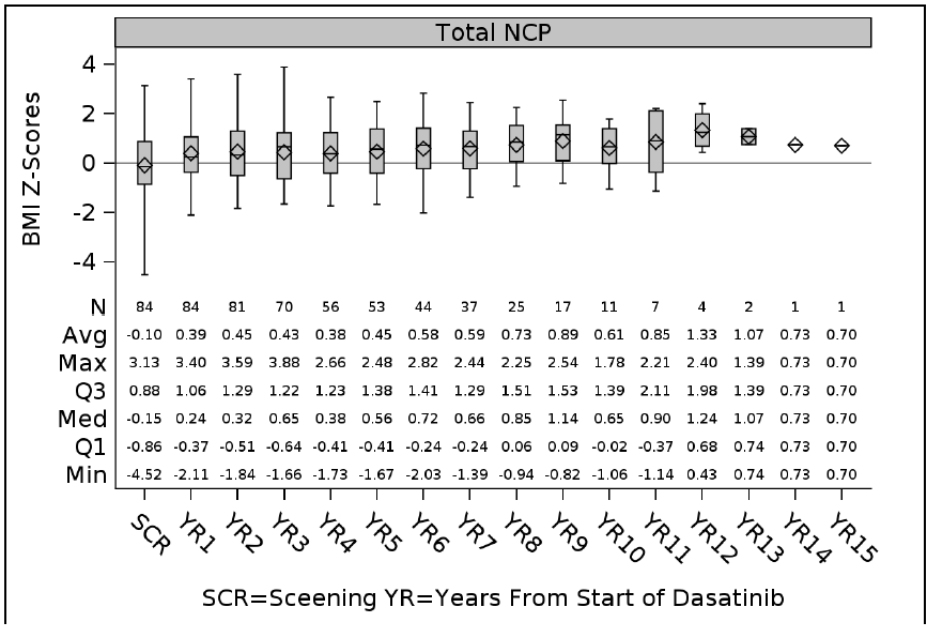
In Cohort 3, 11 (13.1%) subjects had an abnormal echocardiogram on-study, and 14 (16.7%) subjects had cardiac-related AEs during the study:

- Pulmonary arterial pressure increased was reported in 2 (2.4%) subjects on the basis of the echo assessments.
- In 1 case, a right heart catheterization was performed, and the diagnosis of pulmonary hypertension was ruled out; however, due to coding rules, the PT was mapped to pulmonary arterial hypertension.

Long-term Safety - Effects on Growth and Development

The mean (SD) BMIs at baseline in Cohort 3 (n = 84) was 18.67 (4.38) kg/m2. There were minimal changes to BMI with the use of dasatinib.

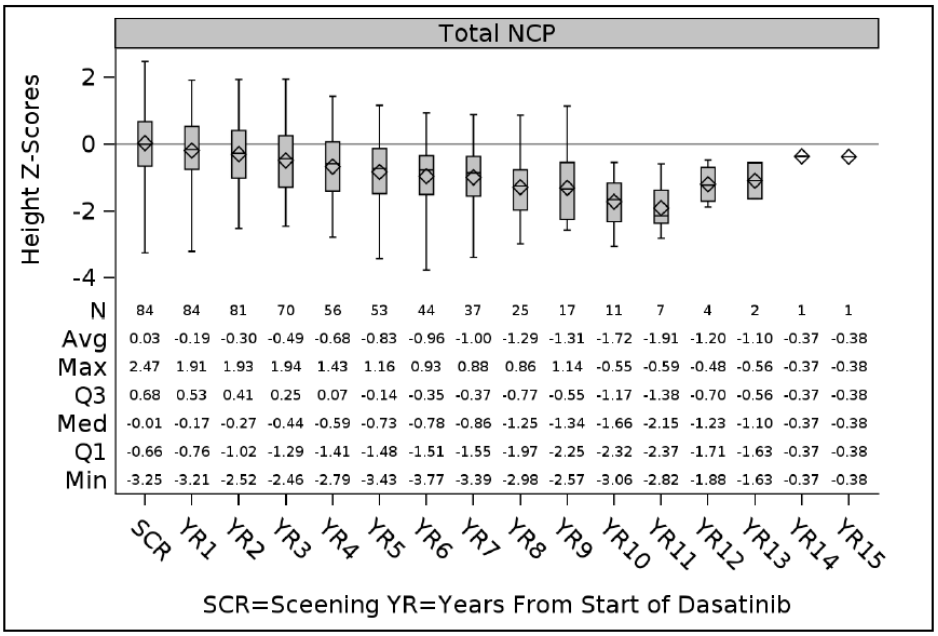
Figure 7.9.1.1-1: Box Plots of BMIs Z-Scores for Cohort 3 over Time- All Treated Subjects



Source: Figure 14.3.4.3.2.3

The mean (SD) height at baseline in Cohort 3 (n = 84) was 147.11 (24.16) cm. Median height Z-score in Cohort 3 decreased from the start of dasatinib treatment, with median Z-scores ranging from -0.01 (baseline) to -2.15 (YR11) (Figure 7.9.1.2-1). Results were consistent between Cohorts 3A and 3B over time. This downward trend was sustained over time with no deeper decline with longer FU.

Figure 7.9.1.2-1: Box Plots of Heights Z-Scores for Cohort 3 over Time - All Treated Subjects



Source: Figure 14.3.4.3.2.1

Hormones, Growth Factors, Bone Alkaline Phosphatase, Urinary N-Telopeptide

Summary statistics for free T4, TSH, FSH, LH, IGF-1 and IGFbeta-3 levels at assessment points over time were not indicative of any clinical abnormality associated with dasatinib in any cohort.

IGF-1 and IGFBP-3 levels

IGF-1 and IGFBP-3 levels reflected normal human growth hormone production.

- 1 subject in Cohort 3A was reported with an extremely low IGF-1 value of 6 ug/L. This subject had a low IGF-1 value of 72 ug/L (normal range: 113 to 261 ug/L) at screening, recovered to normal values during the whole study, until last assessment on Day 2183. An AE of growth suppression was reported at Day 433; however, neither any treatment was given nor any action was taken with study drug. The subject was discontinued due to study completion (Appendix 16.2.1.1). Thus, the value of 6 ug/L was presumed or likely to be an error in data entry.

TSH levels

TSH levels were normal or a mildly increased in most subjects. None required treatment with thyroid replacement, except for 1 subject in Cohort 3B, who was diagnosed with hypothyroidism on Day 2 that required thyroid hormone replacement. In other subjects, levels of free T4 were normal.

FSH and LH levels

Median FSH and LH levels did not suggest any clinically meaningful abnormality.

There were 2 cases of sustained high FSH levels:

- 1 subject in Cohort 3B was diagnosed with hypogonadism on Day 362 and gynecomastia on Day 397 related to dasatinib, did not require therapy and dasatinib dose was not changed; the event was ongoing at the time of study completion (5.5 years later).
- 1 subject in Cohort 3A had experienced FSH elevation on Day 345 (58.6 mU/mL) which gradually decreased by Days 1465 (8.64 mU/mL) to the ULN value. The event was not captured as an AE, and the subject did not receive any medication for the same.

1 subject enrolled (12-Mar-2025) in Cohort 3A was discontinued from the study treatment (15-Feb-2012) to undergo a HSCT. This subject was only followed up for LTGD data collection purposes. One year after transplant (from Day 713 to Day 2209), the FSH values were between 94 and 101 U/L and LH values were between 24 and 41 U/L. However, no ovarian failure or other associated AEs were reported. The stem cell transplant was a confounding factor when assessing relationship with dasatinib and therefore elevated FSH was likely attributable to the stem cell transplantation preparatory regimen and not dasatinib.

Bone Metabolism

Minimal to no changes were observed for urinary N-telopeptide of type I collagen (Ntx) levels, which were not indicative of any clinical abnormality associated with dasatinib in any cohort.

The most accurate areas to assess bone density in children were lumbar spine and whole body.

Among subjects in Cohort 3A and 3B, modest changes in median DXA Z-scores of the lumbar spine were observed from screening to > 7 to ≤ 8 years, with median Z-scores of -0.70 and -0.90 at screening and -0.70 and -0.50 at > 7 to ≤ 8 years in Cohorts 3A and 3B, respectively. The data beyond 8 years could not be interpreted due to the limited number of subjects.

2.3.3. Discussion on clinical aspects

Long-term FU data for Phase 2 study CA180226 assessing dasatinib treatment in children and adolescents with CML or with Ph+ leukaemias resistant or intolerant to imatinib, was collected from Cohort 3. The MAH provided the closeout CSR for study CA180226.

Cohort 3 included children and adolescents with CP-CML who were treatment-naive received dasatinib tablets at 60 mg/m2 QD or PFOS at 72 mg/m2 QD on a continuous oral regimen and had 2 sub-cohorts:

Cohort 3A with 51 subjects treated with the tablet formulation and Cohort 3B with 33 subjects treated with the PFOS.

The primary endpoint was cytogenetic response, the CCyR rate (> 55%) was achieved by 6 months, with a CCyR rate of 94% from 15 months. Molecular response rate gradually increased over time with MMR rate of 84.5% by 72 months. MR4 rate gradually increased over time from 6 months (MR4 any time: 58.3%). CMR rate gradually increased over time from ≥ 6 months, which was sustained until 90 months. Of the subjects who achieved MMR, 4 subjects from Cohort 3A reported loss of response by 42 to 45 months. The OS was 100% and PFS rate was 87.7% (77.5%, 93.4%) at 72 months.

Long-term FU results were presented for Cohort 3 from subjects who received dasatinib tablet treatment for a median of 81.0 months and were followed for a median of 8 years.

Assessment of weight, height, body mass index (BMI), hormones and bone metabolism suggesting clinical abnormality was included as exploratory endpoints in the study.

Dasatinib had a negative impact on linear growth related to a normal distribution in healthy children; even though most subjects remained above the 15th percentile. Median height Z-score in the first line (1L) CP-CML cohort decreased from the start of dasatinib treatment, with median Z-scores ranging from -0.01 (baseline) to -2.15 (YR11); the initial downward trend was sustained but not worsening over time with longer FU. Impact over time on BMI was minimal and also bone density markers did not show worrisome results as dual-energy X-ray absorptiometry Z-scores were within normal limits, and urinary N-telopeptide did not increase. Insulin-like growth factor-1 (IGF)-1 and Insulin-like growth factor-binding protein 3 (IGFBP-3) levels reflected normal human growth hormone production, but one subject in Cohort 3B was diagnosed with hypothyroidism on Day 2, requiring thyroid hormone replacement. In other subjects, levels of free thyroxine (T4) were normal. Median follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels did not suggest any clinically meaningful abnormality. Overall these results were reassuring as the growth impairment was anticipated and the other markers did not raise any new concerns.

The majority of subjects (83.3%) experienced at least 1 drug-related AE (any-grade) in Cohort 3. Neutropenia, headache, thrombocytopenia, and diarrhoea (11 [21.6%] subjects) were the most frequently reported drug-related AEs in ≥ 20% subjects for cohort 3A and decreased platelet count, nausea, vomiting, neutropenia, decreased neutrophil count, fatigue and headache, for cohort 3B respectively.

In both cohorts at least 1 drug-related Grade 3 AE was reported in 28.6% subjects and at least 1 drug-related Grade 4 AE was reported in 10.7% subjects. The most frequently reported Grade ≥ 3 AEs in > 5% subjects were neutropenia, thrombocytopenia and decreased platelet count decreased.

3 drug-related late toxicities reported in 1 subject each were: anaemia (Grade 2), neutropenia (Grade 1), and increased aspartate transaminase (Grade 1). 3 subjects experienced drug-related pleural and/or pericardial effusion, whereas there had been no such events of pleural/pericardial effusion in the first two cohorts. The proportions of subjects who had drug-related hematologic AEs and drug-related serum chemistry AEs reported were consistent with the known effects of dasatinib in this population.

82/84 subjects in Cohort 3 did not have BCR-ABL mutations at baseline or throughout the course of the study. 1 subject each in Cohort 3A, lost mutation by the end of the study and subject developed a T315I mutation.

The overall safety profile of oral dasatinib QD in the paediatric population was generally consistent with the known safety profile for dasatinib and expected AEs in children and adolescents with CML on treatment. The choice of formulation did not impact the safety profile.

No changes or amendments to the SmPC are required.

3. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. For this Application the MAH submitted a final report for Cohort 3 of Study CA180226 which includes ”TABLES, FIGURES, AND LISTINGS NOT INCLUDED IN THE RESULTS SECTIONS” on page 45 of the closeout CSR. These tables and figures however could not be found in the dossier and should be provided together with the original CSR describing the first two cohorts.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

The MAH acknowledges this request and is providing the following as part of this response submission:

- The referenced tables, figures, and listings from the Cohort 3 closeout CSR. These additional documents are being included in Module 5.
- A cross-reference leaf linking to the exact location in eCTD where the previously submitted CSRs, describing the first two cohorts, were provided. A cross-reference leaf is proposed in accordance with the principles of eCTD, to avoid re-submission of identical documents previously included in the backbone.

CHMP comments

The MAH provided the tables and figures referenced as requested.

Issue resolved.

The overall conclusion in section 2.3.3 has been updated to reflect this

4. CHMP's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.