13 December 2018
EMA/CHMP/3851/2019
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Sprycel

International non-proprietary name: dasatinib

Procedure No. EMEA/H/C/000709/II/0059

## Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
**Telephone** +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
**Send a question via our website** www.ema.europa.eu/contact

# Table of contents

# List of abbreviations

| | |
|---|---|
| ALL | Acute lymphoblastic leukemia |
| BCR-ABL | The abnormal fusion tyrosine kinase which causes CML |
| BMS | Bristol-Myers Squibb |
| BP-CML | Blast-phase chronic myeloid leukemia |
| CI | Confidence interval |
| CML | Chronic Myeloid Leukemia |
| CMR | Complete molecular response |
| COG | Children's Oncology Group |
| CP | Chronic Phase |
| CSR | Clinical study report |
| EU | European Union |
| HSCT | Hematopoietic stem-cell transplantation |
| K-M | Kaplan-Meier |
| MO | Major objection |
| MR4 | Rate of molecular response at a 4-log reduction from a standardized baseline |
| MRD | Minimal Residual Disease |
| N or n | Number (of subjects or observations) |
| NA | Not applicable |
| OC | Other concern |
| OS | Overall survival |
| PFOS | Powder for oral suspension |
| Ph | Philadelphia chromosome positive |
| QD | Once per day |
| SAP | Statistical analysis plan |
| SCE | Summary of Clinical Efficacy |
| SD | Standard deviation |
| SRC | Family of non-receptor tyrosine kinases including Hck, Lyn, Lck, and c-Src |
| TKI | Tyrosine-kinase inhibitor |
| US | United States |
| y | years |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bristol-Myers Squibb Pharma EEIG submitted to the European Medicines Agency on 28 November 2017 an application for a variation.

The following variation was requested:

| Variation requested | | Type | Annexes affected |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of Indication to include a paediatric indication for Philadelphia chromosome positive acute lymphoblastic leukaemia for Sprycel; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.2 of the SmPC are updated.
The Package Leaflet is updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to make minor editorial changes to the product information.
The RMP version 16.0 has also been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0042/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0042/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0042/2018.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

## *Scientific advice*

The applicant sought Scientific Advice at the CHMP:

| References of the paediatric scientific advices | Date |
|---|---|
| EMA/CHMP/SAWP/97503/2011 – protocol assistance for the treatment of paediatric patients with newly diagnosed Ph+ ALL, in combination with multiagent chemotherapy. | 2011-02-17 |
| EMA/CHMP/SAWP/629716/2012 - quality and clinical development in paediatric Ph+ CML and ALL | 2012-10-18 |
| EMA/CHMP/SAWP/629717/2012 – protocol assistance for paediatric Ph+ CML and ALL, for clinical development. | 2012-10-18 |

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Fátima Ventura

| Timetable | Actual dates |
|---|---|
| Submission date | 28 November 2017 |
| Start of procedure: | 3 March 2018 |
| CHMP Rapporteur Assessment Report | 2 May 2018 |
| CHMP Co-Rapporteur Assessment Report | 15 May 2018 |
| PRAC Rapporteur Assessment Report | 4 May 2018 |
| PRAC members comments | 7 May 2018 |
| Updated PRAC Rapporteur Assessment Report | 14 May 2018 |
| PRAC Outcome | 17 May 2018 |
| CHMP members comments | 22 May 2018 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 26 May 2018 |
| 1st Request for supplementary information (RSI) | 31 May 2018 |
| CHMP Rapporteur Assessment Report | 24 August 2018 |
| PRAC Rapporteur Assessment Report | 24 August 2018 |
| PRAC members comments | 29 August 2018 |
| Updated PRAC Rapporteur Assessment Report | 30 August 2018 |
| PRAC Outcome | 6 September 2018 |
| CHMP members comments | 10 Sep 2018 |
| Updated CHMP Rapporteur Assessment Report | 13 Sep 2018 |
| 2nd Request for supplementary information (RSI) | 20 September 2018 |
| MAH responses | 12 Oct 2018 |
| Restart of procedure: | 15 Oct 2018 |
| CHMP Rapporteur Assessment Report | 13 Nov 2018 |

| Timetable | Actual dates |
|---|---|
| PRAC Rapporteur Assessment Report | 13 Nov 2018 |
| PRAC members comments | 21 Nov 2018 |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC endorsed relevant sections of the assessment report [3] | 29 Nov 2018 |
| CHMP members comments | 03 Dec 2018 |
| Updated CHMP Rapporteur Assessment Report | 06 Dec 2018 |
| Opinion | 13 Dec 2018 |
| The CHMP adopted a report on similarity of SPRYCEL with Xaluprine, Blincyto, Iglusig and Besponsa on date (Appendix 1) | 13 Dec 2018 |

# 2. Scientific discussion

**Problem statement**

The European Commission granted a Marketing Authorization for Sprycel in November 2006 for the following indications:

For the treatment of adult patients with:

newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) in the chronic phase.

chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib.

Ph+ acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

For the treatment of paediatric patients with:

newly diagnosed Ph+ CML in chronic phase (Ph+ CML-CP) or Ph+ CML-CP resistant or intolerant to prior therapy including imatinib.

The scope of this variation is the extension of indication of dasatinib in combination with chemotherapyfor the treatment of paediatric patients with newly diagnosed Ph+ ALL.

**Disease or condition**

The proposed indication is for the treatment of paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy.

**Epidemiology and risk factors**

The annual incidence of ALL in childhood is approximately 9 to 10 cases per 100,000, with 3% to 5% of cases being Ph+ ALL. ALL is the most common form of cancer during childhood, affecting about 2500 children annually in Europe [1].

**Biologic features, aetiology and pathogenesis**

Paediatric ALL is a biologically heterogeneous cancer with multiple genetically defined subtypes. The disease is characterized by the accumulation of malignant lymphoblasts in the marrow or in various

extramedullary sites, frequently accompanied by suppression of normal hematopoiesis. The presence of the Philadelphia chromosome resulting from a reciprocal translocation between chromosomes 9 and 22 that creates the BCR-ABL fusion protein, defines a well-known subtype of ALL which is associated with a poorer prognosis.

**Clinical presentation, diagnosis and stage / prognosis**

Patients with ALL may present with a variety of hematologic derangements ranging from pancytopenia to hyperleukocytosis. The symptoms of ALL develop rapidly and are indicative of a reduced production of functional blood cells and bone marrow metaplasia, thus including fever, pain, increased risk of infections, increased tendency to bleed and signs indicative of anaemia, including pallor, tachycardia, fatigue, and headache.

**Management**

The standard of care for newly-diagnosed children and adolescents with Ph+ ALL varies somewhat among the paediatric cooperative groups. Before the development of ABL tyrosine kinase inhibitors (TKIs), there was no consensus on the optimal treatment of Ph+ ALL.

In EU, imatinib is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

The survival rate among subjects with Ph+ ALL still lags behind most other cytogenetic subgroups in paediatric ALL. Until recently, HSCT in first complete remission offered the best opportunity for long-term EFS for children with Ph+ ALL, with an improvement in disease free survival of up to 65% and OS 72%. This strategy is limited by the availability of a suitably matched donor, by the risk of post-transplant–related morbidity and mortality and by relapses after HSCT, particularly in those who are MRD positive prior to transplantation. Paediatric patients with no suitable donor for HSCT have an even more critical unmet need for disease management.

***About the product***

Dasatinib inhibits the activity of the BCR ABL kinase and SRC family kinases along with a number of other selected oncogenic kinases including c KIT, ephrin (EPH) receptor kinases, and PDGFβ receptor. Dasatinib is a potent, subnanomolar inhibitor of the BCR ABL kinase with potency at concentration of 0.6 0.8 nM. It binds to both the inactive and active conformations of the BCR ABL enzyme (SmPC, section 5.1).

In vitro, dasatinib is active in leukaemic cell lines representing variants of imatinib sensitive and resistant disease. These non-clinical studies show that dasatinib can overcome imatinib resistance resulting from BCR ABL overexpression, BCR ABL kinase domain mutations, activation of alternate signalling pathways involving the SRC family kinases (LYN, HCK), and multidrug resistance gene overexpression. Additionally, dasatinib inhibits SRC family kinases at subnanomolar concentrations (SmPC, section 5.1).

In vivo, in separate experiments using murine models of CML, dasatinib prevented the progression of chronic CML to blast phase and prolonged the survival of mice bearing patient derived CML cell lines grown at various sites, including the central nervous system (SmPC, section 5.1).

The recommended starting daily dosage of SPRYCEL tablets in paediatric patients is shown in Table 1.

| Table 1 Dosage of Sprycel tablets for paediatric patients with Ph+ ALL | |
|---|---|
| **Body Weight (kg)[a]** | **Daily Dose (mg)** |
| 10 to less than 20 kg | 40 mg |
| 20 to less than 30 kg | 60 mg |
| 30 to less than 45 kg | 70 mg |
| at least 45 kg | 100 mg |
| [a] The tablet is not recommended for patients weighing less than 10 kg. | |

SPRYCEL can be taken with or without a meal, either in the morning or in the evening (SmPC, section 4.2).

***Type of Application and aspects on development***

The applicant requested the approval for the following indication:

SPRYCEL is indicated for the treatment of paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy.

The CHMP adopted this indication without changes.

## *2.1. Introduction*

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity / environmental risk assessment

No ERA studies were submitted (see discussion on non-clinical aspects).

### 2.2.2. Discussion and Conclusion on non-clinical aspects

The justification provided by the MAH for not performing environmental risk assessment studies was considered acceptable. The addition of the paediatric population to the currently approved indications is not expected to significantly increase the use of dasatinib on the EU market. Therefore, it is unlikely that dasatinib will pose a significant risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

**Table 2 Overview of dasatinib paediatric development program of clinical studies**

| Study | Study Description | Patient Population | Dose Regimen | Subjects Treated | Status |
|---|---|---|---|---|---|
| CA180204<br><br>(Children's Oncology Group study Protocol AALL0622) | Phase 2, open-label, multi-center, single-arm study in children and young adults with newly diagnosed Ph+ ALL | Children , adolescents, and young adults from >1 to ≤30 years (at time of diagnosis) with newly diagnosed Ph+ ALL<br><br>Region: : Australia, Canada, New Zealand, and US | All subjects:<br><br>2 weeks of Induction therapy, followed by 2 weeks of Induction + dasatinib 60 mg/m$^2$ QD.<br>Cohort 1 (discontinuous dasatinib): Dasatinib 60 mg/m$^2$ QD during first 2 weeks of each 3-4 week post-Induction treatment block.<br>Cohort 2 (continuous dasatinib):Dasatinib 60 mg/m$^2$ QD during each 3-4 week post-Induction treatment block.<br><br>Dasatinib was offered at 48 mg/m$^2$ QD if 60 mg/m$^2$ QD dose was not tolerated. | Total (All): 62<br><br>Cohort 1: 40<br><br>Cohort 2: 22<br><br>Total (Paediatric): 55<br><br>Cohort 1: 35<br><br>Cohort 2: 20 | Complete<br><br>Final CSR: 26-Aug-2015 |
| CA180372 | Phase 2, open-label, multi-center single-arm, historically-controlled study in children and adolescents with newly diagnosed Ph+ ALL | Paediatric/adolescent subjects with newly diagnosed Ph+ ALL<br><br>Age range: >1 to <18 years (at time of diagnosis)<br><br>Region: Canada, Australia, UK, Italy, and US | Dasatinib PO 60 mg/m$^2$ and/or dasatinib PFOS 60 mg/m$^2$ in combination with the AIEOP-BFM ALL 2000 chemotherapeutic protocol | Total: 106 | Ongoing<br><br>Last patient last visit for the 3-year analysis: 28-May-2017<br><br>Final CSR: 03-Nov-2017 |
| *Bioequivalence Study for PFOS* | | | | | |
| CA180352 | Open-label, randomized, 3-period, 3-treatment crossover | Healthy subjects (not of childbearing potential)<br><br>Age range: 18 to 55 | Dasatinib PO single dose 100 mg as reference tablet (2 x 50 mg tablets; Treatment A)<br>Dasatinib PO single dose | Total: 78 | Complete<br><br>Final CSR: 06-Jun-2012 |

| Study | Study Description | Patient Population | Dose Regimen | Subjects Treated | Status |
|---|---|---|---|---|---|
| | bioequivalence study in healthy subjects | years<br>Region: US | 100 mg administered as 10 mL of the PFOS (10 mg dasatinib/mL; Treatment B)<br>Dasatinib PO single dose 100 mg as dispersed tablet (2 x 50 mg reference tablets; Treatment C) | | |

## 2.3.2. Pharmacokinetics

The clinical pharmacology profile of dasatinib in paediatric cancer patients has been characterized based on the PK data from 3 clinical studies (CA180018 in leukemia patients, CA180226 in CP-CML patients, and CA180038 in solid tumor and leukemia patients) (Table 3).

No PK data have been collected in the two clinical Phase 2 Ph+ ALL studies included in this variation application, CA180204 and CA180372.

**Table 3 Summary of studies contributing to dasatinib clinical pharmacology profile in paediatric Ph+ CML Patients, as assessed in a previous application**

| Study number | Type of study<br>Objective | Patient population | Dose regimen<br>Number of evaluable subjects | Analysis conducted |
|---|---|---|---|---|
| **CA180018** | Phase I, open label, dose-finding design (3+3, intra-subject dose escalation)<br>Establish RP2D of dasatinib in children and adolescents with relapsed or refractory leukemia. | Paediatric subjects (≥1 to ≤ 21 years of age) with:<br>• Ph+ CML in chronic, AP, or BP CML resistant or intolerant to imatinib,<br>• in first or subsequent relapse of Ph+ ALL<br>• Ph+ acute myeloid leukemia (AML) after prior imatinib,<br>• in second or subsequent relapse of Ph- ALL or AML | Dasatinib PO (tablets or tablet for dispersion)<br>60, 80, 100 and 120 mg/m$^2$ QD<br>N = 53 (Plasma PK data available)<br>N = 9 (CSF data) | PK (NCA) and PPK |
| **CA18038** | Phase I, open-label, dose-escalation (3+3 design)<br>To define toxicities, estimate MTD, and recommend a Phase 2 dose of dasatinib | Children (≥1 to ≤ 21 years of age) with:<br>recurrent/refractory solid tumors<br>or<br>imatinib-resistant Ph+ | Dasatinib PO (tablets or tablet for dispersion)<br>50, 65, 85, and 110 mg/m2 BID<br>N = 19 (Plasma PK data available) | PK (NCA) and PPK |

| | | | | |
|---|---|---|---|---|
| | administered as an oral agent given BID in children with solid tumors and imatinib resistant Philadelphia chromosome (Ph+) leukemia. | leukemia | | |
| **CA180226** | A Phase II study to estimate the MCyR rate to dasatinib therapy in children and adolescents with CP-CML who proved resistant or intolerant to imatinib.<br><br>To estimate the CCyR rate to dasatinib therapy in children and adolescents with newly diagnosed CP-CML who are treatment-naïve (except hydroxyurea) | Children and adolescents Children (≥1 to ≤ 21 years of age) with:<br>• newly diagnosed CP CML<br>• with Ph+ leukemias resistant/intolerant to imatinib | For subjects with CP-CML: 60 mg/m$^2$ dose (for subjects receiving tablets or tablet for dispersion) or 72 mg/m$^2$ dose<br><br>Cohort 1: CP-CML<br><br>Cohort 2: Advanced CML and Ph+ ALL<br><br>8 subjects with BP-CML<br><br>9 subjects with Ph+ ALL<br><br>Cohort 3: Treatment Naiive CP-CML<br><br>51 subjects in Cohort 3a (tablet)<br><br>33 (32 evaluable) subjects in Cohort 3b (PFOS) | PPK, D-R/E-R and PFOS Palatability |
| **CA180352** | Phase 1, open-label, randomized, 3-period, 3-treatment crossover.<br><br>BE study to assess the BE of 100 mg dasatinib PFOS and dispersed tablet relative to the intact tablet | Healthy adult subjects | Dasatinib PO<br>• Single dose cross-over: 2 x 50 mg intact tablet,<br>• 100 mg PFOS and<br>• 2 x 50 mg dispersed tablets<br><br>N = 77 | PK (NCA) and PFOS Palatability |

The number and age distribution of paediatric patients providing PK data are presented in Table 4.

**Table 4 Age distribution of paediatric subjects providing PK data in the clinical studies**

| | **CA180018** | **CA180038** | **CA180226** |
|---|---|---|---|
| Infant/toddler < 2 years | 2 | 0 | 2 |
| Children ≥2 to <12 years | 43 | 9 | 16 |
| Adolescents and older ≥12 to <18 years | 28 | 9 | 15 |

There are two dasatinib formulations for use in paediatric patients: (1) film-coated tablets and (2) powder for oral suspension (PFOS) for use in paediatric patients who cannot swallow or choose not to take the tablets. Dasatinib film-coated tablets are available in strengths of 20, 50, 70, 80, 100, and 140 mg and dasatinib PFOS is a powdered drug product, which, when constituted with water, provides a suspension at a dasatinib concentration of 10 mg/mL.

A physiologically-based pharmacokinetic (PBPK) model was developed and used to describe the clinical behaviours (BE, food effect, and particle size effect) of dasatinib PFOS and tablet in paediatric patients.

Body surface area (BSA)-normalized dosing was evaluated in paediatric clinical trials. Additionally, WT-tiered dosing was evaluated using PPK model-based simulations.

Dose-response (D-R) and exposure-response (E-R) relationships were characterized in paediatric patients with newly diagnosed Ph+ CP-CML from the Phase 2 study CA180226.

Pharmacokinetics of dasatinib tablet in paediatric patients

Non-compartmental analysis (NCA) PK analysis of dasatinib tablet formulation was performed using data collected in 72 paediatric subjects age ≥ 1 year old with relapsed or refractory leukemia or solid tumors (CA180018 and CA180038). The investigated once-daily (QD) and twice-daily (BID) doses ranged from 60 to 120 mg/m$^2$ and 50 to 110 mg/m$^2$, respectively. The dasatinib tablet was rapidly absorbed with a mean time of maximum observed concentration (Tmax) between 0.5 and 6 hours. Mean half-life (T-HALF) ranged from 2 to 5 hours across all dose levels and age groups. Similar to that observed in adults, high inter-subject variability was observed in the PK parameters of paediatric subjects, with coefficient of variation (CV) of maximum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC[INF]) greater than 50% for the 60-mg/m$^2$ tablet. Dasatinib PK showed dose proportionality with a dose-related increase in exposure observed in this paediatric population. There was no significant difference in dasatinib PK between children and adolescents. The geometric means of dose-normalized (DN) dasatinib Cmax, area under the concentration-time curve from time zero to time of the last quantifiable concentration (AUC[0-T]), and AUC(INF) were similar between children and adolescents across dose levels.

Pharmacokinetics of dasatinib powder for oral suspension in adult and paediatric patients

Dasatinib PFOS was developed as an age-appropriate formulation for paediatric patients who cannot swallow the tablet formulation. Study CA180352 compared the PK of dasatinib PFOS to the intact tablet formulation in 77 healthy adult subjects. Results showed that the exposure (by AUC[INF]) with PFOS was approximately 19% less than that obtained with intact tablets in healthy adults treated with a dose of 60 mg/m$^2$. On the basis of these results, a PFOS dose of 72 mg/m$^2$ was selected to evaluate the efficacy, safety, and PK of dasatinib in paediatric patients age ≥ 1 year old with newly diagnosed CP-CML (Cohort 3b of CA180226). This dose was selected to match exposure for the selected Phase 2 dose of intact tablet at 60 mg/m$^2$.

The concentration data from the PFOS cohort of Study CA180226 (Cohort 3) was pooled with data from the Phase 1 studies for a population pharmacokinetic (PPK) analysis (694 observed concentrations from 104 paediatric subjects). The analysis characterized the PK of dasatinib in paediatric subjects by a linear 2-compartment model with first-order absorption, similar to that of the PK model in adult CML subjects. Both the apparent clearance (CL/F) and central volume of distribution (VC/F) increased with increasing body weight (WT) in paediatric subjects. The analysis showed that the bioavailability of PFOS was approximately 40% lower than that of tablet in paediatric patients, and as a result of the low bioavailability, the exposure of PFOS (as measured by time-averaged concentration at steady state [Cavgss]) at 72 mg/m$^2$ was approximately 30% lower than that of the tablet at 60 mg/m$^2$ in paediatric subjects newly diagnosed with CP-CML.

*Drug-Drug Interactions*

Dasatinib is extensively metabolized in humans, and CYP3A4 plays a major role in its metabolism.

When a single morning dose of dasatinib was administered in adults following 8 days of continuous evening administration of 600 mg of rifampin, a potent CYP3A4 inducer, the mean Cmax and AUC of dasatinib were decreased by 81% and 82%, respectively. Substances that inhibit CYP3A4 activity may decrease metabolism and increase concentrations of dasatinib. A 20-mg dasatinib QD co-administered with 200 mg of ketoconazole twice daily in adults increased the dasatinib Cmax and AUC by four- and five-fold, respectively.

Dasatinib is a weak CYP3A4 inhibitor and has little potential to induce CYP3A4. Single-dose data from a study in adults indicate that the mean Cmax and AUC of simvastatin, a CYP3A4 substrate, were increased by 37% and 20%, respectively, when simvastatin was administered in combination with a single 100-mg dose of dasatinib.

The list of co-administered chemotherapy agents is provided in Table 5 together with their categories as CYP3A4 substrate, inducer or inhibitor.

**Table 5 List of chemotherapy agents in combination with dasatinib for treating paediatric Ph+ ALL**

| Chemotherapy Regimen | CYP3A4 Substrate | CYP3A4 Inducer | CYP3A4 Inhibitor |
|---|---|---|---|
| Cyclophosphamide | - | - | - |
| Mercaptopurine | - | - | - |
| Cytarabine | - | - | - |
| Methotrexate | - | - | - |
| Dexamethasone | yes | - | - |
| Vincristine | yes | - | - |
| Leucovoin | - | - | - |
| Hydrocortisone | yes | - | - |
| L-Asparaginase | - | - | - |
| Ifosfamide | - | - | - |
| Daunorubicin | - | - | - |
| Etoposide | - | - | - |
| Thioguanine | - | - | - |
| Doxorubicin | - | - | - |

"-" indicates the agent is not a known substrate, inducer, or inhibitor

*Dasatinib exposure comparison in paediatric patients by disease status (AP/BP-CML/ALL/AML and CP-CML)*

Dasatinib plasma concentration data were collected in paediatric leukaemia patients in the Phase 1 Study CA180018. CA180018 was an open-label, dose-escalation (3+3 design, intra-subject dose escalation) study in children and adolescents/adults, ≥ 1 to < 21 years of age, who were treated with dasatinib orally 60, 80, 100 and 120 mg/m$^2$ QD until refractory disease progression, intolerable toxicity, or patient/physician preference.

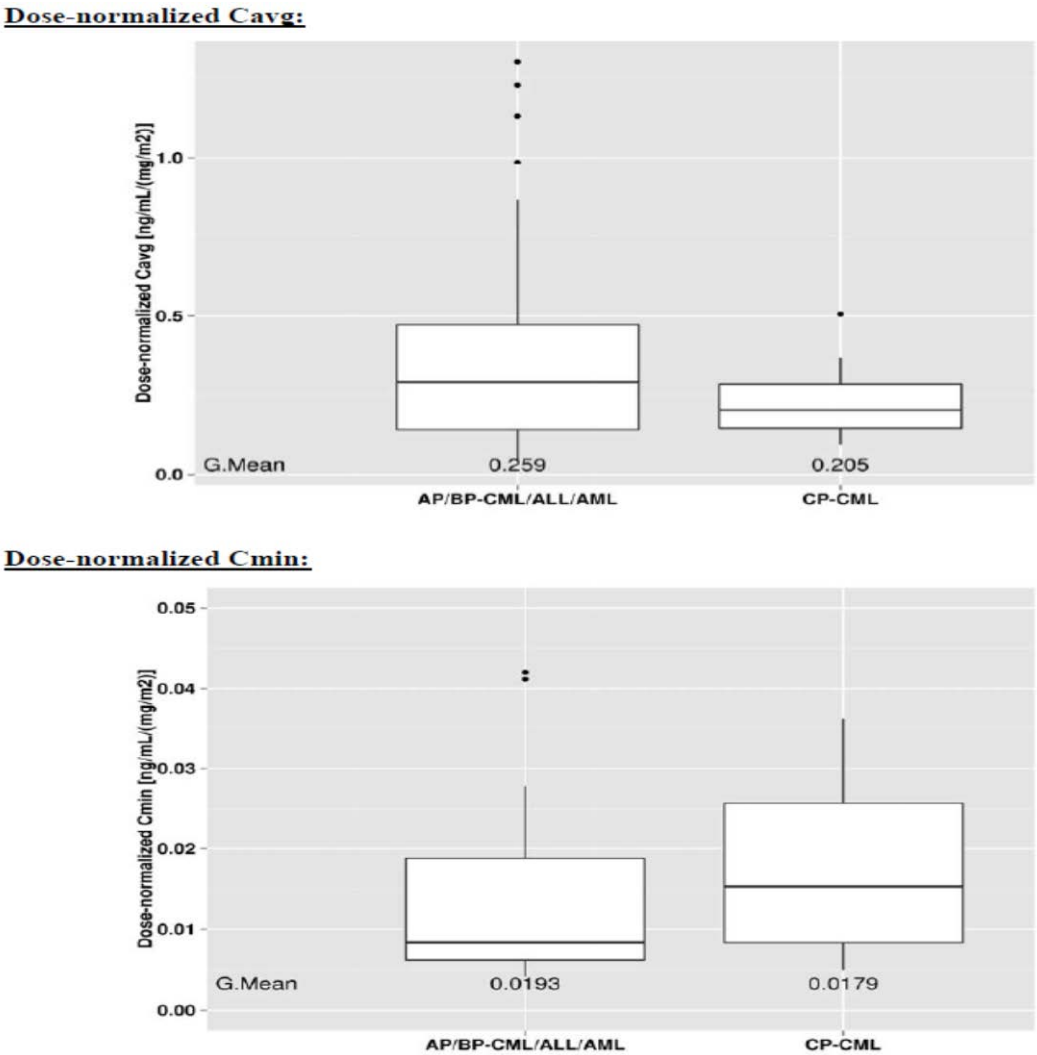
Plasma PK data were available for 53 subjects, including 15 with CP-CML, 3 with advanced phases CML (2 in accelerated phase and 1 in lymphoid blast phase), 12 with Ph+ ALL, and 23 with Ph- ALL or AML.

To support bridging of the dose recommendation from paediatric CP-CML to Ph+ ALL, an assessment was done by comparing the exposure by disease status (ie, CP-CML vs Ph+ ALL).

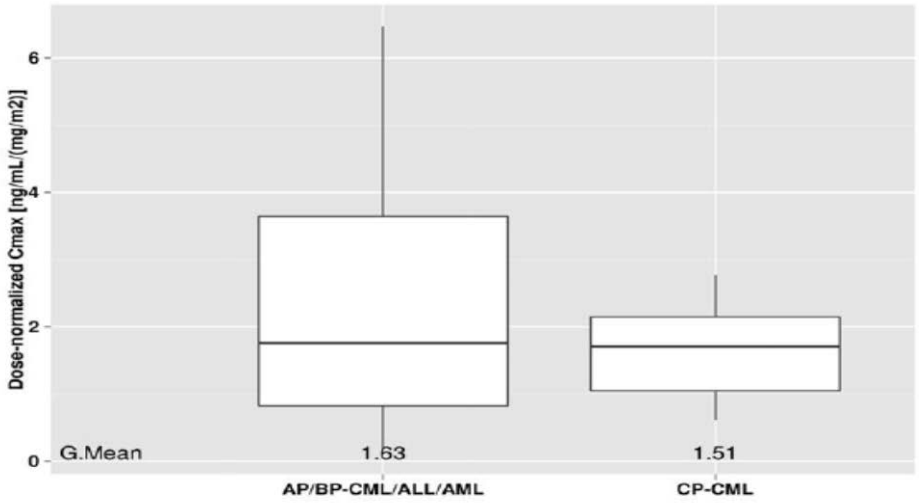
The exposure metrics (Cavg, Cmin and Cmax) were normalized by the mg/m$^2$ dose for comparison. Body weight was shown to have effect on dasatinib PK in paediatric patients. Normalization was performed using the nominal mg/m$^2$ dose in order to account for potential difference of body size between the 2 disease groups (CP-CML and advanced phases CML/Ph+ ALL).

The results are presented in Figure 1.

**Figure 1 Dose-normalized exposure to dasatinib in paediatric patients, by disease status**



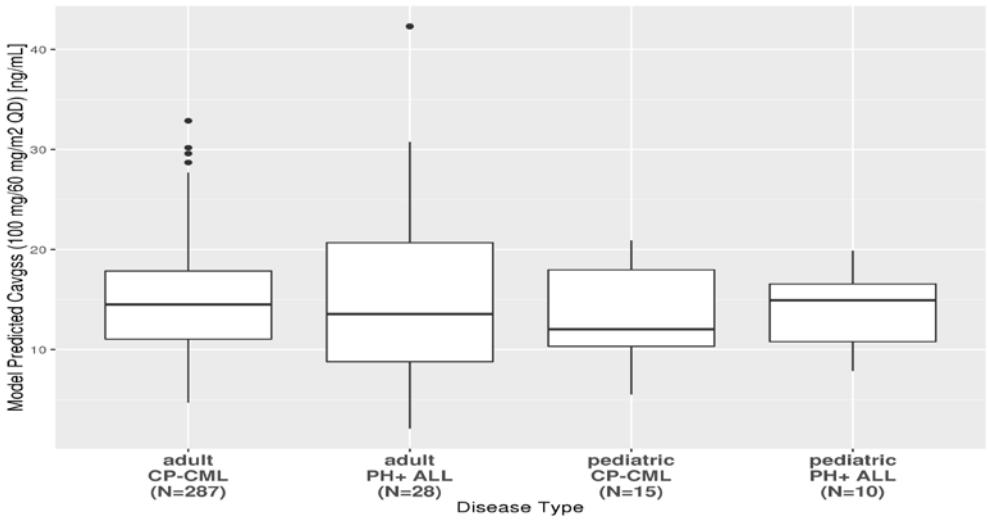
**Dose-normalized Cmax:**

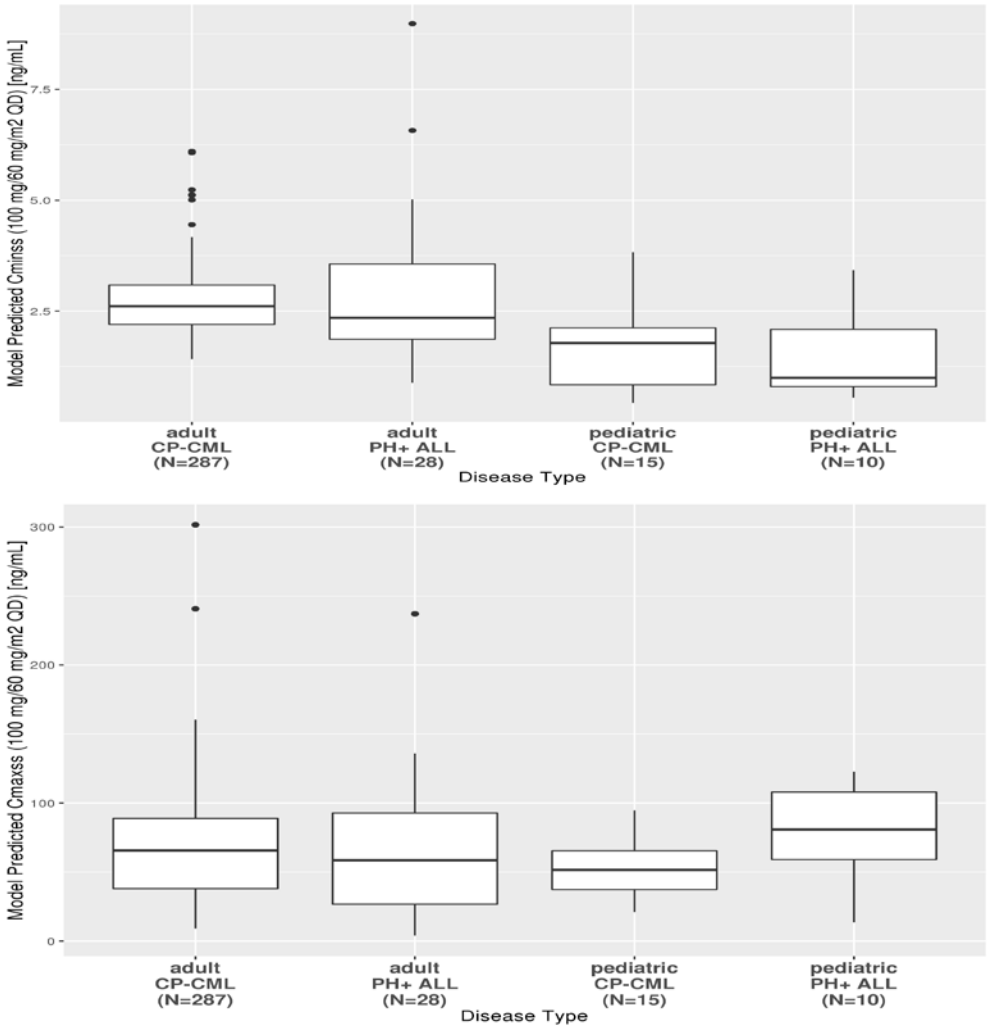



Note: Advanced Phase N = 15; CP-CML N = 21; Accelerated Phase CML N = 4; Blast Phase CML N = 1; Ph+ ALL N = 16; Ph- ALL N = 8; Ph- AML N = 19

Dasatinib exposure measures [Cavgss, Cminss and Cmaxss]) stratified by disease type and separately for adult and paediatric subjects are presented in Figure 2.

**Figure 2 Population PK Model-Estimated Individual Exposure By Disease Status for Dasatinib Tablet Formulation**






1. Abbreviations: Cavgss = time-averaged concentration at steady state; Cminss = minimum concentration at steady state; Cmaxss = maximum concentration at steady state; CP-CML= chronic phase chronic myeloid leukemia; PH+ ALL = Philadelphia chromosome positive acute lymphoblastic leukemia; QD = once daily.
2. Note: The bar inside the box represents the median, edges of the box represent the 25th and 75th percentiles, and whiskers represent the 5th and 95th percentiles.

*Dose Selection and Justification in Paediatric Subjects with Ph+ ALL*

The recommended dose for paediatric patients with Ph+ ALL is identical to the dose recommended for CP-CML, ie, a WT-tiered dosing recommended as presented in Table 6.

**Table 6 Comparability of Predicted Dasatinib Exposure at Recommended WT-Tiered Doses to Tablet 60 mg/m$^2$**

| Body Weight [kg] | OnceDaily Dose [mg] | Formulation | % Difference in Geo. Mean | | |
|---|---|---|---|---|---|
| | | | Cavgss | Cminss | Cmaxss |
| 5 - < 10[a] | 40 | PFOS | -2.67 | -11.2 | 28.54 |
| 10 - < 20 | 40 | tablet | 2.86 | 2.70 | 3.29 |
| | 60 | PFOS | 1.90 | -6.31 | 25.39 |
| 20 - < 30 | 60 | tablet | 8.33 | 8.04 | 8.37 |
| | 90 | PFOS | 9.17 | 0.00 | 40.11 |
| 30 - < 45 | 70 | tablet | -3.62 | -3.23 | -3.63 |
| | 105 | PFOS | -6.52 | -20.89 | 23.36 |
| ≥ 45 | 100 | tablet | 8.00 | 7.94 | 8.08 |
| | 150 | PFOS | 9.33 | -3.97 | 38.22 |

[a] Tablet is not recommended for 5 to < 10 kg group. Patients in this body weight group are not likely to swallow the tablet.

Analysis -Directory: /global/pkms/data/CA/180/PFOS-dose-selection/prd/FDA-19-July2017/final/

Program Source: Analysis-Directory/R/scripts/smr-simresults-uspi-ipred.r

Source: Analysis-Directory/R/export/cmp-t60-tabtier.csv
Analysis-Directory/R/export/cmp-t60-pfostier.csv

- *Dose selection and justification for tablet*

Dasatinib 60-mg/m$^2$ tablet was tested in the Phase 2 study CA180372 in paediatric Ph+ ALL subjects. The study was designed when the optimal schedule was being explored in adults, which showed that the QD schedule had similar overall efficacy and improved safety as compared with the BID schedule in adults. Once-daily dosing in the paediatric population was, therefore, selected over the BID dosing schedule.

In a Phase 1 dose-escalation study (CA180018) of dasatinib in children and adolescents with relapsed or refractory leukemia, treatment responses were seen in Ph+ patients who received single-agent dasatinib 60 or 80 mg/m$^2$. No maximum tolerated dose was identified up to doses of 120 mg/m$^2$ daily. Rates of both major cytogenic response (MCyR) and complete cytogenetic response (CCyR) among 17 paediatric patients with advanced phase CML/Ph+ ALL (stratum 2/3) were 50% and 77.7% with 60 mg/m$^2$ and 80 mg/ m$^2$ QD, respectively. The proportion of subjects in this stratum with drug-related SAEs was 25% and 33% in the 60 and 80 mg/m$^2$ cohorts, respectively. Based on these data and preliminary COG AALL0622 data which showed that 60 mg/m$^2$ QD can be safely combined with chemotherapy, the 60 mg/m$^2$ QD dose was selected for further testing in the Phase 2 study CA180372.

The benefit-risk profile at the tablet dose of 60 mg/m$^2$ in paediatric Ph+ ALL was further characterized in the Phase 2 study CA180372. The 3-year binomial EFS rate with dasatinib plus chemotherapy was 66.0% (90% CI: 57.7, 73.7), which was superior compared to chemotherapy alone in AIEOP-BFM 2000 (49.2% [90% CI: 38.0, 60.4]), and non-inferior (90% CI: -3.3, 17.2) compared to continuous imatinib plus chemotherapy in the Amended EsPhALL Trial (59.1% [90% CI: 51.8, 66.2]). The safety profile of dasatinib treatment in paediatric subjects with treatment-naive Ph+ ALL indicated that daily dasatinib dosing was well-tolerated and safe. No new safety signals were observed. The most common dasatinib-related AEs were anemia (28.3%), neutropenia (24.5%), and febrile neutropenia (23.6%), which were consistent with the known safety profile of dasatinib.

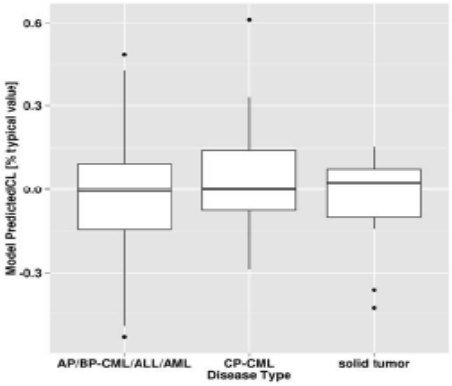
The tablet is available in the strength of 20, 50, 70, 80 and 100 mg. A WT-tiered dosing in paediatric patients was selected to produce similar summary steady-state exposures to target exposures of the

60-mg/m$^2$ tablet QD. The dosing was evaluated by simulating dasatinib exposures for each WT tier using the developed paediatric PPK model (5-120 kg with every 5-kg increment) under various dosing scenarios, taking into account the available tablet dosing strengths. The difference of exposure measures produced by the selected WT-tiered dosing was less than 20% from the reference exposure for all WT tiers.

The WT-tiered dosing is also recommended for paediatric Ph+ ALL based on the same set of simulations, which is supported by the following:

1) There were no marked disease-related differences in the PK parameters of dasatinib, both in adults and in paediatrics. Figure 3 shows the distribution of PPK model estimated dasatinib clearance by paediatric disease status.

**Figure 3 PPK model-estimated individual clearance, by disease status**




2) The same reference dose of tablet 60 mg/m$^2$ has been showed in Study CA180226 to be safe and efficacious in paediatric CP-CML patients, as well as in Study CA180372 with a favorable benefit-risk profile when co-administered with chemotherapy in paediatric Ph+ ALL patients.

3) Dasatinib PK is unlikely to be changed when it is co-administered with chemotherapy in treating paediatric Ph+ ALL.

The previously conducted PPK model based simulation can, therefore, be applied to recommending WT-tiered dosing in paediatric Ph+ ALL, by matching the same reference exposure of the 60 mg/m$^2$ tablet.

- *Dose selection and justification for PFOS in paediatric patients newly diagnosed with Ph+ ALL*

The use of the PFOS formulation was introduced into Study CA180372 in order to provide dosing flexibility for the very young children (as young as 1 year old) enrolled who experienced difficulty with the tablet formulation (whole or dispersed).

In procedure EMEA/H/C/000709/X/0056/G, a bioequivalence study was submitted (CA180352) to compare the ratio and extent of absorption of dasatinib between 100 mg dasatinib PFOS and 2 x 50 mg dasatinib tablet as reference (Table 7).

**Table 7 Bioequivalence of Powder for Oral Suspension (PFOS) and Reference Tablet (Pharmacokinetic Evaluable Population)**

| Treatment and Comparison | AUC(INF) (ng•h/mL) GM [n] | Cmax (ng/mL) GM [n] | AUC(0-T) (ng•h/mL) GM [n] |
|---|---|---|---|
| A | 419 [75][a] | 114 [78] | 374 [78] |
| B | 339 [77] | 106 [77] | 328 [77] |
| | Ratio of Adjusted GMs (90% CI) | | |
| B vs A | 0.808 (0.750, 0.869) | 0.937 (0.822, 1.067) | 0.878 (0.796, 0.967) |

Treatment A: A single oral dose of dasatinib, 100 mg as reference tablet (2 x 50 mg tablets).
Treatment B: A single oral dose of dasatinib, 100 mg administered as PFOS.
[a] AUC(INF) could not be determined in 3 subjects (10052, 10057, and 10060) after receiving Treatment A.

Results showed that the PFOS and the dispersed tablet were not bioequivalent to the reference tablet formulation. The exposure (by AUC[INF]) for PFOS was found to be approximately 19% less than that with intact tablets in healthy adults. These results suggested a dose increase of 20% may be needed when using the PFOS formulation to potentially match the exposure of the tablet formulation in adults.

There were no safety data available at that time on the impact of such a dose increase on Ph+ ALL paediatric patients, who were being treated with chemotherapy. The PFOS dose was not increased to 72 mg/m$^2$ until further safety evidence was available.

PFOS dose of 72 mg/m$^2$ was further studied in paediatric subjects with treatment-naïve CP-CML in Study CA180226. The PK, efficacy, and safety of PFOS 72 mg/m$^2$ provided the basis for dose recommendation of paediatric CP-CML patients. The result of this trial suggested that a dose of dasatinib PFOS 72 mg/m$^2$ may not be sufficient to achieve a comparable exposure level to that from a 60 mg/m$^2$ tablet in CML paediatric patients, and that an increase to 90 mg/m$^2$ may be needed. A PBPK model indicated the mechanism that likely drives reduced bioavailability for suspension treatments relative to tablets is inherent to the *in vivo* gastric behaviour of the two different dosage forms (shorter gastric transit for suspensions) and not likely related to the formulation composition. Safety data from Study CA180226 showed that the PFOS dose could safely be increased from 60 mg/m$^2$ to 72 mg/m$^2$. Since the PK of dasatinib was assessed to be independent of disease state (ie, CML or ALL) and given the safety data already accumulated in Ph+ ALL population with dasatinib 60 mg/m$^2$ tablet combined with chemotherapy, it was determined that a dose increase of PFOS to at least 72 mg/m$^2$ in Ph+ ALL paediatric patients would be safe. However, the PFOS dose was not increased to 72 mg/m$^2$ because study enrollment had closed and the treatment for the remaining subjects was near to completion. Therefore, PFOS continued to be offered at 60 mg/m$^2$ in Study CA180372.

The dasatinib PFOS dose recommendation for paediatric Ph+ ALL is identical to the dose recommendation for CP-CML. In Study CA180372, 24 subjects received at least 1 dose of the PFOS, and 8 out of the 24 were administered this formulation exclusively.

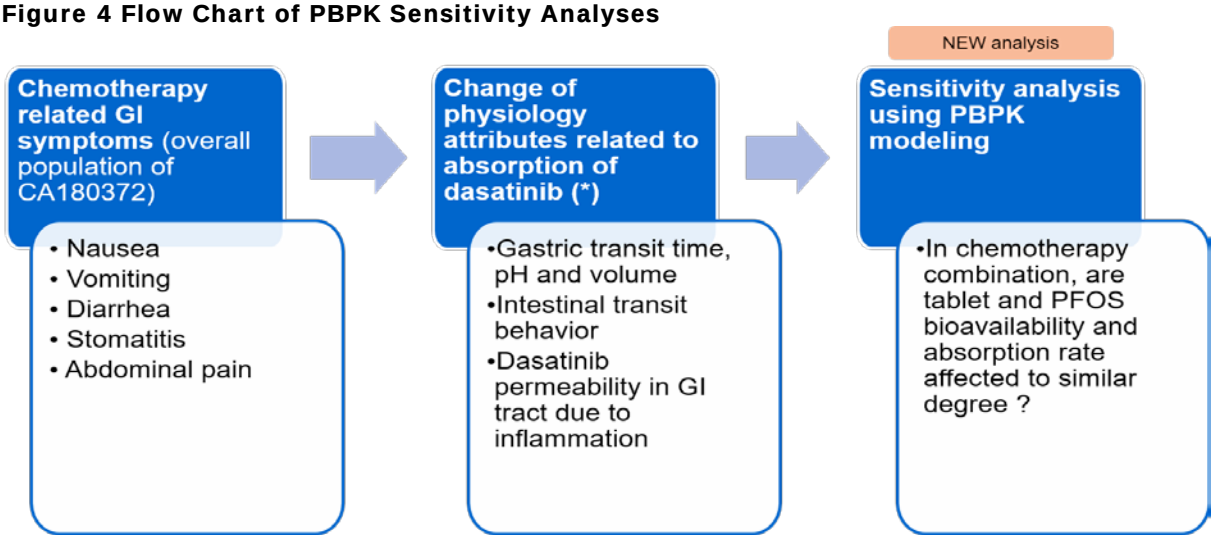
Specifically, the previous PPK model was developed using data from multiple studies including data from Ph+ ALL paediatric subjects. Given the PK similarity between disease statuses, the PPK model inference was expected to apply to Ph+ ALL as well. The model identified ~40% lower bioavailability of PFOS, which was reflected in the WT-tiered dosing table by a fixed ratio between PFOS and tablet doses in each WT tier.

Dasatinib was tolerated at tablet doses up to 120 mg/m$^2$ and showed a safety profile that was manageable in paediatric subjects with leukemia. Exposure resulting from the WT-tiered dosing of PFOS was expected to be similar to tablet 60 mg/m$^2$ and, therefore, within the established safety margin.

*The effect of GI toxicity on the PK of dasatinib*

In order to quantitatively assess the effect of GI toxicity on dasatinib absorption, sensitivity analyses were performed using a physiologically based pharmacokinetic (PBPK) model. The steps of the analyses are illustrated in Figure 4.

**Figure 4 Flow Chart of PBPK Sensitivity Analyses**




The results of the PBPK model predicted percent change of dasatinib exposure related to GI toxicity, by formulation and food is presented in Table 8.

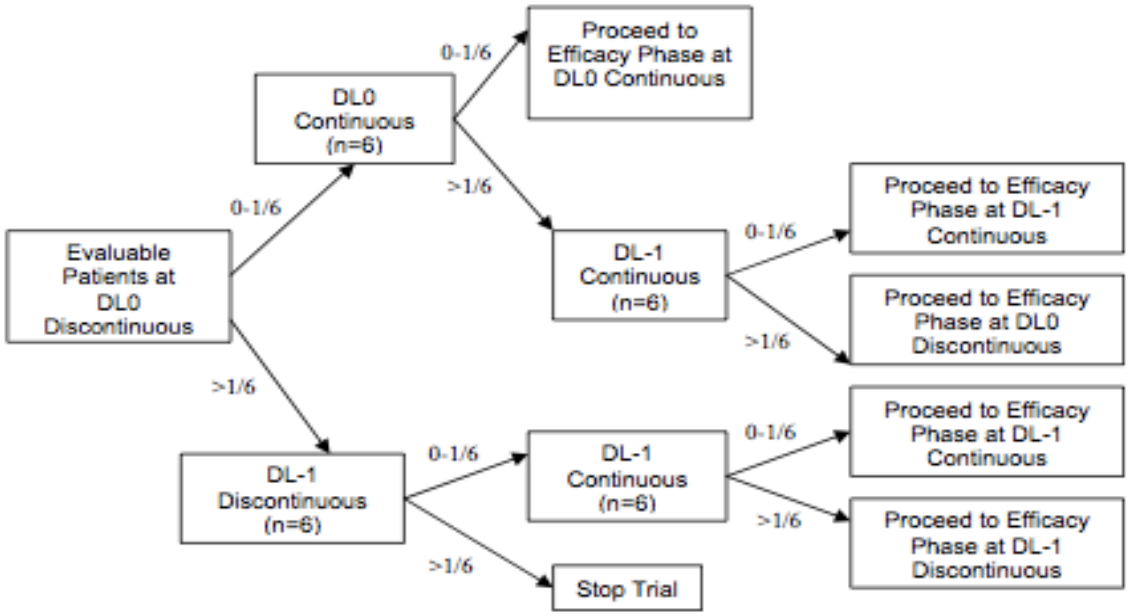
**Table 8 PBPK Model Predicted Percent Change of Dasatinib Exposure Related to GI Toxicity, by Formulation and Food**

| Tablet (60mg/m$^2$) | | | |
|---|---|---|---|
| | Baseline Fasted | GI Tox Fasted | % Change from Baseline |
| GM Cmax (%CV) ng/mL | 82.2 (60.3) | 101 (47.2) | 22.9 |
| GM AUC(0-24hr) (%CV) ng-hr/mL | 338.1 (69.7) | 482.7 (59) | 42.8 |
| Median Tmax (Range) | 1.16 (0.68-1.84) | 1.56 (0.8-3.2) | NA |
| PFOS (90mg/m$^2$) | | | |
| | Baseline Fasted | GI Tox Fasted | % Change from Baseline |
| GM Cmax (%CV) ng/mL | 108.9 (59.4) | 153.2 (47.3) | 40.7 |
| GM AUC(0-24hr) (%CV) ng-hr/mL | 386.4 (67) | 598.7 (61.0) | 54.9 |
| Median Tmax (Range) | 0.7 (0.4-1.64) | 1.36 (0.68-2.7) | NA |

Abbreviations: CV = coefficient of variation; GI = gastrointestinal; GM = geometric mean; NA = not applicable; Tox = toxicity. Source: /global/pkms/data/CA/180/EMA-ALL-response/dev/pk/final

Study CA180204, included a safety phase (dose finding phase) dedicated to a stepwise incorporation of dasatinib into the backbone chemotherapy as used in COG study AALL0031 – which included imatinib. Study CA180204 was an open-label, multi-center, single-arm Phase 2 study in children and young adults with newly diagnosed ALL (see description of the study under section ''Supportive study'').

**Figure 5 Diagram of Safety Phase**




Note: Six subjects were evaluated beginning at DL0 (60 mg/m$^2$ daily), dose given discontinuously. If 2 or more of the 6 subjects had unacceptable delays, then the dose of dasatinib was reduced to 48 mg/m$^2$ daily (DL-1). An additional 6 subjects were then accrued at this lower dose level (DL-1). If ≥ 5/6 subjects safely completed Intensification Block 1 at a given dose level, Cohort 2 opened at DL0, with the dose given continuously. When a safe dose level was established, the efficacy phase of the trial opened to accrual. Subjects treated at the established dose level during the safety phase were included in the analyses for the efficacy phase.

Subjects included in this phase received dasatinib discontinuously in 2-week periods followed by 1 to 2 weeks off. A tolerable level of 60 mg/m$^2$ was established, enrolment into the safety phase was stopped and the efficacy phase of the trial opened with dasatinib administered continuously. Patients in this trial are later reviewed and referred to the discontinuous and (part of the) continuous tablet group.

## 2.3.3. Discussion on clinical pharmacology

Two clinical studies have been conducted in paediatric subjects with Ph+ ALL where dasatinib has been co-administered with chemotherapy. Most patients have been treated with tablets. Out of 106 subjects in study CA180372, 24 received at least one PFOS dose and 8 subjects were treated with PFOS exclusively.

Dasatinib is primarily metabolised by CYP3A4 however most chemotherapeutic agents used for Ph+ ALL are not inhibitors or inducers of CYP3A4 and no change in PK is expected when dasatinib is co-administered with chemotherapy.

Concomitant use of dexamethasone, a weak CYP3A4 inducer, with dasatinib is allowed; dasatinib AUC is predicted to decrease approximately 25% with concomitant use of dexamethasone, which is not likely to be clinically meaningful (SmPC, section 4.5).

A BE study in healthy adults concluded that the bioavailability of PFOS was approximately 19 % lower compared to tablets and therefore a dose of 72 mg/m$^2$ PFOS was expected to be comparable to the tablet dose of 60 mg/m2 and used in the CP-CML studies. However, the PFOS dose of 60 mg/m$^2$ was not increased in the Ph+ ALL study CA 180372 as enrolment was completed. In study CA180372, out of 106 subjects, 24 received at least one PFOS dose and only 8 subjects were treated with PFOS exclusively.

Dasatinib exposure measures appeared to be consistent across disease type (CP-CML and Ph+-ALL) for both adult and paediatric subjects, though PK data from paediatric Ph+ ALL subjects are limited. Pop PK analysis in paediatric subjects has showed that the bioavailability of PFOS is even lower in paediatric subjects. The analysis showed that the bioavailability of PFOS was approximately 40% lower than that of tablet in paediatric patients. This is expected to be due to faster gastric transit time of the formulation. The importance of an oral solution is acknowledged. Paediatric subjects treated also with chemotherapy may have difficulties swallowing tablets and will have a high need for an alternative oral formulation. However, no clinical data are available to support the proposed dose and no PK data are available from paediatric Ph+ ALL patients treated only or partly with PFOS. With the use of a PBPK model the applicant has adequately justified the proposed PFOS dose.

The MAH has not planned to conduct a “window” study with the PFOS dose 90 mg/m$^2$ in Ph-positive paediatric ALL. A PBPK model has been used to justify the proposed PFOS dose. The results showed that dasatinib exposure is likely to increase modestly for both tablet and PFOS with GI toxicity (including change in gastric transit time and small intestinal transit time, inflammation related change in permeability, and variations of gastric pH values). The modest increase in exposure is not considered to be clinically relevant and especially no impact on clinical efficacy due to GI toxicity is expected. Even though the model has some limitations, it is acknowledged that PK should not be further explored in the rare and vulnerable target population of this application. The presented simulations and justifications for a bridging strategy between CP-CML and Ph+-ALL are considered adequate.

For CP-CML a PFOS dose of 90 mg/m$^2$ has been proposed and endorsed by CHMP, but bioequivalence will be investigated in a PK window study in CP-CML conducted post-approval. As the PK, including bioavailability, of dasatinib appear to be comparable across disease status, the PFOS dose used in CP-CML has also been endorsed for the Ph+ ALL indication. The MAH is committed to provide the results of this PK-window study post-approval. In relation to this it needs to stressed that although (based on the mechanistic understanding, the analysis of efficacy versus GI toxicity, formulation and patient populations, and the analysis of PK in the different patient populations) the PBPK model is considered to provide reassuring data on the extrapolation of PK across the patient populations, the PBPK model is not fully validated. The CHMP recommended the MAH to confirm (post-approval) that post-approval analysis will be conducted to demonstrate that the PBPK model adequately captures the effects of chemotherapy on absorption in line with the existing guideline on Reporting and Qualification of PBPK models. .

## 2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of dasatinib has been investigated to a reasonable extent in the paediatric population in ALL. The PK of dasatinib appears to be similar in paediatric patients with CP-CML and

Ph+ ALL. The impact of chemotherapy -related gastrointestinal side effects on dasatinib absorption and bioavailability in the paediatric population has been explored with a PBPK model, and no concerns have been identified.

## *2.4. Clinical efficacy*

N/A

## *2.5. Dose response studies*

Please refer to section 2.3.2. Pharmacokinetics.

## Main study – Study CA180372 ()

Study CA180372 was a Phase 2, open-label, multi-centre, single-arm, historically-controlled study of dasatinib added to standard chemotherapy in paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL).

### *Methods*

#### Study participants

##### *Inclusion Criteria*

- Children and adolescents > 1 year and < 18 years of age with newly diagnosed Ph+ ALL, and have documented presence of t(9;22) determined by cytogenetics or BCR-ABL fusion via RTPCR or FISH (local laboratory), who are candidates for standard multi-agent chemotherapy (AIEOP-BFM ALL 2000 regimen)
- Started induction chemotherapy up to 14 days prior to enrolment according to institutional standard of care
- Performance status >=60% (Karnofsky for subjects > 16 years of age and Lansky for subjects ≤16 years of age)
- Direct bilirubin ≤3 times the ULN for age
- ALT and AST >10 times the ULN for age
- Serum creatinine ≤1.5 times the institutional ULN for age/gender or
- Creatinine clearance or GFR ≥80 ml/min/1.73 m2
- QTc < 450 msec on baseline ECG (within 21 days prior to study enrollment)
- LVEF ≥50% by gated radionuclide study or shortening fraction > 27% by echocardiogram

For COG sites (excluding DFCI Consortium sites), subjects must had been enrolled in the COG classification trial (AALL08B1 or successor).

##### *Exclusion Criteria*

- Prior treatment with a BCR-ABL inhibitor (e.g. imatinib)

- Biopsy-proven Ph+ ALL extramedullary involvement of the testicles
- Active systemic infection in conjunction with septic shock syndrome that requires either vasopressor support or mechanical ventilation.
- Known clinically significant disorder of platelet function (eg, von Willebrand's disease)
- Clinically significant cardiovascular disease including ANY one of the following:
    - Congenital long QT syndrome
    - History of ventricular arrhythmias or heart block
- Down syndrome (constitutional trisomy 21)
- Prior stem cell transplant
- Ph+ ALL occurring as a second malignant neoplasm after treatment of a prior malignancy

## Treatments

Dasatinib was orally delivered as a tablet, as a dispersed tablet, or as a suspension from a powder (PFOS) at a dose of 60 mg/$m^2$ daily. For children and adolescents capable of swallowing tablets, the existing tablets in strengths of 5 mg, 20 mg, and 50 mg were given to cover the anticipated dose range. If necessary for administration in young children not able to swallow tablets, dasatinib tablets were allowed to be dispersed in 100% preservative-free juice (ie, orange or apple juice or lemonade). The PFOS bottle was constituted with 77 mL purified water or sterile water for injection to give a total volume of 99 mL with a 10 mg/mL suspension. Dasatinib PFOS (offered at the same dose as the tablet [60 mg/$m^2$]) was developed for paediatric patients who are unable to swallow the tablet.

This study utilized the standard Associazione Italiana di Ematologia Paediatrica - Berlin-Frankfurt-Muenster (AIEOP BFM) ALL 2000 chemotherapeutic protocol. Chemotherapy was obtained by the investigating site's standard prescribing procedures according to country availability and specific regulatory requirements. The chemotherapy regimen used in study CA180372 was the same as the chemotherapy regimen used in European Intergroup Study on Post-induction Treatment of Philadelphia Positive Acute Lymphoblastic Leukemia (EsPhALL) and AIEOP BFM ALL 2000 trials.

**Table 9 Non-investigational Products - Study CA180372**

| Phase | Chemotherapy Regimen | Phase | Chemotherapy Regimen |
|---|---|---|---|
| 1. Induction Block IB | Cyclophosphamide<br>Mercaptopurine<br>Cytarabine<br>Methotrexate | 5) 1st Reinduction Block (R1) | Dexamethasone<br>Vincristine<br>Doxorubicin<br>L-Asparaginase<br>Cyclophosphamide<br>Cytarabine<br>Thioguanine<br>Methotrexate |
| 2. High Risk Block 1 (HR1) | Dexamethasone<br>Vincristine<br>Methotrexate<br>Leucovorin<br>Cytarabine<br>Hydrocortisone<br>Cyclophosphamide<br>L-Asparaginase | 6) Interim Maintenance (IM) | Mercaptopurine<br>Methotrexate |
| 3. High Risk Block #2 (HR2) | Dexamethasone<br>Vincristine<br>Methotrexate<br>Leucovorin<br>Ifosfamide<br>Cytarabine<br>Hydrocortisone<br>Daunorubicin<br>L-Asparaginase | 7) 2nd Reinduction Block (R2) | Dexamethasone<br>Vincristine<br>Doxorubicin<br>L-Asparaginase<br>Cyclophosphamide<br>Cytarabine<br>Thioguanine<br>Methotrexate |
| 4. High Risk Block #3 (HR3) | Dexamethasone<br>Cytarabine<br>Etoposide<br>L-Asparaginase<br>Methotrexate<br>Hydrocortisone | 8) Continuation Therapy | Mercaptopurine<br>Methotrexate |

The components of treatment were divided into successive blocks as follows:

*Phase I - For all subjects:*

- Induction IA (4 - 5 weeks): During the first 2 weeks, the subjects received frontline ALL induction chemotherapy outside the protocol. They were enrolled in the study and started to receive dasatinib when Ph+ status was confirmed via cytogenetics, FISH, or PCR prior to Day 15.
- Induction IB (dasatinib continued) (28 days, 4 weeks)
- Recovery period (dasatinib continued, no chemotherapy given) (2 - 4 weeks)
- Three successive consolidation blocks (HR1, HR2, and HR3) of 21 days each, 3 weeks each
- Recovery period (dasatinib continued, no chemotherapy given) (14 days, 2 weeks)

*Phase IIa - For the subjects who do not meet the criteria for HSCT:*

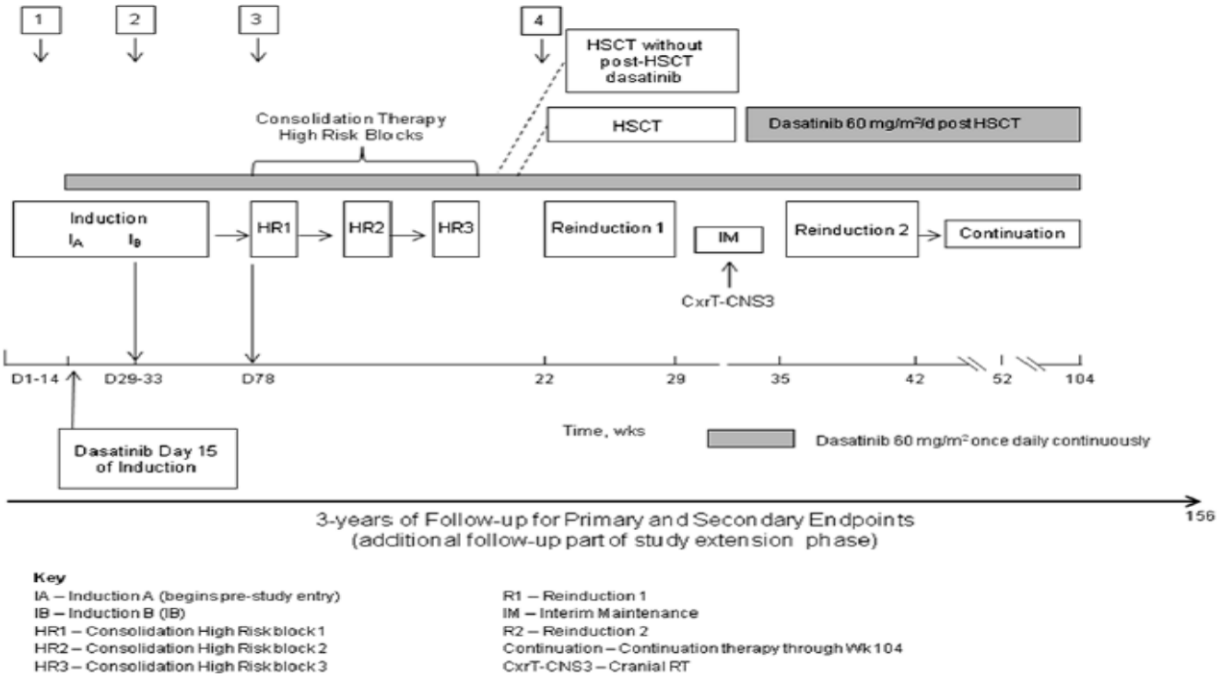
- Re-induction Block 1, including phase IIa and IIb (63 days, 9 weeks)
- Interim maintenance (29 days, 4 weeks). Subjects with CNS3 disease at diagnosis received cranial irradiation during the Interim Maintenance period.
- Re-induction Block 2 (63 days, 9 weeks)

- Continuation therapy (62 weeks)

*Phase IIb - For the subjects who met the criteria for HSCT:*

- Subjects who met pre-defined criteria at specific time points in treatment received a HSCT and had the option to receive 12 additional months of post-HSCT dasatinib (not mandatory).

**Figure 6 Schematic Study Design - Study CA180372**




## Objectives

The primary objective of the study was to compare the 3-year efficacy based on event free survival (EFS) of dasatinib plus chemotherapy with external historical controls.

Secondary objectives included the estimation of the below:

- The safety and feasibility of dasatinib added to standard chemotherapy
- The EFS of dasatinib plus chemotherapy (including 3 and 5-year rates)
- Complete remission rates (< 5% blasts in bone marrow and no peripheral blasts) at end of induction compared with AIEOP BFM 2000 and the amended EsPhALL trials
- The difference in 3-year EFS rate with the 3-year EFS rate of available historical controls such as the COG AALL0031 study
- Minimal residual disease (MRD) quantification (defined by PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements) using three methods
- BCR-ABL mutation status at baseline and time of disease progression or relapse

Exploratory objectives included the assessment of the following:

- Disease-free survival (DFS)
- Overall survival (OS)
- Growth and development and bone mineral content
- Prognostic value of MRD on EFS
- Correlation between the 3 methods of assessing MRD: real-time qPCR for clone specific immunoglobulin and T-cell receptor gene rearrangements, real-time qPCR for BCR-ABL transcripts, and multiparameter flow cytometry
- Rates of HSCT and safety of post-HSCT dasatinib

## Outcomes/Endpoints

- The primary efficacy endpoint of the study was the 3-year binomial EFS rate. EFS was defined as the time from the starting date of dasatinib (upon confirmation that ALL is Ph+ ALL) until an event. In the primary analysis, the 3-year EFS response rate was defined as the number of subjects without event after 3 years since the start of dasatinib divided by the number of treated subjects. Events for EFS are defined as any first one of the following: lack of complete response in bone marrow; relapse at any site; development of second malignant neoplasm; death from any cause.

Secondary endpoints:

- EFS defined as the time from the starting date of dasatinib (upon confirmation that ALL is Ph+ ALL) until an event.

The EFS endpoint is also considered for secondary/sensitivity analyses, including:

1. HSCT considered as an event if the subject discontinues
2. Lost to follow-up considered as an event (at the date of last contact)
3. Induction failures considered as an event at time 0
4. Stratified subgroup analysis of 3-year EFS rates for HSCT status looking at 3 groups: subjects who had HSCT, subjects who were eligible to have HSCT but did not, and subjects who were ineligible for HSCT.
5. Using Kaplan-Meier estimates of EFS probabilities (for overall EFS estimation including the 3-year and 5-year Kaplan-Meier estimates)
6. Stratified by high versus low/standard risk
7. Comparing 3-year EFS with results in COG AALL0031 (with alignment of EFS definition)

### *Historical Control Studies*

- Complete Remission Rate (CRR) defined as < 5% lymphoblasts in the bone marrow (ie, M1 bone marrow) and CSF with no evidence of other extra medullary disease.
- Minimal Residual Disease (MRD): The MRD levels are the proportion of leukemic cells in a sample at a specific time point. The method of reference is the quantitative PCR detection of

clone-specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR). The limit of detection of this assay will be approximately $10^{-4}$ - $10^{-5}$ or 0.01% - 0.001%.

- PCR for BCR-ABL defined as a ratio of BCR-ABL transcripts compared to a control gene (eg ABL) with log reduction compared to baseline.
- BCR-ABL mutation defined as the presence of a detectable amino acid substitution in the ABL kinase domain.

Exploratory endpoints:

- EFS by MRD level and concordance between assessment methods.
- Disease-free survival (DFS) defined as the time of first day of complete response (M1 bone marrow) until relapse at any site, development of a second malignant neoplasm, or death without relapse. The definition of relapse used for DFS is the same as for EFS. Subjects who neither relapse nor die or who are lost to follow-up will be censored on the date of their last assessment. Subjects who undergo HSCT would not be considered as having an event, and would continue to be followed.
- Overall survival defined as time from the first day of dasatinib treatment until the time of death. Subjects who have not died or who are lost to follow-up will be censored on the last date the subject is known to be alive.

## Sample size

The sample size and power calculations incorporated the following assumptions:

- 3-year EFS rate of chemotherapy alone in AIEOP-BFM was 52% (41 event free out of 79 subjects)
- 3-year EFS rate of continuous imatinib plus chemotherapy (amended EsPhALL trial) will be 78% (70 event free out of 90) (assumes the same rate as 3-year EFS rate of continuous imatinib plus chemotherapy in COG AALL0031)
- 3-year EFS rate of continuous dasatinib plus chemotherapy will be 88% (absolute improvement of 10% over imatinib plus chemotherapy)
- A non-inferiority margin of 5% (corresponding to approximately 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only historical control)
- One-sided type I error rate of 0.05

Based on the above assumptions, this study required 75 subjects evaluable for the primary endpoint, including at least 20 subjects evaluable for the primary endpoint in each of the following age ranges: 1 to < 12 years and 12 to < 18 years. This sample size yielded 100% power to detect a true difference of 36% in 3-year EFS of dasatinib plus chemotherapy (AIEOP BFM 2000) over chemotherapy alone (AIEOP-BFM 2000).

For non-inferiority testing against imatinib plus chemotherapy 75 subjects would yield 83% power to reject the null hypothesis and declare non-inferiority of dasatinib/chemotherapy and imatinib/chemotherapy (EsPhALL).

Under the same assumptions, a sample size of 75 subjects would yield 54% power to detect a true difference of 10% in 3-year EFS between dasatinib/chemotherapy over imatinib /chemotherapy (EsPhALL).

It was assumed that the rate of subjects discontinuing study participation prior to reaching 3 years of follow-up from the start of dasatinib without having an event, might potentially reach 20%. Additional 15 subjects were to be treated in order to assure robustness of the long-term efficacy and safety analysis results. The planned number of subjects to be treated was between 75 and 90. Under the assumption of treating 90 subjects, the power for the non-inferiority analysis would be 85%, and for the final superiority analysis the power would be 56%.

## Randomisation

The study was a single arm study.

## Blinding (masking)

The study was an open-label study.

## Statistical methods

*General Methods*

Analyses and summaries were, except where indicated otherwise, based on the whole target study population, as well as on the following sub-populations:

- Subjects treated with dasatinib tablets only (identified in table presentations as tablet only),
- Subjects who at any time received dasatinib in the PFOS formulation (identified in table presentations as PFOS used)

*Efficacy Analyses*

Efficacy analyses were based on all treated subjects and mainly consisted of response rates, Kaplan-Meier plots for time to event variables, and 3-year and 5-year EFS and DFS rates. The subjects who were enrolled in this study (CA180372) were considered Cohort 1 and the external historical controls AIEOP-BFM 2000 and Amended EsPhALL were considered Cohort 2 and Cohort 3, respectively.

Primary endpoint analyses were performed in hierarchical order as follows:

- Superiority of cohort 1 over cohort 2
- Non-inferiority of cohort 1 to cohort 3
- Superiority of cohort 1 over cohort 3

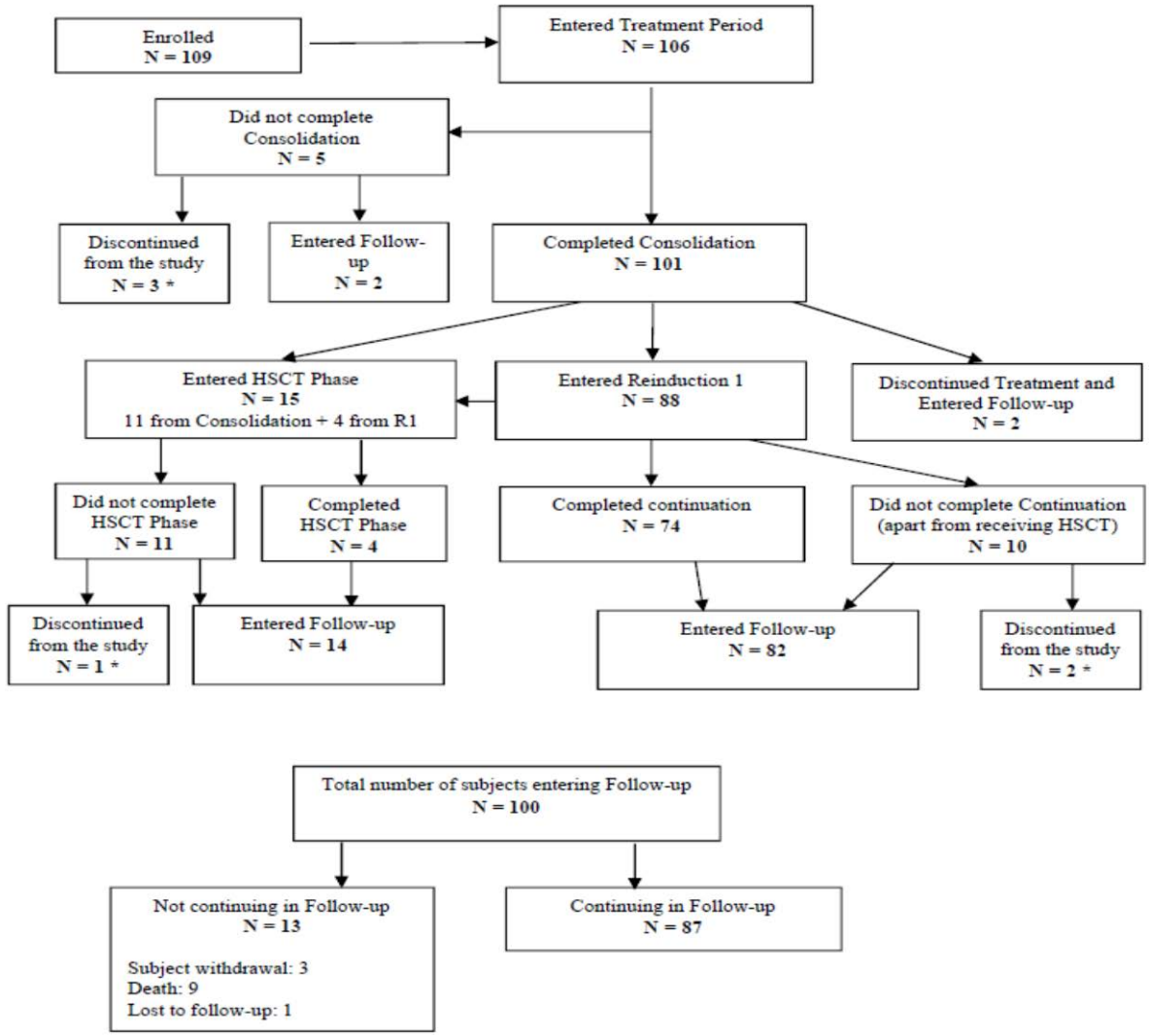
The differences in 3-year EFS rates were computed using binomial proportions of subjects who were free of events at 3 years over all treated subjects. Subjects lost to follow-up at any time without an event were considered event free in the primary analysis. Event rates were provided with exact 2-sided 90% Clopper-Pearson CI's. Differences in event rates were tested at the 0.05 1-sided significance level using a Pearson $\chi^2$ test. Non-inferiority testing against the study treatment in the amended EsPhALL trial were carried out using the corresponding 2-sided 90% CI for the treatment difference (3-year EFS rate in dasatinib+chemo minus 3-year EFS rate in imatinib+chemo) and comparing the lower confidence limit to the non-inferiority margin of -5%. Next to performing the above analyses on all treated subjects, the same analyses were performed on subjects with

uncontested Ph+ ALL diagnosis, meaning that any subject that was considered during treatment not to have Ph+ ALL was excluded.

## *Results*

## Participant flow

**Figure 7 Summary of Subject Disposition - Study CA180372**




* Reason for discontinuing study is death.
Abbreviations: DBL = data base lock; HR = high risk; HSCT = hematopoietic stem cell transplant

**Table 10 Subject Disposition- Study CA180372**

| Status (%) | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| Completing the treatment period | 59 (72.0) | 19 (79.2) | 78 (73.6) |
| Not completing the treatment period | 23 (28.0) | 5 (20.8) | 28 (26.4) |
| Reason for not completing the treatment period | | | |
| Lack of efficacy | 3 ( 3.7) | 0 | 3 ( 2.8) |
| Study drug toxicity | 2 ( 2.4) | 0 | 2 ( 1.9) |
| Adverse event | 8 ( 9.8) | 0 | 8 ( 7.5) |
| Withdrawal by subject | 4 ( 4.9) | 0 | 4 ( 3.8) |
| Death | 0 | 2 ( 8.3) | 2 ( 1.9) |
| Other | 6 ( 7.3) | 3 (12.5) | 9 ( 8.5) |
| Continuing in the study | 78 (95.1) | 22 (91.7 | 100 (94.3) |
| Not continuing in the study | 4 ( 4.9) | 2 ( 8.3) | 6 ( 5.7) |
| Reason for not continuing in the study | | | |
| Death | 4 ( 4.9) | 2 ( 8.3) | 6 ( 5.7) |
| Continuing in the follow-up period | 67 (85.9) | 20 (90.9) | 87 (87.0) |
| Not continuing in the follow-up period | 11 (14.1) | 2 ( 9.1) | 13 (13.0) |
| Reason for not continuing in the follow-up period | | | |
| Withdrawal by subject | 3 ( 3.8) | 0 | 3 ( 3.0) |
| Death | 7 ( 9.0) | 2 ( 9.1) | 9 ( 9.0) |
| Lost to follow-up | 1 ( 1.3) | 0 | 1 ( 1.0) |

## Recruitment

Study initiation date: 13 April 2012. The last patient visit for this report was 28 May 2017 and the database lock was 26 July 2017.

## Conduct of the study

Changes to the protocol

**Table 11 Summary of Changes to Protocol CA180372**

| Document | Date of Issue | Summary of Change |
|---|---|---|
| Amendment 04 | 28-Oct-2013 | This amendment:<br>• Added mandatory supportive care measures during the 3 High Risk Blocks<br>• Provided updates to the WOCBP language to harmonize this language with the current BMS directives for WOCBP. |
| Amendment 03 | 31-Jul-2013 | This amendment:<br>• Increased the number of treated subjects from 75 to at least 75 and up to 90.<br>• Modified language regarding pregnancy prevention.<br>• Incorporated recommendations for subject management and supportive care during HR Blocks 1-3.<br>• Provided clarifications, fixed inconsistencies across sections of the protocol and corrected various typographical errors. |
| Amendment 02 | 07-Dec-2012 | This amendment:<br>• Introduced a new pediatric formulation of dasatinib.<br>• Addressed lack of availability of native-asparaginase in the United States and allowed use of Peg-Asparaginase upfront in such instances as well as provided more detailed instruction for dose modifications of the various asparaginase formulations.<br>• Indicated that the BCR-ABL mutation status will be reported for baseline and at time of progression as a secondary objective instead of as an exploratory objective.<br>• Allowed Philadelphia chromosome positivity from peripheral blood to be acceptable for study entry.<br>• Expanded the window for screening activities to 21 days.<br>• Modified the definition of high risk group and low/standard risk group in response to Induction 1A treatment.<br>• Provided clarifications, fixed inconsistencies across sections of the protocol and corrected various typographical errors. |
| Amendment 01 | 20-Sep-2011 | This amendment:<br>• Changed the statistical design of the trial to allow comparison to historical external controls. Specifically, the 3-year EFS of dasatinib plus chemotherapy to be compared to the 3-year EFS of chemotherapy alone from the AIEOP BFM 2000 trial and the 3-year EFS of imatinib plus chemotherapy from the EsPhALL study.<br>• Incorporated additional supportive care options for chemotherapy to accommodate the standard of care at sites in the UK. Additionally, typographical errors were also corrected. |

Abbreviations: WOBCP = Women of Childbearing Potential; HR = High Risk; BCR-ABL = Oncogene fusion protein; EFS = event free survival; AIEOP BFM = Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster; UK = United Kingdom

Protocol deviations

Protocol deviations were identified via 1) on-site monitoring, 2) review of data listings and reported in monitoring visit reports and protocol deviation monitoring forms and 3) programmed checks based on data collected in the CRFs.

Clinically relevant protocol deviations were significant protocol deviations that were prespecified, programmable, and defined as events that may have had considerable impact on the outcome of the study or interpretation of the results of the study.

Overall, there were 42 clinically relevant protocol deviations reported in 40 subjects: 40 deviations due to use of concomitant medications with potential to prolong QTc, and 2 deviations due to subjects with blast-phase CML who were misclassified with Ph+ ALL. Inclusion of these 2 subjects in analysis did not impact interpretability of study results. Most of the deviations (30 subjects) were subjects who received short-term prophylactic antibiotics with a macrolide and/or pentamidine. Other prohibited medications included droperidol, methadone, haloperidol, domepridone and chlorpromazine.

**Table 12 Relevant Protocol Deviations Summary - All Treated Subjects- Study CA180372**

| | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| AT LEAST ONE RELEVANT PROTOCOL DEVIATION | 32 (39.0) | 8 (33.3) | 40 (37.7) |
| Concomitant meds that prolong QT | 32 (39.0) | 8 (33.3) | 40 (37.7) |
| No diagnosis of ALL | 2 ( 2.4) | 0 | 2 ( 1.9) |

## Baseline data

A summary of baseline demographic characteristics is presented in **Table 13**.

**Table 13 Demographic Characteristics Summary - All treated subjects- Study CA180372**

| | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| **Age (years) at consent** | | | |
| N | 82 | 24 | 106 |
| Mean | 10.33 | 5.73 | 9.29 |
| Median | 10.48 | 4.19 | 9.37 |
| Min, max | 2.6, 17.9 | 1.6, 14.0 | 1.6, 17.9 |
| Q1, q3 | 6.15, 13.60 | 2.57, 8.67 | 5.08, 12.87 |
| Sd | 4.160 | 3.612 | 4.467 |
| **Age (years) at initial all diagnosis** | | | |
| N | 82 | 24 | 106 |
| Mean | 10.30 | 5.70 | 9.26 |
| Median | 10.46 | 4.16 | 9.34 |
| Min, max | 2.6, 17.9 | 1.6, 13.9 | 1.6, 17.9 |
| Q1, q3 | 6.12, 13.56 | 2.54, 8.65 | 5.06, 12.83 |
| Sd | 4.160 | 3.614 | 4.467 |
| **Age categorization (%) at initial all diagnosis** | | | |
| >1 to <2 | 0 | 4 (16.7) | 4 ( 3.8) |
| >=2 to <7 | 21 (25.6) | 11 (45.8) | 32 (30.2) |
| >=7 to <12 | 27 (32.9) | 8 (33.3) | 35 (33.0) |
| >=12 to <18 | 34 (41.5) | 1 ( 4.2) | 35 (33.0) |
| **Gender (%)** | | | |
| Male | 45 (54.9) | 12 (50.0) | 57 (53.8) |
| Female | 37 (45.1) | 12 (50.0) | 49 (46.2) |
| **Race (%)** | | | |
| White | 66 (80.5) | 19 (79.2) | 85 (80.2) |
| Black or African American | 9 (11.0) | 4 (16.7) | 13 (12.3) |
| Asian | 5 ( 6.1) | 0 | 5 ( 4.7) |
| American Indian or Alaska native | 0 | 1 ( 4.2) | 1 ( 0.9) |
| Native Hawaiian or other pacific islander | 1 ( 1.2) | 0 | 1 ( 0.9) |
| Other | 1 ( 1.2) | 0 | 1 ( 0.9) |
| **Ethnicity (%)** | | | |
| Hispanic or Latino | 19 (23.2) | 5 (20.8) | 24 (22.6 |
| Not Hispanic or Latino | 40 (48.8) | 15 (62.5) | 55 (51.9) |
| Not reported | 23 (28.0) | 4 (16.7) | 27 (25.5) |

A summary of baseline disease characteristics is presented in Table 14.

**Table 14 Disease History Summary - All treated Subjects- Study CA180372**

| | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| TIME FROM INITIAL LEUKEMIA DIAGNOSIS TO FIRST DASATINIB DOSING DATE (DAYS) | | | |
| N | 82 | 24 | 106 |
| MEDIAN | 16.0 | 16.0 | 16.0 |
| MIN, MAX | 8, 19 | 15, 17 | 8, 19 |
| IMMUNOPHENOTYPE DISEASE DIAGNOSIS (%) | | | |
| PRECURSOR B-CELL ALL | 82 (100.0) | 22 (91.7) | 104 (98.1) |
| T-CELL ALL | 0 | 2 ( 8.3) | 2 ( 1.9) |
| BASELINE CNS LEUKEMIA DISEASE STATUS | | | |
| CNS1 | 55 (67.1) | 20 (83.3) | 75 (70.8) |
| CNS2 | 2 ( 2.4) | 1 ( 4.2) | 3 ( 2.8) |
| CNS2A | 9 (11.0) | 1 ( 4.2) | 10 ( 9.4) |
| CNS2B | 8 ( 9.8) | 2 ( 8.3) | 10 ( 9.4) |
| CNS2C | 2 ( 2.4) | 0 | 2 ( 1.9) |
| CNS3 | 3 ( 3.7) | 0 | 3 ( 2.8) |
| CNS3A | 1 ( 1.2) | 0 | 1 ( 0.9) |
| CNS3C | 1 ( 1.2) | 0 | 1 ( 0.9) |
| NOT ASSESSED | 1 ( 1.2) | 0 | 1 ( 0.9) |
| PHILADELPHIA POSITIVITY (%) | | | |
| FLUORESCENT IN SITU HYBRIDIZATION (FISH) ONLY | 21 (25.6) | 5 (20.8) | 26 (24.5) |
| RT-PCR ONLY | 11 (13.4) | 3 (12.5) | 14 (13.2) |
| BOTH | 50 (61.0) | 16 (66.7) | 66 (62.3) |
| BCR-ABL TRANSCRIPT (%) | | | |
| P190 | 60 (73.2) | 15 (62.5) | 75 (70.8) |
| P210 | 11 (13.4) | 5 (20.8) | 16 (15.1) |
| NOT AVAILABLE | 11 (13.4) | 4 (16.7) | 15 (14.2) |
| WBC COUNT AT DISEASE DIAGNOSIS (x 1000 CELLS/uL) | | | |
| N | 82 | 24 | 106 |
| MEAN | 113.40 | 138.89 | 119.17 |
| MEDIAN | 37.31 | 55.05 | 40.30 |
| MIN, MAX | 0.6, 1098.0 | 1.9, 1074.0 | 0.6, 1098.0 |
| Q1, Q3 | 16.50, 162.30 | 21.30, 177.15 | 18.87, 165.80 |
| SD | 173.71 | 230.82 | 187.25 |
| WBC COUNT AT DISEASE DIAGNOSIS (%) | | | |
| < 50,000 / mm3 | 48 (58.5) | 11 (45.8) | 59 (55.7) |
| 50,000 - 100,000 / mm3 | 9 (11.0) | 4 (16.7) | 13 (12.3) |
| > 100,000 / mm3 | 25 (30.5) | 9 (37.5) | 34 (32.1) |

## Numbers analysed

- All enrolled subjects: all subjects who had a signed informed consent form (N = 109).
- All treated/evaluable subjects: all subjects who received at least 1 dose of dasatinib (N = 106).
- Mutation data set: all treated subjects who had mutation data available (N = 80).

## Outcomes and estimation

- *Primary endpoint: 3-year binomial EFS rates vs. historical controls*

The 3-year binomial EFS rate with dasatinib plus chemotherapy was 66.0% (90% CI: 57.7, 73.7) compared to 49.2% (90% CI: 38.0, 60.4) observed with chemotherapy alone in AIEOP-BFM 2000 and to 59.1% (90% CI: 51.8, 66.2) observed with continuous imatinib plus chemotherapy in the amended EsPhALL trial in all treated subjects.

**Table 15 Difference in 3-Year binomial EFS Response Rates vs Historical Controls (AIEOP-BFM 2000 and EsPhALL)**

| | Response Rate (%) | | Difference in Response Rates | | |
|---|---|---|---|---|---|
| | n/N (%) | 90% CI (%) (1) | Diff (%) | 90% CI (%) | P-value (2) |
| Historical Control AIEOP-BFM 2000 | 30/ 61 (49.2) | ( 38.0, 60.4) | | | |
| ALL TREATED SUBJECTS | 70/106 (66.0) | ( 57.7, 73.7) | 16.86 | ( 3.9, 29.8) | 0.032 |
| TABLET ONLY | 54/ 82 (65.9) | ( 56.3, 74.5) | 16.67 | ( 3.1, 30.3) | 0.045 |
| PFOS USED (AT LEAST 1 DOSE) | 16/ 24 (66.7) | ( 47.9, 82.2) | 17.49 | ( -1.5, 36.5) | 0.145 |
| Historical Control Amended EsPhALL | 81/137 (59.1) | ( 51.8, 66.2) | | | |
| ALL TREATED SUBJECTS | 70/106 (66.0) | ( 57.7, 73.7) | 6.91 | ( -3.3, 17.2) | 0.271 |
| TABLET ONLY | 54/ 82 (65.9) | ( 56.3, 74.5) | 6.73 | ( -4.3, 17.8) | 0.322 |
| PFOS USED (AT LEAST 1 DOSE) | 16/ 24 (66.7) | ( 47.9, 82.2) | 7.54 | ( -9.7, 24.8) | 0.486 |

Difference in response rate: dasatinib response rate - historical control response rate.
(1) Exact Clopper-Pearson confidence interval. (2) Pearson Chi-square 1-sided test.
Data Source: ADRS

- *Secondary endpoint: 3-year binomial EFS rates vs COG study (AALL0031)*

**Table 16 Difference in 3-year binomial EFS Response Rate versus COG Study AALL0031**

| | Response Rate (%) | | Difference in Response Rates | | |
|---|---|---|---|---|---|
| | n/N (%) | 90% CI (%) (1) | Diff (%) | 90% CI (%) | P-value (2) |
| Historical Control Study COG AALL0031 | 43/ 56 (76.8) | (65.6, 85.7) | | | |
| ALL TREATED SUBJECTS | 70/106 (66.0) | (57.7, 73.7) | -10.75 | (-22.7,1.2) | 0.157 |
| TABLET ONLY | 54/ 82 (65.9) | (56.3, 74.5) | -10.93 | (-23.6, 1.7) | 0.168 |
| PFOS USED (AT LEAST 1 DOSE) | 16/ 24 (66.7) | (47.9, 82.2) | -10.12 | (-28.5, 8.2) | 0.346 |

Difference in response rate: dasatinib response rate - historical control response rate.
(1) Exact Clopper-Pearson confidence interval. (2) Pearson Chi-square 1-sided test.
Data Source: ADRS

- *Secondary endpoint: yearly EFS rates*

**Table 17 Kaplan-Meier Estimates of Event Free Survival at Yearly Intervals- Study CA180372**

| | Event-free Survival (%) with 95% Confidence Interval | | |
|---|---|---|---|
| | Tablet Only | At Least 1 Dose of PFOS | Total |
| Time point | N=82 | N=24 | N=106 |
| Year 1 | 95.1 (87.5, 98.1) | 91.7 (70.6, 97.8) | 94.3 (87.8, 97.4) |
| Year 2 | 85.3 (75.5, 91.4) | 83.3 (61.5, 93.4) | 84.8 (76.4, 90.4) |
| Year 3 | 65.1 (53.6, 74.4) | 66.7, (44.3, 81.7) | 65.5 (55.5, 73.7) |
| Year 4 | 56.5 (44.2, 67.1) | 53.3 (29.4, 72.4) | 55.8 (44.9, 65.4) |
| Year 5 | 54.1 (41.4, 65.1) | 53.3 (29.4, 72.4) | 48.7 (34.8, 61.2) |

**Figure 8 Kaplan-Meier Plot of Event Free Survival - All treated Subjects- Study CA180372**

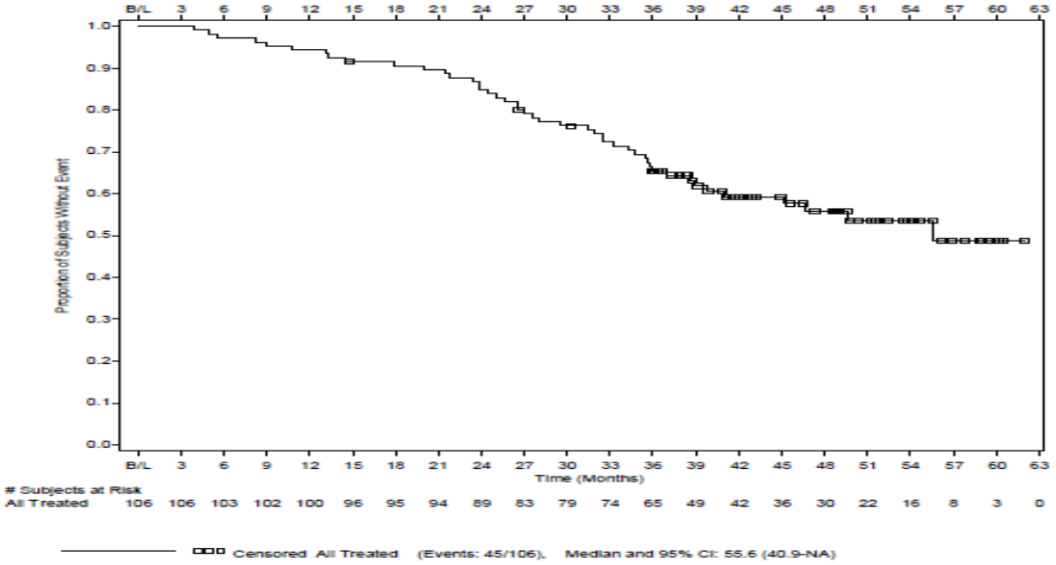
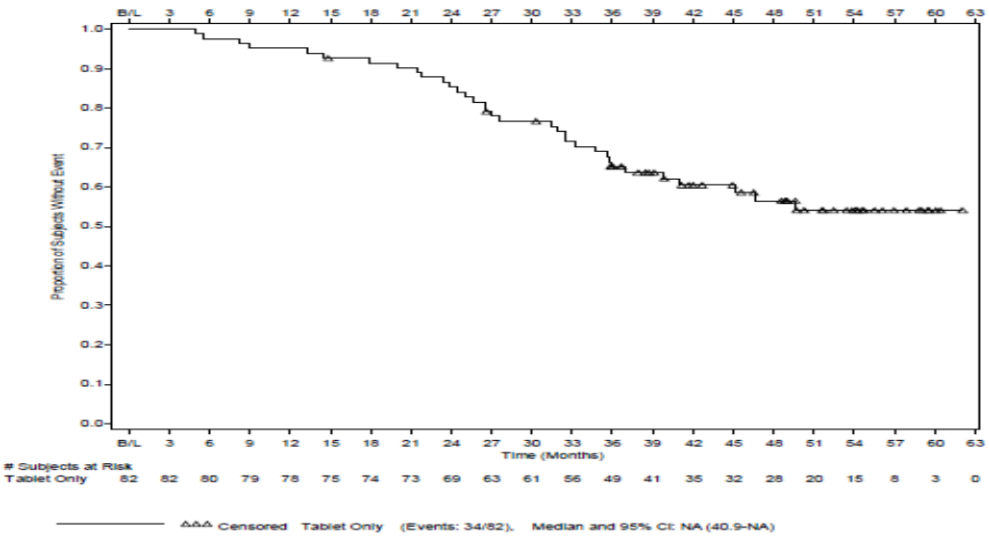



**Figure 9 Kaplan Meier Plot of Event Free Survival - Tablet Only- Study CA180372**




- *Secondary endpoint: yearly EFS rates Historical Control Studies*

**Table 18 EFS Rates over Time in Historical Control Studies**

| | AIEOP-BFM 2000 N=61 | Amended EsPhALL N=137 | COG AALL0031 N=56 |
|---|---|---|---|
| KAPLAN-MEIER ESTIMATES OF EFS RATE (95% CI) | | | |
| YEAR1 | 78.7 ( 66.1, 87.0) | 81.8 ( 71.4, 88.7) | 89.3 ( 77.7, 95.0) |
| YEAR2 | 54.1 ( 40.9, 65.6) | 67.9 ( 56.4, 76.9) | 80.2 ( 67.2, 88.5) |
| YEAR3 | 49.2 ( 36.2, 60.9) | 59.0 ( 47.4, 68.9) | 76.6 ( 63.1, 85.7) |
| YEAR4 | 49.2 ( 36.2, 60.9) | 55.4 ( 43.6, 65.7) | 69.1 ( 55.1, 79.6) |
| YEAR5 | 42.3 ( 29.8, 54.3) | 55.4 ( 43.6, 65.7) | 65.2 ( 51.0, 76.2) |

- *Secondary endpoint: CRR*

**Table 19 Complete Remission Rates in Historical Control Studies**

| | AIEOP-BFM 2000 N=61 | Amended EsPhALL N=137 | COG AALL0031 N=56 |
|---|---|---|---|
| COMPLETE REMISSION RATE AT END OF INDUCTION n/N (%) | 49/ 61 (80.3) | 134/137 (97.8) | 49/ 56 (87.5) |

Complete remission: < 5% lymphoblasts in bone marrow and in CSF without evidence of other extra medullary disease.

**Table 20 Summary of Complete Remission - Study CA180372**

| | Number of Subjects (%) N=106 | | |
|---|---|---|---|
| | Induction IA | Induction IB | End Consolidation |
| All Treated Subjects (N=106) | | | |
| COMPLETE REMISSION | 69 (65.1) | 94 (88.7) | 99 (93.4) |
| FIRST CR | 69 | 25 | 8 |
| CCR | | 69 | 91 |
| NO CR | 25 (23.6) | 6 ( 5.7) | 2 ( 1.9) |
| UNABLE TO DETERMINE | 11 (10.4) | 4 ( 3.8) | 0 |
| SUBJECTS NOT COMPLETING PERIOD | 1 ( 0.9) | 2 ( 1.9) | 5 ( 4.7) |
| Tablet Only (N=82) | | | |
| COMPLETE REMISSION | 53 (64.6) | 72 (87.8) | 77 (93.9) |
| FIRST CR | 53 | 19 | 7 |
| CCR | | 53 | 70 |
| NO CR | 20 (24.4) | 6 ( 7.3) | 1 ( 1.2) |
| UNABLE TO DETERMINE | 8 ( 9.8) | 2 ( 2.4) | 0 |
| SUBJECTS NOT COMPLETING PERIOD | 1 ( 1.2) | 2 ( 2.4) | 4 ( 4.9) |
| PFOS Used (N=24) | | | |
| COMPLETE REMISSION | 16 (66.7) | 22 (91.7) | 22 (91.7) |
| FIRST CR | 16 | 6 | 1 |
| CCR | | 16 | 21 |
| NO CR | 5 (20.8) | 0 | 1 ( 4.2) |
| UNABLE TO DETERMINE | 3 (12.5) | 2 ( 8.3) | 0 |
| SUBJECTS NOT COMPLETING PERIOD | 0 | 0 | 1 ( 4.2) |

Complete remission: < 5% lymphoblasts in bone marrow and in CSF without evidence of other extra medullary disease.
CCR = Continuous Complete Remission, i.e. no relapse occurred since Complete Remission (CR) was achieved.
Data Source: ADRS

- *Secondary endpoint: MRD*

**Table 21 MRD- Negative Rates Summary - Study CA180372**

| | TABLET ONLY | | PFOS USED | | ALL TREATED SUBJECTS | |
|---|---|---|---|---|---|---|
| Time point | n/N (%) | 95% CI (%) | n/N (%) | 95% CI (%) | n/N (%) | 95% CI (%) |
| End of Ind. IA (MRD2) | 23/ 82 (28.0) | ( 18.68, 39.06) | 7/ 24 (29.2) | ( 12.62, 51.09) | 30/106 (28.3) | ( 19.98, 37.88) |
| End of Ind. IB (MRD3) | 44/ 82 (53.7) | ( 42.30, 64.75) | 12/ 24 (50.0) | ( 29.12, 70.88) | 56/106 (52.8) | ( 42.89, 62.60) |
| End of HR3 (MRD4) | 61/ 82 (74.4) | ( 63.56, 83.40) | 15/ 24 (62.5) | ( 40.59, 81.20) | 76/106 (71.7) | ( 62.12, 80.02) |

Confidence intervals: Clopper-Pearson
Data Source: ADZP

**Table 22 MRD- Negative Rates Summary - All Treated Subjects with Evaluable Ig/TCR Assessments- Study CA180372**

| | TABLET ONLY | | PFOS USED | | ALL TREATED SUBJECTS | |
|---|---|---|---|---|---|---|
| Time Point | n/N (%) | 95% CI (%) | n/N (%) | 95% CI (%) | n/N (%) | 95% CI (%) |
| End of Ind. IA (MRD2) | 23/ 69 (33.3) | ( 22.44, 45.71) | 7/ 17 (41.2) | ( 18.44, 67.08) | 30/ 86 (34.9) | ( 24.92, 45.92) |
| End of Ind. IB (MRD3) | 44/ 72 (61.1) | ( 48.89, 72.38) | 12/ 18 (66.7) | ( 40.99, 86.66) | 56/ 90 (62.2) | ( 51.38, 72.23) |
| End of HR3 (MRD4) | 61/ 70 (87.1) | ( 76.99, 93.95) | 15/ 15(100.0) | ( 78.20, 100.00) | 76/ 85 (89.4) | ( 80.85, 95.04) |

Confidence intervals: Clopper-Pearson
Data Source: ADZP

- *Secondary endpoint: BCR-ABL mutation status*

**Table 23 Summary of BCR- ABL Mutations at Disease Progression or Relapse - Mutation Dataset- Study CA180372**

| | Ph+ ALL | | |
|---|---|---|---|
| | Tablet Only n/N (%) | PFOS Used n/N (%) | Total n/N (%) |
| Number of Subjects with | | | |
| Mutations | 2 / 25 ( 8.0) | 0 / 6 | 2 / 31 ( 6.5) |
| No Mutations* | 17 / 25 (68.0) | 3 / 6 (50.0) | 20 / 31 (64.5) |
| Not Reported | 6 / 25 (24.0) | 3 / 6 (50.0) | 9 / 31 (29.0) |
| Mutations in: | | | |
| P-Loop | 0 / 2 | | 0 / 2 |
| Activation Loop | 0 / 2 | | 0 / 2 |
| Other Location Only | 2 / 2 (100.0) | | 2 / 2 (100.0) |
| Mutations with: | | | |
| IC50 to dasatinib >>3nM | 1 / 2 (50.0) | | 1 / 2 (50.0) |
| IC50 to dasatinib >3nM# | 1 / 2 (50.0) | | 1 / 2 (50.0) |
| IC50 to dasatinib <=3nM## | 0 / 2 | | 0 / 2 |
| IC50 to Dasatinib Unknown### | 0 / 2 | | 0 / 2 |
| More than 1 Mutation | 0 / 2 | | 0 / 2 |
| Specific Mutation: | | | |
| F317L | 1 / 2 (50.0) | | 1 / 2 (50.0) |
| T315I | 1 / 2 (50.0) | | 1 / 2 (50.0) |

(*) May include subjects with polymorphisms only (T240T, K247R, F311V, Y320C, and E499E).
# and no mutations with IC50 to dasatinib >> 3 nM. ## and no mutations with IC50 > 3 nM. ### and no mutations with known IC50.
P-Loop: Subjects with at least 1 mutation in the P-loop (248-256) and possibly mutations in the activation loop or other locations.
Activation Loop: Subjects with >= 1 mut. in the activation loop (379-398) and possibly mutations in the P-loop/other locations.
Mutations with IC50 to dasatinib >> 3 nM: T315I/A. Mutations with IC50 to dasatinib > 3 nM: L248V, G250E, Q252H, E255K/V, V299L, F317L, L384M, Y253H, and F486S. Mutations with IC50 to dasatinib <= 3 nM: M244V, Y253F, D276G, E279K, F311L, M351T, F359V, V379I, L387M, and H396P/R.
Mutations with unknown IC50 to dasatinib: all other mutations. Data Source: ADMJ

- *Exploratory endpoints: EFS by MRD level*

**Figure 10 Landmark Kaplan-Meier Plot of EFS by MRD Level Based on Ig/TCR - All Treated Subjects at Risk of Event at MRD2- Study CA180372**

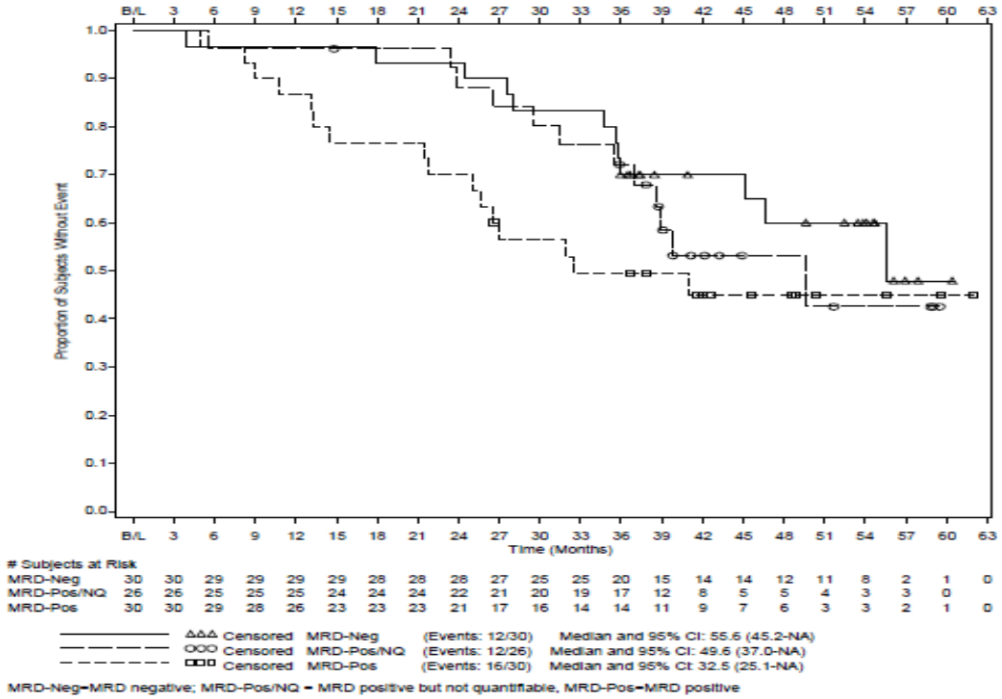



**Figure 11 Landmark Kaplan-Meier Plot of EFS by MRD level Based on Ig/TCR - All treated Subjects at Risk of Event at MRD3- Study CA180372**

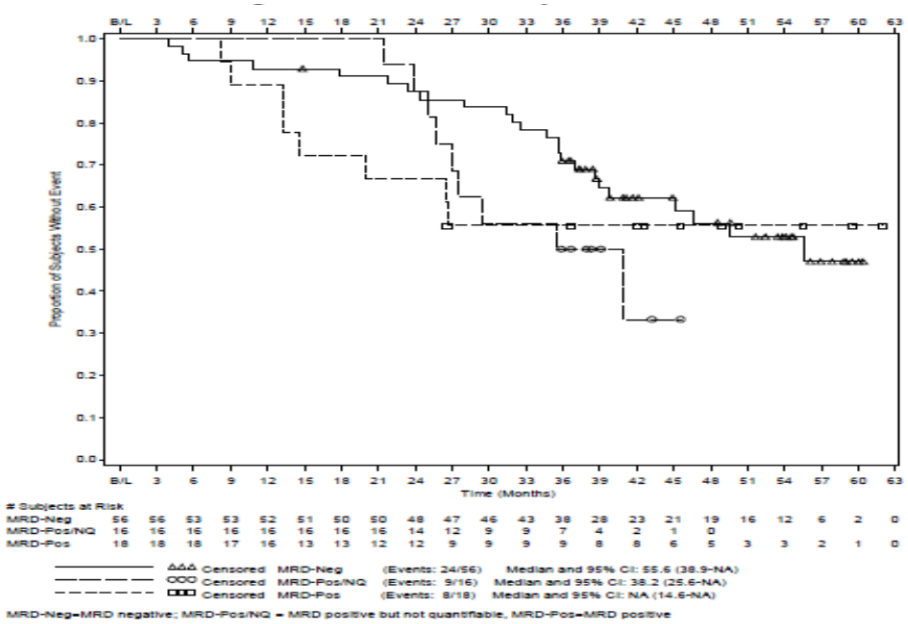
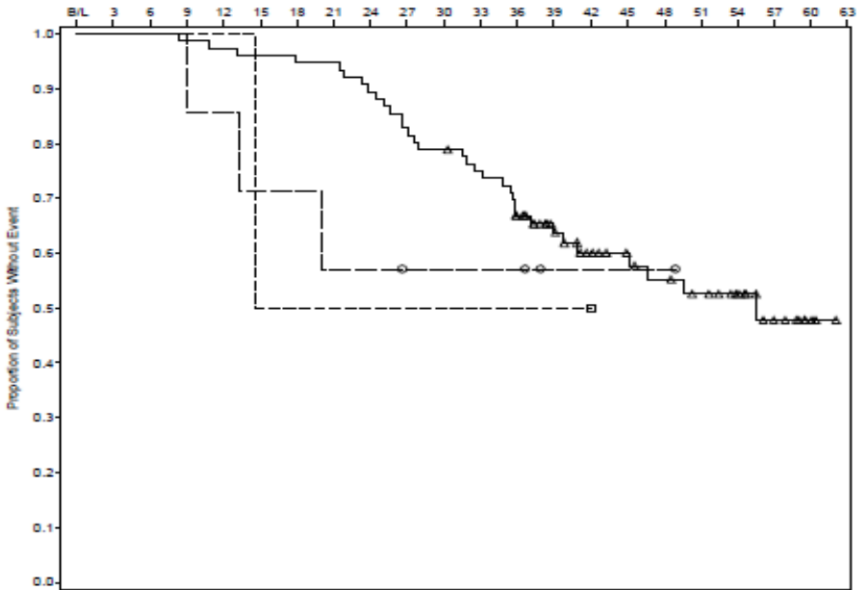


**Figure 12 Landmark Kaplan-Meier Plot of EFS by MRD level Based on Ig/TCR - All treated Subjects at Risk of Event at MRD4- Study CA180372**




- *Exploratory endpoint: Correlation between 3 methods of assessing MRD*

The proportion of subjects with non-evaluable results was lower with the FLOW method (2% to 6%) than with the Ig/TCR method (15% to 20%) and the BCR-ABL method (35% to 56%; subjects without MRD assessment because of treatment discontinuation were included as "non-evaluable"). Concordance between MRD detection methods is summarized in Table 24.

**Table 24 Numerical Concordance between MRD Methods - All treated Subjects with Available Data**

| | % Concordance (Method A vs Method B) | | |
|---|---|---|---|
| MRD Time point | IG/TCR vs BCR-ABL | IG/TCR vs FLOW | BCR-ABL vs FLOW |
| MRD2 | 89.5 | 94.1 | 72.1 |
| MRD3 | 87.0 | 98.9 | 88.3 |
| MRD4 | 95.0 | 100.0 | 89.4 |
| Across MRD2, MRD3, and MRD4 | 90.1 | 97.7 | 82.3 |

Abbreviations: MRD = minimal residual disease; IG/TCR = immunoglobulin and T-cell receptor gene rearrangements; FLOW = flow cytometry.
MRD2 = End of Induction period IA; MRD3 = End of Induction period IB/Start of High Risk Block 1; MRD4 = End of High Risk Block 3.

- *Exploratory endpoint: DFS*

**Table 25 Kaplan Meier Estimates of Disease-free Survival at yearly intervals**

| | Disease-free Survival (%) with 95% Confidence Interval | | |
|---|---|---|---|
| | Tablet Only | PFOS Used | Total |
| Time point | N=82 | N=24 | N=106 |
| Year 1 | 93.9 (86.0, 97.4) | 91.7 (70.6, 97.8) | 93.4 (86.6, 96.8) |
| Year 2 | 82.8 (72.7, 89.4) | 83.3 (61.5, 93.4) | 82.9 (74.3, 88.9) |
| Year 3 | 65.0 (53.5, 74.4) | 66.7 (44.3, 81.7) | 65.4 (55.4, 73.7) |
| Year 4 | 56.4 (44.1, 67.0) | 53.3 (29.4, 72.4) | 55.7 (44.8, 65.3) |
| Year 5 | 53.8 (41.1, 65.0) | 0 (NE, NE) | 48.5 (34.7, 61.1) |

NE=not evaluable.

- *Exploratory endpoint: OS*

**Table 26 Kaplan Meier Estimates of Overall Survival at Yearly Intervals**

| | Overall Survival (%) with 95% Confidence Interval | | |
|---|---|---|---|
| | Tablet Only | PFOS Used | Total |
| Time point | N=82 | N=24 | N=106 |
| Year 1 | 96.3 (89.1, 98.8) | 91.7 (70.6, 97.8) | 95.3 (89.0, 98.0) |
| Year 2 | 93.9 (85.9, 97.4) | 87.5 (66.1, 95.8) | 92.4 (85.4, 96.1) |
| Year 3 | 92.6 (84.3, 96.6) | 87.5 (66.1, 95.8) | 91.5 (84.2, 95.5) |
| Year 4 | 83.2 (71.0, 90.5) | 87.5 (66.1, 95.8) | 83.4 (72.7, 90.1) |
| Year 5 | 83.2 (71.0, 90.5) | 0 (NE, NE) | 78.1 (62.1, 88.0) |

NE=not evaluable.

## Ancillary analyses

### *Subjects who received dasatinib PFOS exclusively*

Of the 24 subjects in the PFOS group (received at least 1 dose of PFOS), 8 (7.54%) subjects received PFOS exclusively. At the time of DBL, 5 of them were alive with no relapse, 2 had a bone marrow relapse and were alive after receiving subsequent therapy. One subject had a positive MRD and underwent a HSCT, reinitiated dasatinib until Month 5 post-transplantation; 3 months after discontinuing dasatinib, the patient relapsed and died 2.5 months later. Hence, the OS rate was 7/8 (87.5%) and EFS rate was 5/8 (62.5%).

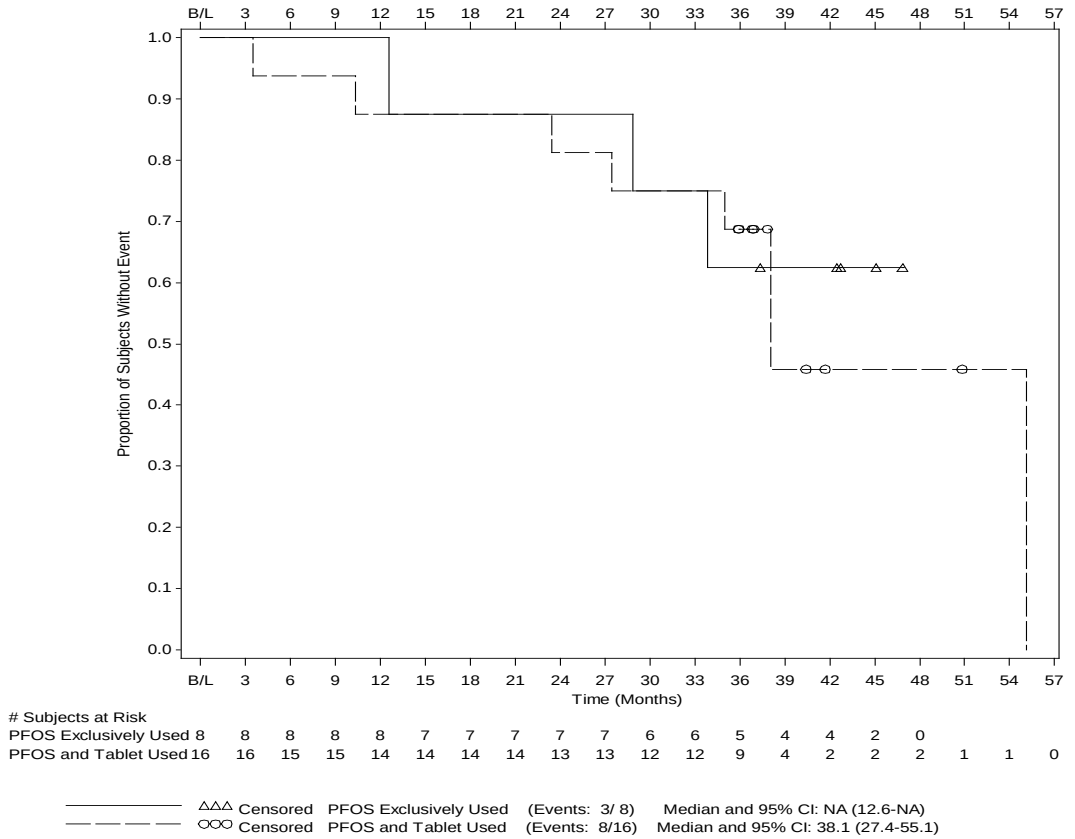
- *Updated 3-year data, PFOS (only) vs. PFOS (once)*

The Kaplan-Meier estimate of 3-year DFS of dasatinib plus chemotherapy treatment in the 8 patients who received PFOS exclusively was 62.5% (95% CI: 22.9, 86.1). The Kaplan-Meier estimate of 3-year DFS of dasatinib plus chemotherapy treatment in the patients who received both PFOS and tablets was 68.8% (95% CI: 40.5, 85.6).

**Table 27 Study CA180372 Kaplan-Meier estimates of DFS in subjects treated exclusively with PFOS**

| Time Interval (Month) | # Subjects at Risk of Event | Number of Subjects with Events: During Time Interval | Number of Subjects with Events: Cumulative | Number of Subjects Censored: During Time Interval | Number of Subjects Censored: Cumulative | Remain at Risk | Kaplan-Meier Estimates at Last Event in Time Interval: % DFS | Kaplan-Meier Estimates at Last Event in Time Interval: 95% CI |
|---|---|---|---|---|---|---|---|---|
| 0 | 8 | 0 | 0 | 0 | | 8 | 100.0 | (100.0, 100.0) |
| 0-3 | 8 | 0 | 0 | 0 | 0 | 8 | | |
| 3-6 | 8 | 0 | 0 | 0 | 0 | 8 | | |
| 6-9 | 8 | 0 | 0 | 0 | 0 | 8 | | |
| 9-12 | 8 | 0 | 0 | 0 | 0 | 8 | | |
| 12-15 | 8 | 1 | 1 | 0 | 0 | 7 | 87.5 | (38.7, 98.1) |
| 15-18 | 7 | 0 | 1 | 0 | 0 | 7 | | |
| 18-21 | 7 | 0 | 1 | 0 | 0 | 7 | | |
| 21-24 | 7 | 0 | 1 | 0 | 0 | 7 | | |
| 24-27 | 7 | 0 | 1 | 0 | 0 | 7 | | |
| 27-30 | 7 | 1 | 2 | 0 | 0 | 6 | 75.0 | (31.5, 93.1) |
| 30-33 | 6 | 0 | 2 | 0 | 0 | 6 | | |
| 33-36 | 6 | 1 | 3 | 0 | 0 | 5 | 62.5 | (22.9, 86.1) |
| 36-39 | 5 | 0 | 3 | 1 | 1 | 4 | | |
| 39-42 | 4 | 0 | 3 | 0 | 1 | 4 | | |
| 42-45 | 4 | 0 | 3 | 2 | 3 | 2 | | |
| 45-48 | 2 | 0 | 3 | 2 | 5 | 0 | | |

**Figure 13 Study CA180372 Kaplan-Meier Plot of DFS All PFOS treated subjects**




One patient who exclusively received PFOS died. The Kaplan-Meier estimate of 3-year OS was 87.5% (95% CI: 38.7, 98.1).

Two out of 16 patients who received both PFOS and tablets have died; the 3-year OS was 87.5% (95% CI: 58.6, 96.7).

## *Summary of main study*

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 28 Summary of Efficacy for trial CA180372**

| **Title: A Phase 2 multi-centre, historically-controlled study of dasatinib added to standard chemotherapy in paediatric patients with newly diagnosed philadelphia chromosome positive acute lymphoblastic leukaemia** | | |
|---|---|---|
| Study identifier | CA180372 | |
| Design | Open-label, multi-centre, single-arm, Phase 2, historically-controlled study | |
| | Duration of main phase: | 3 Years (completed) |
| | Duration of Run-in phase: | not applicable |
| | Duration of Extension phase: | 2 Years (ongoing) |
| Hypothesis | Superiority over chemotherapy alone of AIEOP-BFM 2000<br>Non-inferiority to imatinib plus chemotherapy of EsPhALL trial<br>Superiority over continuous imatinib plus chemotherapy of EsPhALL trial | |

| | | | |
|---|---|---|---|
| Treatments group | paediatric Ph + ALL | | dasatinib 60 mg/m$^2$ daily (Tablet or PFOS) + chemotherapy (ALL 2000 regimen) for a maximum duration of 2 years; 109 subjects enrolled, 106 treated. |
| Endpoints and definitions | Primary endpoint | 3-year event free survival (EFS) binomial rates vs. historical controls | The number of subjects without event after 3 years since the start of dasatinib divided by the number of treated subjects. |
| | Secondary endpoint | MRD negative rate | The MRD levels are the proportion of leukemic cells in a sample at a specific time point. The limit of detection will be approximately $10^{-4}$ - $10^{-5}$ or 0.01% - 0.001%. |
| | Secondary endpoint | Complete Remission Rate (CRR) | Defined as < 5% lymphoblasts in the bone marrow (ie, M1 bone marrow) and CSF with no evidence of other extra medullary disease. |
| Database lock | 26-Jul-2017 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | modified intention to treat | | |
| Descriptive statistics and estimate variability | Treatment group | dasatinib + chemotherapy | |
| | Number of subjects | 106 | |
| | 3-year binomial EFS rate (%) | 66.0 | |
| | 90% exact CI | (57.7 - 73.7) | |
| | KM estimate of EFS at 3 years | 65.5 % | |
| | 95% CI | (55.5 , 73.7) | |
| | Complete remission rates at End of Induction 1A | 65.1% | |
| | | | |
| Effect estimate per comparison | Primary endpoint<br>3-year EFS rate | Comparison groups | AIEOP- BFM2000 |
| | | Dasatinib-Control | 16.86 |
| | | 90% CI | [3.9 29.8] |
| | | P-value ($\chi^2$ test) | 0.032 |
| | Primary endpoint<br>3-year EFS rate | Comparison groups | EsPhal |
| | | Pearson $\chi^2$ test | 6.91 |
| | | 90% CI | (-3.3, 172.2) |
| | | P-value | 0.271 |
| | Primary endpoint<br>3-year EFS rate | Comparison groups | COG ALL0031 |
| | | Pearson $\chi^2$ test | -10.75 |
| | | 90% CI | (-22.7, 1.2) |
| | | P-value | 0.157 |
| Notes | study CA180204 functioned as run-in for this study | | |

## *Analysis performed across trials (pooled analyses and meta-analysis)*

N/A

## *Clinical studies in special populations*

N/A

## *Supportive study*

## *Study CA180204*

Study CA180204 was an open-label, multi-center, single-arm Phase II study in 62 paediatric and young adult patients with newly diagnosed Ph+ ALL. A total of 55 paediatric subjects were treated (35 in the discontinuous dasatinib group and 20 in the continuous dasatinib group; 3 non-eligible subjects were excluded from the efficacy analysis). A total of 33 (60%) paediatric subjects completed study treatment. The most common reason in paediatric subjects in the combined cohorts for not completing study treatment was bone marrow transplant (N = 13, 23.6%). Two paediatric subjects were reported to have disease progression during the study. Reasons for not continuing in the study included: enrolment onto another COG study with therapeutic intent (9.1%), death (12.7%), and 3 (5.5%) subjects considered ineligible after having started treatment. A summary of key demographic characteristics of study CA180204 is presented in Table 29.

**Table 29 Summary of Key Demographic Characteristics-Study CA180204**

| | CA180372 Tablet Only and CA180204 Continuous Dasatinib N=99 | CA180372 Tablet Only and CA180204 Efficacy Sample N=132 | CA180372 and CA180204 Efficacy Sample (Total) N=156 |
|---|---|---|---|
| **Demographics** | | | |
| Median age, years (min-max) | 10.36 (1.8, 17.9) | 9.72 (1.5, 17.9) | 9.11 (1.5, 17.9) |
| Median age at initial diagnosis, years (min-max) | 10.34 (1.8, 17.9) | 9.69 (1.5, 17.9) | 9.10 (1.5, 17.9) |
| Age categorization at diagnosis, n (%) | | | |
| > 1 year - <2 years | 1 (1.0) | 2 (1.5) | 6 (3.8) |
| ≥ 2 years - < 7 years | 26 (26.3) | 40 (30.3) | 51 (32.7) |
| ≥ 7 years - < 12 years | 33 (33.3) | 42 (31.8) | 50 (32.1) |
| ≥ 12 years - < 18 years | 39 (39.4) | 48 (36.4) | 49 (31.4) |
| Sex, n (%) | | | |
| Male | 57 (57.6) | 79 (59.8) | 91 (58.3) |
| Female | 42 (42.4) | 53 (40.2) | 65 (41.7) |
| Race, n (%) | | | |
| White | 77 (77.8) | 100 (75.8) | 119 (76.3) |
| Black/African American | 12 (12.1) | 17 (12.9) | 21 (13.5) |
| Asian | 6 (6.1) | 7 (5.3) | 7 (4.5) |
| Other | 4 (4.0) | 8 (6.1) | 9 (5.8) |

Note: Pediatric Efficacy Sample = pediatric subjects treated with at least 1 dose of dasatinib.

The median duration of dasatinib therapy from first through last dasatinib dose date was 31.31 months.

Subjects were categorized by risk: Standard Risk was defined as M1 (bone marrow status of < 5% lymphoblasts/complete response in bone marrow) with MRD < 1% at end Induction and MRD < 0.01% at end Consolidation Block 2; High Risk was defined as MRD ≥ 1% at end Induction or MRD ≥ 0.01% at end Consolidation Block 2. Any Risk is both groups combined.

A summary of efficacy results in Study CA180204 is presented in Table 30.

**Table 30 Summary of Efficacy in Study CA180204**

| Endpoint | Discontinuous Dasatinib Any Risk N = 33 | Continuous Dasatinib Any Risk N = 19 | Continuous + Discontinuous Dasatinib Any Risk N = 52 |
|---|---|---|---|
| K-M estimate of 3-year EFS | | | |
| % (95% CI) | 87.9 (76.9, 98.8) | 68.4 (48.3, 88.6) | 80.8 (70.2, 91.4) |
| K-M estimate of 3-year OS | | | |
| % (95% CI) | 97.0 (91.2, 100) | 89.5 ( 76.1, 100) | 94.2 (88.0, 100) |
| MRD positive, n/N (%)[a] | | | |
| End of Induction | 11/32 (34.4) | 9/19 (47.4) | 20/51 (39.2) |
| 90% CI | (17.9, 50.8) | (24.9, 69.8) | (25.8, 52.6) |
| End of Consolidation | 2/33 ( 6.1) | 3/19 (15.8) | 5/52 (9.6) |
| 90% CI | (2.0, 16.8) | (6.5, 33.6) | (4.8, 18.5) |

Abbreviations: K-M = Kaplan-Meier, EFS = event-free survival, OS = overall survival, MRD = minimal residual disease, CI = confidence interval, NA = not available.
[a] MRD-detection method was flow cytometry.
Note: The lower confidence limit is obtained from the normal approximation to the binomial distribution. The upper confidence limit is 100%.
The proportion was estimated from the corresponding EFS Kaplan-Meier curve.
Pediatric Efficacy Sample = pediatric subjects treated with at least 1 dose of dasatinib.

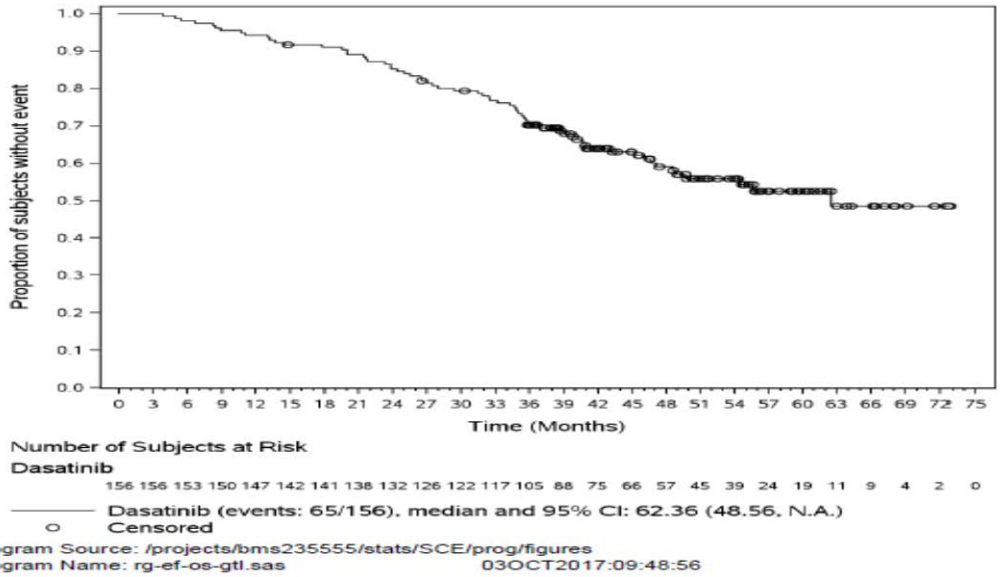
A summary of EFS from pooled CA180204 and CA180372 data are presented below.

**Table 31 Kaplan Meier Estimates Event-free Survival**

| | CA180372 Tablet Only and CA180204 Continuous Dasatinib N=99 | CA180372 Tablet Only and CA180204 Efficacy Sample N=132 | CA180372 and CA180204 Efficacy Sample (Total) N=156 |
|---|---|---|---|
| K-M Estimate of EFS, % (95% CI) | | | |
| 3-Year estimate | 65.1 (54.7, 73.6) | 70.8 (62.2, 77.9) | 70.2 (62.3, 76.8) |
| 5-Year estimate[a] | 52.4 (40.7, 62.8) | 55.2 (45.3, 64.0) | 52.6 (43.0, 61.3) |

Abbreviations: K-M = Kaplan-Meier; EFS = event-free survival, CI = confidence interval.
[a] Based on immature data (the percentage of subjects censored by 5 years was over 40% in all pooled subject samples)

**Figure 14 Kaplan-Meier plot of Event-free survival - Total Pooled CA180204 and CA 180372**



## 2.5.1. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

This application is based on two studies. The main study CA180372 is a Phase 2, open-label, multi-center single-arm, historically-controlled study in children and adolescents with newly diagnosed Ph+ ALL. Included patients were given continuous dasatinib added to a Ph+ ALL chemotherapy regimen, based on regimens from the AIEOP-BFM ALL 2000 study and the amended EsPhALL. The primary objective was to compare the 3-year EFS of dasatinib in combination with chemotherapy with external historical controls.

The supportive study CA180204 was a Phase 2, open-label, multi-center, single-arm study including children and young adults with newly diagnosed Ph+ ALL to be treated also with dasatinib 60 mg/m$^2$ daily by oral tablet. Study CA180204 was based on a different chemotherapy backbone therapy than that used in CA180372, and the number of subjects in study CA180204 who received dasatinib continuously was limited to 20 subjects. This study was terminated early due to the opening of the main study.

The clinical studies were performed with few amendments, withdrawals or lost to follow-up. Introduction of an oral suspension of medication for the ALL, otherwise only available as tablet and not for parenteral use, will definitely meet an unmet medical need in children. Likewise, this PFOS may also be of interest in some adult patients, who may have difficulties swallowing tablets for various reasons.

The clinical development program for dasatinib in paediatric ALL includes single-arm studies. Imatinib was the first TKI to be developed and therefore also the first introduced as targeted therapy in childhood leukemia. The trials included randomization of chemotherapy to treatment with and without imatinib and demonstrated the superiority of the combination therapy. The design of the main and supportive studies introducing dasatinib were single-arm studies because activity of dasatinib against Ph+ ALL in adults and of imatinib against Ph+ ALL in children has been established and hence comparing the activity of dasatinib in combination to chemotherapy alone is acceptable. However, the review and interpretation of previous advice is accepted. It is noticed that in the introduction of imatinib in paediatric ALL, trials did include a randomization in subgroups between chemotherapy plus imatinib versus chemotherapy alone but were amended to all patients receiving imatinib shortly after favourable results of other paediatric trials with imatinib became known [2].

The patient population included in the dasatinib clinical studies are representative for paediatric Ph+ ALL, with very few patients below the age of 7, and the majority up to the age of 18. Patients often present severe leucocytosis and two T-ALL were included. Some more characteristics may influence the prognosis, and treatment progress in all acute leukaemia therapy has emphasized the importance of the cytogenetic aberrations. The secondary genetic abnormalities have not been included in previous advice, nor have data been collected later, e.g. from conventional chromosome analysis, which it is anticipated have been performed in many patients, because the banding technique is a standard analysis. The importance of secondary clonal aberrations was known before 2005 [3], but it is accepted that the information was not collected and consequently not included in the interpretation of results of dasatinib in paediatric ALL.

#### *Efficacy data and additional analyses*

The Performance status is not commented in reviews on paediatric ALL (Ph-positive and -negative), but the symptoms involves fever, recurrent infections, organomegaly, bleeding, weight loss, bone pain etc [7]. The PS is not mentioned in the criteria for the EsPhALL study, which states that the patient should be eligible for the current local prospective therapeutic study of childhood ALL (link:

https://clinicaltrials.gov/ct2/show/NCT00287105). However, only 1 subject out of 109 screened patients in study CA180372 was excluded due to an active infection.

In study CA180372, the 3-year binomial EFS rate with dasatinib plus chemotherapy was 66.0% (90% CI: 57.7, 73.7) compared to 49.2% (90% CI: 38.0, 60.4) observed with chemotherapy alone in AIEOP-BFM 2000 and to 59.1% (90% CI: 51.8, 66.2) observed with continuous imatinib plus chemotherapy in the amended EsPhALL trial in all treated subjects.

Regarding the secondary endpoints, the OS rate was 91.5% (95% CI: 84.2 - 95.5) at 3 years and the CR was 93.4% (99/106) after consolidation chemotherapy. The results of 3-year DFS are in the same range to results obtained with imatinib.

The inferior CR rate at the end of Induction IA vs AIEOP-BFM 2000 and the Amended EsPhALL trial showed a relevant flaw in the CA180372 study design and conduct, as patients undergoing the CR assessment not in the last day of Induction IA, as determined, but on the following day, just prior to start Induction IB, were not recognised, as per protocol criteria, to be in CR. However, the CR data with one day extension is clinically acceptable, as that extra day is not expected to significantly change the patient's CR status and allows for the inclusion of CR cases excluded for lack of information. The CR analyses results with one extra day are in line with historical trials, including AIEOP-BFM 2000 and Amended EsPhALL.

Not all patients were assessed for MRD-negativity by Ig/TCR PCR technique, mainly due to poor baseline samples, e.g. no clones identified, no reliable targets, primers failed to amplify target, inadequate volume of BM at DX, etc. The MRD negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD-negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

The results of the oral suspension, which may be very valuable in the treatment of young children – or perhaps adult patients with Ph+ ALL for reasons like mucositis, swallowing disturbances and more – are presented in 24 patients, who all had the PFOS at least once. Eight patients are characterized as treated exclusively by PFOS. The OS rate was 7/8 (87.5%) and EFS rate at 3 years was 5/8 (62.5%). The relapse and survival rates in the PFOS subgroup of subjects are consistent with the overall population. It may be anticipated that children may use PFOS and tablets intermittently. Updated data for PFOS (only) and PFOS (once) treated patients are restricted by low numbers, as expected, but are comparable demographically, and seems to show similar results and clinically meaningful on the endpoint DFS, EFS and OS.

The study-design did not include previously imatinib-treated children, and the experience in the molecular biological details in such patients is also limited. However, it appears that eight of nine samples from imatinib-treated patients in the COGAALL0031 trial showed no BCR-ABL1 kinase domain mutation, only one presenting an acquired mutation [9].

It is a concern if long-term outcome is reduced by insufficient dosing, even if the initial effect may still be high response rates and encouraging results. Acute leukaemia may in most cases be sensitive to treatment, and it is important to maintain the efficacy by the successive therapies. The results obtained in the main single arm study must be assessed in the context of the data from historical controls. Induction of deeper remissions are obtained more rapidly by dasatinib in CML than obtained by imatinib [10]. A survival advantage has not been demonstrated clearly in CML by any TKI, but the disease biology in the acute leukaemia is different, and a more rapid and deep remission may be valuable for survival. The efficacy results on dasatinib treatment are interpreted as a contribution to

reduce the need for HSCT as second-line treatment in paediatric Ph+ ALL. This implication is very encouraging due to risks for fatal outcome or morbidity by HSCT.

In the supportive study CA180204, the 3-year EFS rate was 80.8% (95% CI: 70.2, 91.4) in the 52 paediatric patients considered evaluable for efficacy and 68.4% (95% CI: 48.3, 88.6) in the 19 subjects on continuous dasatinib.

### 2.5.2. Conclusions on the clinical efficacy

The main study CA180372 showed a clinically relevant effect in terms of the 3-year binomial EFS rate compared to historical controls treated without dasatinib by the same combination chemotherapy backbone. This was supported by improvements on all relevant secondary endpoints.

Therefore, clinically relevant efficacy of dasatinib in combination with chemotherapy in newly diagnosed Ph+ ALL was demonstrated in the paediatric population.

## *2.6. Clinical safety*

### *Introduction*

Dasatinib was combined with 2 different multi-agent chemotherapeutic “backbone” regimens to treat a total of 161 paediatric subjects with Ph+ ALL: the COG AALL0031 treatment regimen in Study CA180204, and the Associazione Italiana di Ematologia Paediatrica - Berlin-Frankfurt- Muenster (AIEOP-BFM) ALL 2000 regimen in Study CA180372. In Study CA180204, the COG AALL0031 regimen was combined with dasatinib treatment as a “discontinuous” regimen (ie, 2-week periods of dasatinib treatment followed by 1 to 2 weeks off) in the first cohort and a “continuous” regimen in the second cohort. Study CA180372 also used the dasatinib powder for oral suspension (PFOS) formulation for subjects who could not swallow tablets.

Subject disposition, exposure, adverse events (AEs), and AEs of special interest (AEOSIs) were analyzed from paediatric subject data pooled from Studies CA180204 and CA180372 and are presented by the following categories of dasatinib treatment:

- Discontinuous dasatinib: N = 35 (exclusively from CA180204)
- Continuous dasatinib tablet only: N = 102 (20 from CA180204, and 82 from CA180372)
- Continuous dasatinib: N = 126 (20 from CA180204, and 106 from CA180372)
- All treated subjects: N = 161 (55 from CA180204, and 106 from CA180372)

## *Patient exposure*

### Table 32 Extent of exposure of Dasatinib Summary - All Treated Subjects in the Pooled Population

| | Discontinuous Dasatinib N = 35 | Continuous Dasatinib Tablet Only N = 102 | Continuous Dasatinib N = 126 | All Treated N = 161 |
|---|---|---|---|---|
| DURATION OF THERAPY (MONTHS) | | | | |
| MEAN (SD) | 21.27 (14.306) | 20.24 (8.596) | 20.12 (8.337) | 20.37 (9.900) |
| MEDIAN (MIN - MAX) | 31.57 (1.08 - 34.96) | 23.56 (1.41 - 33.02) | 23.56 (1.41 - 33.02) | 23.56 (1.08 - 34.96) |
| N OF SUBJECTS (%) WITH <=3 | 10 ( 28.6) | 5 ( 4.9) | 5 ( 4.0) | 15 ( 9.3) |
| N OF SUBJECTS (%) WITH >3 - 6 | 0 | 9 ( 8.8) | 12 ( 9.5) | 12 ( 7.5) |
| N OF SUBJECTS (%) WITH >6 - 12 | 4 ( 11.4) | 9 ( 8.8) | 11 ( 8.7) | 15 ( 9.3) |
| N OF SUBJECTS (%) WITH >12 - 18 | 0 | 4 ( 3.9) | 5 ( 4.0) | 5 ( 3.1) |
| N OF SUBJECTS (%) WITH >18 - 24 | 0 | 52 ( 51.0) | 67 ( 53.2) | 67 ( 41.6) |
| N OF SUBJECTS (%) WITH >24 | 21 ( 60.0) | 23 ( 22.5) | 26 ( 20.6) | 47 ( 29.2) |
| AVERAGE DAILY DOSE (MG/M2/DAY) | | | | |
| MEAN (SD) | 32.42 (6.351) | 55.28 (7.588) | 56.03 (7.169) | 50.90 (12.004) |
| MEDIAN (MIN - MAX) | 30.04 (22.07 - 46.66) | 57.89 (31.47 - 76.12) | 58.30 (31.47 - 76.12) | 55.70 (22.07 - 76.12) |
| NUMBER OF DASATINIB DOSE DAYS (MONTHS) | | | | |
| MEAN (SD) | 10.35 (6.675) | 18.98 (8.352) | 18.99 (8.097) | 17.11 (8.571) |
| MEDIAN (MIN - MAX) | 15.18 (0.69 - 16.23) | 22.87 (0.95 - 31.77) | 22.82 (0.95 - 31.77) | 21.19 (0.69 - 31.77) |
| N OF SUBJECTS (%) WITH <=3 | 10 ( 28.6) | 7 ( 6.9) | 7 ( 5.6) | 17 ( 10.6) |
| N OF SUBJECTS (%) WITH >3 - 6 | 4 ( 11.4) | 8 ( 7.8) | 11 ( 8.7) | 15 ( 9.3) |
| N OF SUBJECTS (%) WITH >6 - 12 | 0 | 8 ( 7.8) | 10 ( 7.9) | 10 ( 6.2) |
| N OF SUBJECTS (%) WITH >12 - 18 | 21 ( 60.0) | 8 ( 7.8) | 9 ( 7.1) | 30 ( 18.6) |
| N OF SUBJECTS (%) WITH >18 - 24 | 0 | 55 ( 53.9) | 72 ( 57.1) | 72 ( 44.7) |
| N OF SUBJECTS (%) WITH >24 | 0 | 16 ( 15.7) | 17 ( 13.5) | 17 ( 10.6) |
| ADJUSTED AVERAGE DAILY DOSE (MG/M2/DAY) | | | | |
| MEAN (SD) | 59.96 (2.777) | 59.91 (4.947) | 60.12 (4.561) | 60.08 (4.231) |
| MEDIAN (MIN - MAX) | 60.52 (50.00 - 66.84) | 60.40 (46.58 - 92.13) | 60.47 (46.58 - 92.13) | 60.51 (46.58 - 92.13) |
| NUMBER OF DASATINIB TABLET DOSE DAYS (MONTHS) | | | | |
| MEAN (SD) | 10.35 (6.675) | 18.98 (8.352) | 16.30 (9.892) | 15.01 (9.590) |
| MEDIAN (MIN - MAX) | 15.18 (0.69 - 16.23) | 22.87 (0.95 - 31.77) | 21.98 (0.00 - 31.77) | 16.13 (0.00 - 31.77) |
| N OF SUBJECTS (%) WITH <=3 | 10 ( 28.6) | 7 ( 6.9) | 21 ( 16.7) | 31 ( 19.3) |
| N OF SUBJECTS (%) WITH >3 - 6 | 4 ( 11.4) | 8 ( 7.8) | 12 ( 9.5) | 16 ( 9.9) |
| N OF SUBJECTS (%) WITH >6 - 12 | 0 | 8 ( 7.8) | 10 ( 7.9) | 10 ( 6.2) |
| N OF SUBJECTS (%) WITH >12 - 18 | 21 ( 60.0) | 8 ( 7.8) | 9 ( 7.1) | 30 ( 18.6) |
| N OF SUBJECTS (%) WITH >18 - 24 | 0 | 55 ( 53.9) | 57 ( 45.2) | 57 ( 35.4) |
| N OF SUBJECTS (%) WITH >24 | 0 | 16 ( 15.7) | 17 ( 13.5) | 17 ( 10.6) |
| NUMBER OF DASATINIB PFOS DOSE DAYS (MONTHS) | | | | |
| MEAN (SD) | 0.00 (0.000) | 0.00 (0.000) | 2.69 (6.758) | 2.10 (6.076) |
| MEDIAN (MIN - MAX) | 0.00 (0.00 - 0.00) | 0.00 (0.00 - 0.00) | 0.00 (0.00 - 23.52) | 0.00 (0.00 - 23.52) |
| N OF SUBJECTS (%) WITH <=3 | 35 (100.0) | 102 (100.0) | 106 ( 84.1) | 141 ( 87.6) |
| N OF SUBJECTS (%) WITH >3 - 6 | 0 | 0 | 3 ( 2.4) | 3 ( 1.9) |
| N OF SUBJECTS (%) WITH >6 - 12 | 0 | 0 | 2 ( 1.6) | 2 ( 1.2) |
| N OF SUBJECTS (%) WITH >12 - 18 | 0 | 0 | 3 ( 2.4) | 3 ( 1.9) |
| N OF SUBJECTS (%) WITH >18 - 24 | 0 | 0 | 12 ( 9.5) | 12 ( 7.5) |
| N OF SUBJECTS (%) WITH >24 | 0 | 0 | 0 | 0 |

## *Adverse events*

### Table 33 Summary of Safety Results Pooled from CA180372 and CA180204 - All treated Paediatric Subjects

| | Discontinuous Dasatinib N = 35 | | Continuous Dasatinib Tablet Only N = 102 | | Continuous Dasatinib N = 126 | | All Treated N = 161 | |
|---|---|---|---|---|---|---|---|---|
| Number of Subjects (%) | All | Grade 3-4 | All | Grade 3-4 | All | Grade 3-4 | All | Grade 3-4 |
| **Adverse Events (pooled population)** | | | | | | | | |
| All causality | 34 (97.1) | 33 (94.3) | 101 (99.0) | 100 (98.0) | 125 (99.2) | 122 (96.8) | 159 (98.8) | 155 (96.3) |
| Dasatinib-related | 27 (77.1) | 27 (77.1) | 88 (86.3) | 76 (74.5) | 106 (84.1) | 91 (72.2) | 133 (82.6) | 118 (73.3) |
| **Dasatinib-related Adverse Events of Special Interest (pooled population)** | | | | | | | | |
| Fluid retention | 0 | 0 | 13 (12.7) | 8 (7.8) | 15 (11.9) | 8 (6.3) | 15 (9.3) | 8 (5.0) |
| Superficial edema | 0 | 0 | 7 (6.9) | 3 (2.9) | 8 (6.3) | 3 (2.4) | 8 (5.0) | 3 (1.9) |
| Pleural effusion | 0 | 0 | 6 (5.9) | 4 (3.9) | 7 (5.6) | 4 (3.2) | 7 (4.3) | 4 (2.5) |
| Generalized edema | 0 | 0 | 2 (2.0) | 1 (1.0) | 3 (2.4) | 1 (0.8) | 3 (1.9) | 1 (0.6) |
| Ascites | 0 | 0 | 3 (2.9) | 2 (2.0) | 3 (2.4) | 2 (1.6) | 3 (1.9) | 2 (1.2) |
| Pericardial effusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CHF/Cardiac dysfunction | 0 | 0 | 1 (1.0) | 1 (1.0) | 1 (0.8) | 1 (0.8) | 1 (0.6) | 1 (0.6) |
| Pulmonary edema | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Respiratory disorders | 1 (2.9) | 0 | 4 (3.9) | 0 | 7 (5.6) | 0 | 8 (5.0) | 0 |
| Chest pain | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.6) | 0 |
| Non-productive cough | 0 | 0 | 3 (2.9) | 0 | 5 (4.0) | 0 | 5 (3.1) | 0 |
| Shortness of breath | 1 (2.9) | 0 | 2 (2.0) | 0 | 4 (3.2) | 0 | 5 (3.1) | 0 |
| Cardiac disorders | 1 (2.9) | 0 | 5 (4.9) | 0 | 8 (6.3) | 0 | 9 (5.6) | 0 |
| Pulmonary arterial hypertension | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hemorrhage | 2 (5.7) | 2 (5.7) | 15 (14.7) | 6 (5.9) | 18 (14.3) | 7 (5.6) | 20 (12.4) | 9 (5.6) |
| GI bleeding | 1 (2.9) | 1 (2.9) | 9 (8.8) | 3 (2.9) | 11 (8.7) | 4 (3.2) | 12 (7.5) | 5 (3.1) |
| CNS bleeding | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other hemorrhage | 1 (2.9) | 1 (2.9) | 9 (8.8) | 3 (2.9) | 12 (9.5) | 3 (2.4) | 13 (8.1) | 4 (2.5) |
| Pediatric growth and development | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.6) | 0 |
| Osteopenia | 0 | 0 | 0 | 0 | 1 (0.8) | 0 | 1 (0.6) | 0 |

Source: Appendix 5.1, Appendix 5.3, Table 12

Note: dasatinib was dosed at 60 mg/m$^2$ per scheduled treatment day in both studies.

### Table 34 Summary of Safety Results from Individuals studies - CA180372 and CA180204 - All treated Subjects

*Safety Results from Study CA180372*

| Number of Subjects (%) | Dasatinib Tablet Only (N=82) | | Dasatinib PFOS Used (N=24) | | All Treated Subjects (N=106) | |
|---|---|---|---|---|---|---|
| Deaths | 11 (13.4) | | 4 (16.7) | | 15 (14.2) | |
| Primary reason of death: | | | | | | |
| Disease | 1 (1.2) | | 1 (4.2) | | 2 (1.9) | |
| HSCT | 2 (2.4) | | 0 | | 2 (1.9) | |
| Other | 8 (9.8) | | 3 (12.5) | | 11 (10.4) | |
| In Continued Complete Remission | 6 (7.3) | | 3 (12.5) | | 9 (8.5) | |
| Within 30 days from last dose | 3 (3.7) | | 2 (8.3) | | 5 (4.7) | |
| | **All** | **Grade 3-5** | **All** | **Grade 3-5** | **All** | **Grade 3-5** |
| SAEs | | | | | | |
| All causality[a] | 79 (96.3) | 79 (96.3) | 22 (91.7) | 22 (91.7) | 101 (95.3) | 101 (95.3) |
| Dasatinib-related | 36 (43.9) | 34 (41.5) | 8 (33.3) | 8 (33.3) | 44 (41.5) | 42 (39.6) |
| AEs leading to discontinuation | | | | | | |
| All causality | 7 (8.5) | 4 (4.9) | 0 | 0 | 7 (6.6) | 4 (3.8) |
| Dasatinib-related | 2 (2.4) | 1 (1.2) | 0 | 0 | 2 (1.9) | 1 (0.9) |

*Safety Results from All Treated Subjects in Study CA180204*[b]

| Number of Subjects (%) | Discontinuous Dasatinib (N=40) | Continuous Dasatinib (N=22) | All Treated Subjects (N=62) |
|---|---|---|---|
| Deaths | | | |
| At any time | 4 (10.0) | 4 (18.2) | 8 (12.9) |
| Within 30 days from last dose | 0 | 0 | 0 |
| SAEs (based on primary event)[c] | | | |
| All causality | 19 (47.5) | 10 (45.5) | 29 (46.8) |
| Dasatinib-related | 14 (35.0) | 7 (31.8) | 21 (33.9) |

[a] Includes Grade 5 events. There were no dasatinib-related Grade 5 AEs

[b] Numbers of deaths and of subjects reported with SAEs (%) in CA180204 are based here on all treated subjects (pediatric and adults) in the discontinuous dasatinib (N=40), continuous dasatinib (N=22), and all subject groups (N=62).

[c] The AdEERS form was the source for capturing SAEs in Study CA180204 (Refer to CA180204 final CSR Appendix 6). Some inconsistencies were noted between the AdEERS forms and COG AE database. Because AdEERS were submitted rapidly and may not have been revised based on subsequent information, the COG AE database was considered to be the definitive source for AE information including dates, severity, and relatedness.

Source: CA180204 final CSR Table 7.1 (overall safety summary); CA180372 final CSR Table 8.1-1 (Overall Safety Summary) and Table S.6.2 (deaths)

- *Common AEs*

**Table 35 Summary of On-treatment adverse Events Reported for at least 10% of subjects by CTC grade - All treated Paediatric Subjects in the Pooled Population**

| System Organ Class (%)<br>Preferred Term (%) | Discontinuous Dasatinib N = 35 | | Continuous Dasatinib Tablet Only N = 102 | | Continuous Dasatinib N = 126 | | All Treated N = 161 | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| TOTAL SUBJECTS WITH AN EVENT | 34 ( 97.1) | 33 ( 94.3) | 101 ( 99.0) | 100 ( 98.0) | 125 ( 99.2) | 122 ( 96.8) | 159 ( 98.8) | 155 ( 96.3) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 28 ( 80.0) | 28 ( 80.0) | 93 ( 91.2) | 93 ( 91.2) | 117 ( 92.9) | 117 ( 92.9) | 145 ( 90.1) | 145 ( 90.1) |
| FEBRILE NEUTROPENIA | 26 ( 74.3) | 26 ( 74.3) | 83 ( 81.4) | 83 ( 81.4) | 106 ( 84.1) | 105 ( 83.3) | 132 ( 82.0) | 131 ( 81.4) |
| ANAEMIA | 11 ( 31.4) | 11 ( 31.4) | 71 ( 69.6) | 69 ( 67.6) | 88 ( 69.8) | 86 ( 68.3) | 99 ( 61.5) | 97 ( 60.2) |
| NEUTROPENIA | 0 | 0 | 47 ( 46.1) | 46 ( 45.1) | 58 ( 46.0) | 57 ( 45.2) | 58 ( 36.0) | 57 ( 35.4) |
| THROMBOCYTOPENIA | 0 | 0 | 45 ( 44.1) | 43 ( 42.2) | 55 ( 43.7) | 51 ( 40.5) | 55 ( 34.2) | 51 ( 31.7) |
| LEUKOPENIA | 0 | 0 | 10 ( 9.8) | 10 ( 9.8) | 13 ( 10.3) | 13 ( 10.3) | 13 ( 8.1) | 13 ( 8.1) |
| INFECTIONS AND INFESTATIONS | 29 ( 82.9) | 29 ( 82.9) | 94 ( 92.2) | 81 ( 79.4) | 115 ( 91.3) | 99 ( 78.6) | 144 ( 89.4) | 128 ( 79.5) |
| UPPER RESPIRATORY TRACT INFECTION | 5 ( 14.3) | 5 ( 14.3) | 31 ( 30.4) | 10 ( 9.8) | 41 ( 32.5) | 13 ( 10.3) | 46 ( 28.6) | 18 ( 11.2) |
| SEPSIS | 16 ( 45.7) | 16 ( 45.7) | 23 ( 22.5) | 23 ( 22.5) | 27 ( 21.4) | 27 ( 21.4) | 43 ( 26.7) | 43 ( 26.7) |
| DEVICE RELATED INFECTION | 1 ( 2.9) | 1 ( 2.9) | 20 ( 19.6) | 17 ( 16.7) | 22 ( 17.5) | 19 ( 15.1) | 23 ( 14.3) | 20 ( 12.4) |
| SKIN INFECTION | 5 ( 14.3) | 5 ( 14.3) | 17 ( 16.7) | 10 ( 9.8) | 18 ( 14.3) | 11 ( 8.7) | 23 ( 14.3) | 16 ( 9.9) |
| LUNG INFECTION | 2 ( 5.7) | 2 ( 5.7) | 15 ( 14.7) | 14 ( 13.7) | 20 ( 15.9) | 18 ( 14.3) | 22 ( 13.7) | 20 ( 12.4) |
| URINARY TRACT INFECTION | 3 ( 8.6) | 3 ( 8.6) | 17 ( 16.7) | 13 ( 12.7) | 19 ( 15.1) | 15 ( 11.9) | 22 ( 13.7) | 18 ( 11.2) |
| PNEUMONIA | 5 ( 14.3) | 5 ( 14.3) | 13 ( 12.7) | 11 ( 10.8) | 16 ( 12.7) | 14 ( 11.1) | 21 ( 13.0) | 19 ( 11.8) |
| SINUSITIS | 1 ( 2.9) | 1 ( 2.9) | 18 ( 17.6) | 9 ( 8.8) | 19 ( 15.1) | 10 ( 7.9) | 20 ( 12.4) | 11 ( 6.8) |
| CELLULITIS | 5 ( 14.3) | 5 ( 14.3) | 12 ( 11.8) | 4 ( 3.9) | 13 ( 10.3) | 4 ( 3.2) | 18 ( 11.2) | 9 ( 5.6) |
| OTITIS MEDIA | 3 ( 8.6) | 3 ( 8.6) | 13 ( 12.7) | 7 ( 6.9) | 15 ( 11.9) | 8 ( 6.3) | 18 ( 11.2) | 11 ( 6.8) |
| ENTEROCOLITIS INFECTIOUS | 4 ( 11.4) | 4 ( 11.4) | 12 ( 11.8) | 7 ( 6.9) | 13 ( 10.3) | 7 ( 5.6) | 17 ( 10.6) | 11 ( 6.8) |
| BACTERAEMIA | 0 | 0 | 12 ( 11.8) | 12 ( 11.8) | 15 ( 11.9) | 15 ( 11.9) | 15 ( 9.3) | 15 ( 9.3) |
| CLOSTRIDIUM DIFFICILE COLITIS | 1 ( 2.9) | 0 | 12 ( 11.8) | 7 ( 6.9) | 14 ( 11.1) | 8 ( 6.3) | 15 ( 9.3) | 8 ( 5.0) |
| CLOSTRIDIUM DIFFICILE INFECTION | 0 | 0 | 12 ( 11.8) | 7 ( 6.9) | 15 ( 11.9) | 9 ( 7.1) | 15 ( 9.3) | 9 ( 5.6) |
| CONJUNCTIVITIS | 0 | 0 | 14 ( 13.7) | 1 ( 1.0) | 14 ( 11.1) | 1 ( 0.8) | 14 ( 8.7) | 1 ( 0.6) |
| ORAL CANDIDIASIS | 0 | 0 | 14 ( 13.7) | 1 ( 1.0) | 14 ( 11.1) | 1 ( 0.8) | 14 ( 8.7) | 1 ( 0.6) |
| RHINITIS | 2 ( 5.7) | 2 ( 5.7) | 11 ( 10.8) | 0 | 11 ( 8.7) | 0 | 13 ( 8.1) | 2 ( 1.2) |
| CANDIDA INFECTION | 0 | 0 | 12 ( 11.8) | 4 ( 3.9) | 12 ( 9.5) | 4 ( 3.2) | 12 ( 7.5) | 4 ( 2.5) |
| INVESTIGATIONS | 31 ( 88.6) | 30 ( 85.7) | 90 ( 88.2) | 78 ( 76.5) | 113 ( 89.7) | 97 ( 77.0) | 144 ( 89.4) | 127 ( 78.9) |
| NEUTROPHIL COUNT DECREASED | 23 ( 65.7) | 23 ( 65.7) | 47 ( 46.1) | 46 ( 45.1) | 57 ( 45.2) | 56 ( 44.4) | 80 ( 49.7) | 79 ( 49.1) |
| ALANINE AMINOTRANSFERASE INCREASED | 21 ( 60.0) | 20 ( 57.1) | 41 ( 40.2) | 38 ( 37.3) | 55 ( 43.7) | 49 ( 38.9) | 76 ( 47.2) | 69 ( 42.9) |
| PLATELET COUNT DECREASED | 17 ( 48.6) | 17 ( 48.6) | 41 ( 40.2) | 40 ( 39.2) | 51 ( 40.5) | 47 ( 37.3) | 68 ( 42.2) | 64 ( 39.8) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 18 ( 51.4) | 17 ( 48.6) | 28 ( 27.5) | 19 ( 18.6) | 41 ( 32.5) | 29 ( 23.0) | 59 ( 36.6) | 46 ( 28.6) |
| WHITE BLOOD CELL COUNT DECREASED | 13 ( 37.1) | 13 ( 37.1) | 21 ( 20.6) | 20 ( 19.6) | 27 ( 21.4) | 25 ( 19.8) | 40 ( 24.8) | 38 ( 23.6) |
| WEIGHT DECREASED | 0 | 0 | 24 ( 23.5) | 6 ( 5.9) | 28 ( 22.2) | 8 ( 6.3) | 28 ( 17.4) | 8 ( 5.0) |
| BLOOD BILIRUBIN INCREASED | 3 ( 8.6) | 2 ( 5.7) | 13 ( 12.7) | 9 ( 8.8) | 14 ( 11.1) | 9 ( 7.1) | 17 ( 10.6) | 11 ( 6.8) |
| BLOOD CREATININE INCREASED | 1 ( 2.9) | 1 ( 2.9) | 13 ( 12.7) | 3 ( 2.9) | 15 ( 11.9) | 3 ( 2.4) | 16 ( 9.9) | 4 ( 2.5) |
| CARDIAC MURMUR | 0 | 0 | 11 ( 10.8) | 0 | 12 ( 9.5) | 0 | 12 ( 7.5) | 0 |
| GASTROINTESTINAL DISORDERS | 20 ( 57.1) | 16 ( 45.7) | 93 ( 91.2) | 65 ( 63.7) | 114 ( 90.5) | 81 ( 64.3) | 134 ( 83.2) | 97 ( 60.2) |
| VOMITING | 3 ( 8.6) | 3 ( 8.6) | 75 ( 73.5) | 20 ( 19.6) | 92 ( 73.0) | 23 ( 18.3) | 95 ( 59.0) | 26 ( 16.1) |
| NAUSEA | 4 ( 11.4) | 3 ( 8.6) | 74 ( 72.5) | 14 ( 13.7) | 87 ( 69.0) | 16 ( 12.7) | 91 ( 56.5) | 19 ( 11.8) |
| DIARRHOEA | 4 ( 11.4) | 4 ( 11.4) | 70 ( 68.6) | 20 ( 19.6) | 84 ( 66.7) | 29 ( 23.0) | 88 ( 54.7) | 33 ( 20.5) |
| ABDOMINAL PAIN | 3 ( 8.6) | 3 ( 8.6) | 62 ( 60.8) | 13 ( 12.7) | 78 ( 61.9) | 17 ( 13.5) | 81 ( 50.3) | 20 ( 12.4) |
| STOMATITIS | 11 ( 31.4) | 8 ( 22.9) | 53 ( 52.0) | 31 ( 30.4) | 62 ( 49.2) | 36 ( 28.6) | 73 ( 45.3) | 44 ( 27.3) |
| CONSTIPATION | 1 ( 2.9) | 0 | 46 ( 45.1) | 1 ( 1.0) | 58 ( 46.0) | 2 ( 1.6) | 59 ( 36.6) | 2 ( 1.2) |
| ORAL PAIN | 1 ( 2.9) | 1 ( 2.9) | 25 ( 24.5) | 7 ( 6.9) | 28 ( 22.2) | 7 ( 5.6) | 29 ( 18.0) | 8 ( 5.0) |
| COLITIS | 1 ( 2.9) | 1 ( 2.9) | 19 ( 18.6) | 11 ( 10.8) | 23 ( 18.3) | 13 ( 10.3) | 24 ( 14.9) | 14 ( 8.7) |
| ABDOMINAL PAIN UPPER | 0 | 0 | 17 ( 16.7) | 2 ( 2.0) | 19 ( 15.1) | 2 ( 1.6) | 19 ( 11.8) | 2 ( 1.2) |
| NEUTROPENIC COLITIS | 4 ( 11.4) | 4 ( 11.4) | 12 ( 11.8) | 11 ( 10.8) | 14 ( 11.1) | 12 ( 9.5) | 18 ( 11.2) | 16 ( 9.9) |
| PROCTALGIA | 0 | 0 | 14 ( 13.7) | 5 ( 4.9) | 16 ( 12.7) | 6 ( 4.8) | 16 ( 9.9) | 6 ( 3.7) |
| HAEMATOCHEZIA | 0 | 0 | 12 ( 11.8) | 1 ( 1.0) | 14 ( 11.1) | 1 ( 0.8) | 14 ( 8.7) | 1 ( 0.6) |
| METABOLISM AND NUTRITION DISORDERS | 24 ( 68.6) | 22 ( 62.9) | 80 ( 78.4) | 65 ( 63.7) | 97 ( 77.0) | 77 ( 61.1) | 121 ( 75.2) | 99 ( 61.5) |
| HYPOKALAEMIA | 18 ( 51.4) | 17 ( 48.6) | 55 ( 53.9) | 45 ( 44.1) | 64 ( 50.8) | 50 ( 39.7) | 82 ( 50.9) | 67 ( 41.6) |
| DECREASED APPETITE | 4 ( 11.4) | 4 ( 11.4) | 34 ( 33.3) | 20 ( 19.6) | 43 ( 34.1) | 26 ( 20.6) | 47 ( 29.2) | 30 ( 18.6) |
| HYPOALBUMINAEMIA | 5 ( 14.3) | 3 ( 8.6) | 30 ( 29.4) | 15 ( 14.7) | 39 ( 31.0) | 18 ( 14.3) | 44 ( 27.3) | 21 ( 13.0) |
| HYPONATRAEMIA | 8 ( 22.9) | 8 ( 22.9) | 28 ( 27.5) | 22 ( 21.6) | 32 ( 25.4) | 24 ( 19.0) | 40 ( 24.8) | 32 ( 19.9) |
| HYPOCALCAEMIA | 6 ( 17.1) | 5 ( 14.3) | 26 ( 25.5) | 14 ( 13.7) | 31 ( 24.6) | 15 ( 11.9) | 37 ( 23.0) | 20 ( 12.4) |
| DEHYDRATION | 4 ( 11.4) | 4 ( 11.4) | 20 ( 19.6) | 11 ( 10.8) | 24 ( 19.0) | 13 ( 10.3) | 28 ( 17.4) | 17 ( 10.6) |
| HYPERGLYCAEMIA | 4 ( 11.4) | 4 ( 11.4) | 18 ( 17.6) | 5 ( 4.9) | 24 ( 19.0) | 5 ( 4.0) | 28 ( 17.4) | 9 ( 5.6) |
| HYPOPHOSPHATAEMIA | 4 ( 11.4) | 4 ( 11.4) | 18 ( 17.6) | 11 ( 10.8) | 24 ( 19.0) | 14 ( 11.1) | 28 ( 17.4) | 18 ( 11.2) |
| HYPOMAGNESAEMIA | 0 | 0 | 14 ( 13.7) | 1 ( 1.0) | 19 ( 15.1) | 1 ( 0.8) | 19 ( 11.8) | 1 ( 0.6) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 4 ( 11.4) | 1 ( 2.9) | 86 ( 84.3) | 42 ( 41.2) | 109 ( 86.5) | 60 ( 47.6) | 113 ( 70.2) | 61 ( 37.9) |
| PYREXIA | 2 ( 5.7) | 0 | 73 ( 71.6) | 17 ( 16.7) | 95 ( 75.4) | 24 ( 19.0) | 97 ( 60.2) | 24 ( 14.9) |
| MUCOSAL INFLAMMATION | 0 | 0 | 46 ( 45.1) | 24 ( 23.5) | 59 ( 46.8) | 36 ( 28.6) | 59 ( 36.6) | 36 ( 22.4) |
| FATIGUE | 0 | 0 | 45 ( 44.1) | 2 ( 2.0) | 58 ( 46.0) | 2 ( 1.6) | 58 ( 36.0) | 2 ( 1.2) |
| PAIN | 1 ( 2.9) | 0 | 27 ( 26.5) | 5 ( 4.9) | 31 ( 24.6) | 6 ( 4.8) | 32 ( 19.9) | 6 ( 3.7) |
| CHILLS | 1 ( 2.9) | 1 ( 2.9) | 17 ( 16.7) | 0 | 21 ( 16.7) | 0 | 22 ( 13.7) | 1 ( 0.6) |
| NON-CARDIAC CHEST PAIN | 0 | 0 | 16 ( 15.7) | 4 ( 3.9) | 19 ( 15.1) | 4 ( 3.2) | 19 ( 11.8) | 4 ( 2.5) |
| OEDEMA PERIPHERAL | 0 | 0 | 18 ( 17.6) | 2 ( 2.0) | 19 ( 15.1) | 2 ( 1.6) | 19 ( 11.8) | 2 ( 1.2) |
| CATHETER SITE PAIN | 0 | 0 | 10 ( 9.8) | 0 | 14 ( 11.1) | 0 | 14 ( 8.7) | 0 |
| ASTHENIA | 0 | 0 | 11 ( 10.8) | 0 | 11 ( 8.7) | 0 | 11 ( 6.8) | 0 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| NERVOUS SYSTEM DISORDERS | 15 ( 42.9) | 9 ( 25.7) | 81 ( 79.4) | 31 ( 30.4) | 96 ( 76.2) | 35 ( 27.8) | 111 ( 68.9) | 44 ( 27.3) |
| HEADACHE | 3 ( 8.6) | 3 ( 8.6) | 66 ( 64.7) | 14 ( 13.7) | 76 ( 60.3) | 16 ( 12.7) | 79 ( 49.1) | 19 ( 11.8) |
| PERIPHERAL MOTOR NEUROPATHY | 6 ( 17.1) | 2 ( 5.7) | 15 ( 14.7) | 4 ( 3.9) | 16 ( 12.7) | 4 ( 3.2) | 22 ( 13.7) | 6 ( 3.7) |
| PERIPHERAL SENSORY NEUROPATHY | 5 ( 14.3) | 1 ( 2.9) | 16 ( 15.7) | 6 ( 5.9) | 17 ( 13.5) | 6 ( 4.8) | 22 ( 13.7) | 7 ( 4.3) |
| DIZZINESS | 1 ( 2.9) | 0 | 14 ( 13.7) | 0 | 14 ( 11.1) | 0 | 15 ( 9.3) | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 6 ( 17.1) | 5 ( 14.3) | 79 ( 77.5) | 29 ( 28.4) | 98 ( 77.8) | 33 ( 26.2) | 104 ( 64.6) | 38 ( 23.6) |
| COUGH | 0 | 0 | 63 ( 61.8) | 1 ( 1.0) | 78 ( 61.9) | 2 ( 1.6) | 78 ( 48.4) | 2 ( 1.2) |
| RHINORRHOEA | 0 | 0 | 24 ( 23.5) | 1 ( 1.0) | 37 ( 29.4) | 1 ( 0.8) | 37 ( 23.0) | 1 ( 0.6) |
| OROPHARYNGEAL PAIN | 0 | 0 | 31 ( 30.4) | 2 ( 2.0) | 35 ( 27.8) | 2 ( 1.6) | 35 ( 21.7) | 2 ( 1.2) |
| EPISTAXIS | 1 ( 2.9) | 1 ( 2.9) | 25 ( 24.5) | 5 ( 4.9) | 28 ( 22.2) | 5 ( 4.0) | 29 ( 18.0) | 6 ( 3.7) |
| NASAL CONGESTION | 0 | 0 | 24 ( 23.5) | 1 ( 1.0) | 28 ( 22.2) | 1 ( 0.8) | 28 ( 17.4) | 1 ( 0.6) |
| DYSPNOEA | 1 ( 2.9) | 0 | 17 ( 16.7) | 6 ( 5.9) | 21 ( 16.7) | 6 ( 4.8) | 22 ( 13.7) | 6 ( 3.7) |
| PLEURAL EFFUSION | 0 | 0 | 17 ( 16.7) | 7 ( 6.9) | 21 ( 16.7) | 8 ( 6.3) | 21 ( 13.0) | 8 ( 5.0) |
| HYPOXIA | 2 ( 5.7) | 1 ( 2.9) | 14 ( 13.7) | 11 ( 10.8) | 18 ( 14.3) | 13 ( 10.3) | 20 ( 12.4) | 14 ( 8.7) |
| WHEEZING | 0 | 0 | 12 ( 11.8) | 1 ( 1.0) | 13 ( 10.3) | 1 ( 0.8) | 13 ( 8.1) | 1 ( 0.6) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 3 ( 8.6) | 1 ( 2.9) | 77 ( 75.5) | 27 ( 26.5) | 94 ( 74.6) | 33 ( 26.2) | 97 ( 60.2) | 34 ( 21.1) |
| PAIN IN EXTREMITY | 1 ( 2.9) | 0 | 54 ( 52.9) | 11 ( 10.8) | 66 ( 52.4) | 13 ( 10.3) | 67 ( 41.6) | 13 ( 8.1) |
| BACK PAIN | 1 ( 2.9) | 1 ( 2.9) | 41 ( 40.2) | 7 ( 6.9) | 49 ( 38.9) | 9 ( 7.1) | 50 ( 31.1) | 10 ( 6.2) |
| ARTHRALGIA | 0 | 0 | 34 ( 33.3) | 4 ( 3.9) | 39 ( 31.0) | 5 ( 4.0) | 39 ( 24.2) | 5 ( 3.1) |
| BONE PAIN | 0 | 0 | 19 ( 18.6) | 3 ( 2.9) | 23 ( 18.3) | 3 ( 2.4) | 23 ( 14.3) | 3 ( 1.9) |
| MUSCULAR WEAKNESS | 0 | 0 | 15 ( 14.7) | 3 ( 2.9) | 22 ( 17.5) | 6 ( 4.8) | 22 ( 13.7) | 6 ( 3.7) |
| PAIN IN JAW | 0 | 0 | 18 ( 17.6) | 1 ( 1.0) | 19 ( 15.1) | 1 ( 0.8) | 19 ( 11.8) | 1 ( 0.6) |
| MYALGIA | 0 | 0 | 14 ( 13.7) | 2 ( 2.0) | 17 ( 13.5) | 3 ( 2.4) | 17 ( 10.6) | 3 ( 1.9) |
| MUSCULOSKELETAL PAIN | 0 | 0 | 14 ( 13.7) | 3 ( 2.9) | 16 ( 12.7) | 3 ( 2.4) | 16 ( 9.9) | 3 ( 1.9) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 8 ( 22.9) | 4 ( 11.4) | 72 ( 70.6) | 9 ( 8.8) | 89 ( 70.6) | 9 ( 7.1) | 97 ( 60.2) | 13 ( 8.1) |
| RASH | 0 | 0 | 38 ( 37.3) | 3 ( 2.9) | 49 ( 38.9) | 3 ( 2.4) | 49 ( 30.4) | 3 ( 1.9) |
| PRURITUS | 0 | 0 | 21 ( 20.6) | 0 | 27 ( 21.4) | 0 | 27 ( 16.8) | 0 |
| RASH MACULO-PAPULAR | 4 ( 11.4) | 1 ( 2.9) | 17 ( 16.7) | 1 ( 1.0) | 22 ( 17.5) | 1 ( 0.8) | 26 ( 16.1) | 2 ( 1.2) |
| ERYTHEMA | 0 | 0 | 18 ( 17.6) | 1 ( 1.0) | 22 ( 17.5) | 1 ( 0.8) | 22 ( 13.7) | 1 ( 0.6) |
| ALOPECIA | 0 | 0 | 19 ( 18.6) | 0 | 21 ( 16.7) | 0 | 21 ( 13.0) | 0 |
| DRY SKIN | 0 | 0 | 16 ( 15.7) | 1 ( 1.0) | 19 ( 15.1) | 1 ( 0.8) | 19 ( 11.8) | 1 ( 0.6) |
| PETECHIAE | 0 | 0 | 14 ( 13.7) | 0 | 17 ( 13.5) | 0 | 17 ( 10.6) | 0 |
| VASCULAR DISORDERS | 8 ( 22.9) | 7 ( 20.0) | 71 ( 69.6) | 38 ( 37.3) | 86 ( 68.3) | 46 ( 36.5) | 94 ( 58.4) | 53 ( 32.9) |
| HYPOTENSION | 6 ( 17.1) | 5 ( 14.3) | 37 ( 36.3) | 26 ( 25.5) | 46 ( 36.5) | 34 ( 27.0) | 52 ( 32.3) | 39 ( 24.2) |
| HYPERTENSION | 0 | 0 | 41 ( 40.2) | 12 ( 11.8) | 50 ( 39.7) | 14 ( 11.1) | 50 ( 31.1) | 14 ( 8.7) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 1 ( 2.9) | 1 ( 2.9) | 52 ( 51.0) | 11 ( 10.8) | 65 ( 51.6) | 14 ( 11.1) | 66 ( 41.0) | 15 ( 9.3) |
| CONTUSION | 0 | 0 | 24 ( 23.5) | 1 ( 1.0) | 32 ( 25.4) | 1 ( 0.8) | 32 ( 19.9) | 1 ( 0.6) |
| ALLERGIC TRANSFUSION REACTION | 0 | 0 | 10 ( 9.8) | 2 ( 2.0) | 13 ( 10.3) | 4 ( 3.2) | 13 ( 8.1) | 4 ( 2.5) |
| CARDIAC DISORDERS | 2 ( 5.7) | 1 ( 2.9) | 41 ( 40.2) | 11 ( 10.8) | 53 ( 42.1) | 13 ( 10.3) | 55 ( 34.2) | 14 ( 8.7) |
| TACHYCARDIA | 0 | 0 | 25 ( 24.5) | 4 ( 3.9) | 36 ( 28.6) | 4 ( 3.2) | 36 ( 22.4) | 4 ( 2.5) |
| SINUS TACHYCARDIA | 2 ( 5.7) | 1 ( 2.9) | 19 ( 18.6) | 4 ( 3.9) | 22 ( 17.5) | 5 ( 4.0) | 24 ( 14.9) | 6 ( 3.7) |
| PSYCHIATRIC DISORDERS | 4 ( 11.4) | 3 ( 8.6) | 38 ( 37.3) | 6 ( 5.9) | 48 ( 38.1) | 8 ( 6.3) | 52 ( 32.3) | 11 ( 6.8) |
| ANXIETY | 1 ( 2.9) | 0 | 13 ( 12.7) | 2 ( 2.0) | 17 ( 13.5) | 3 ( 2.4) | 18 ( 11.2) | 3 ( 1.9) |
| DEPRESSION | 1 ( 2.9) | 0 | 14 ( 13.7) | 1 ( 1.0) | 17 ( 13.5) | 1 ( 0.8) | 18 ( 11.2) | 1 ( 0.6) |
| INSOMNIA | 0 | 0 | 14 ( 13.7) | 1 ( 1.0) | 17 ( 13.5) | 1 ( 0.8) | 17 ( 10.6) | 1 ( 0.6) |
| EYE DISORDERS | 1 ( 2.9) | 1 ( 2.9) | 40 ( 39.2) | 2 ( 2.0) | 50 ( 39.7) | 2 ( 1.6) | 51 ( 31.7) | 3 ( 1.9) |
| VISION BLURRED | 1 ( 2.9) | 1 ( 2.9) | 15 ( 14.7) | 0 | 16 ( 12.7) | 0 | 17 ( 10.6) | 1 ( 0.6) |
| IMMUNE SYSTEM DISORDERS | 2 ( 5.7) | 2 ( 5.7) | 35 ( 34.3) | 19 ( 18.6) | 42 ( 33.3) | 22 ( 17.5) | 44 ( 27.3) | 24 ( 14.9) |
| DRUG HYPERSENSITIVITY | 0 | 0 | 16 ( 15.7) | 6 ( 5.9) | 19 ( 15.1) | 6 ( 4.8) | 19 ( 11.8) | 6 ( 3.7) |
| ANAPHYLACTIC REACTION | 1 ( 2.9) | 1 ( 2.9) | 10 ( 9.8) | 10 ( 9.8) | 13 ( 10.3) | 13 ( 10.3) | 14 ( 8.7) | 14 ( 8.7) |
| RENAL AND URINARY DISORDERS | 0 | 0 | 36 ( 35.3) | 8 ( 7.8) | 43 ( 34.1) | 10 ( 7.9) | 43 ( 26.7) | 10 ( 6.2) |
| HAEMATURIA | 0 | 0 | 12 ( 11.8) | 1 ( 1.0) | 14 ( 11.1) | 2 ( 1.6) | 14 ( 8.7) | 2 ( 1.2) |
| ACUTE KIDNEY INJURY | 0 | 0 | 12 ( 11.8) | 3 ( 2.9) | 13 ( 10.3) | 4 ( 3.2) | 13 ( 8.1) | 4 ( 2.5) |
| EAR AND LABYRINTH DISORDERS | 2 ( 5.7) | 2 ( 5.7) | 25 ( 24.5) | 0 | 29 ( 23.0) | 1 ( 0.8) | 31 ( 19.3) | 3 ( 1.9) |
| EAR PAIN | 0 | 0 | 21 ( 20.6) | 0 | 25 ( 19.8) | 0 | 25 ( 15.5) | 0 |

- *On-Treatment Dasatinib-related Adverse Events*

**Table 36 Summary of On-Treatment Dasatinib-related Adverse Events Reported for at least 10% of Subjects by CTC Grade - All Treated Subjects in the Pooled Population-CA180372**

| System Organ Class (%) Preferred Term (%) | Discontinuous Dasatinib N = 35 | | Continuous Dasatinib Tablet Only N = 102 | | Continuous Dasatinib N = 126 | | All Treated N = 161 | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| TOTAL SUBJECTS WITH AN EVENT | 27 ( 77.1) | 27 ( 77.1) | 88 ( 86.3) | 76 ( 74.5) | 106 ( 84.1) | 91 ( 72.2) | 133 ( 82.6) | 118 ( 73.3) |
| INVESTIGATIONS | 24 ( 68.6) | 23 ( 65.7) | 55 ( 53.9) | 52 ( 51.0) | 65 ( 51.6) | 61 ( 48.4) | 89 ( 55.3) | 84 ( 52.2) |
| ALANINE AMINOTRANSFERASE INCREASED | 17 ( 48.6) | 16 ( 45.7) | 29 ( 28.4) | 27 ( 26.5) | 38 ( 30.2) | 34 ( 27.0) | 55 ( 34.2) | 50 ( 31.1) |
| NEUTROPHIL COUNT DECREASED | 15 ( 42.9) | 15 ( 42.9) | 28 ( 27.5) | 28 ( 27.5) | 31 ( 24.6) | 31 ( 24.6) | 46 ( 28.6) | 46 ( 28.6) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 12 ( 34.3) | 11 ( 31.4) | 13 ( 12.7) | 9 ( 8.8) | 20 ( 15.9) | 13 ( 10.3) | 32 ( 19.9) | 24 ( 14.9) |
| PLATELET COUNT DECREASED | 10 ( 28.6) | 10 ( 28.6) | 21 ( 20.6) | 21 ( 20.6) | 22 ( 17.5) | 22 ( 17.5) | 32 ( 19.9) | 32 ( 19.9) |
| WHITE BLOOD CELL COUNT DECREASED | 7 ( 20.0) | 7 ( 20.0) | 8 ( 7.8) | 8 ( 7.8) | 9 ( 7.1) | 9 ( 7.1) | 16 ( 9.9) | 16 ( 9.9) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 19 ( 54.3) | 19 ( 54.3) | 49 ( 48.0) | 48 ( 47.1) | 57 ( 45.2) | 55 ( 43.7) | 76 ( 47.2) | 74 ( 46.0) |
| FEBRILE NEUTROPENIA | 18 ( 51.4) | 18 ( 51.4) | 28 ( 27.5) | 28 ( 27.5) | 34 ( 27.0) | 33 ( 26.2) | 52 ( 32.3) | 51 ( 31.7) |
| ANAEMIA | 7 ( 20.0) | 7 ( 20.0) | 29 ( 28.4) | 28 ( 27.5) | 34 ( 27.0) | 33 ( 26.2) | 41 ( 25.5) | 40 ( 24.8) |
| NEUTROPENIA | 0 | 0 | 22 ( 21.6) | 21 ( 20.6) | 26 ( 20.6) | 25 ( 19.8) | 26 ( 16.1) | 25 ( 15.5) |
| THROMBOCYTOPENIA | 0 | 0 | 16 ( 15.7) | 15 ( 14.7) | 21 ( 16.7) | 19 ( 15.1) | 21 ( 13.0) | 19 ( 11.8) |
| GASTROINTESTINAL DISORDERS | 11 ( 31.4) | 9 ( 25.7) | 42 ( 41.2) | 20 ( 19.6) | 52 ( 41.3) | 23 ( 18.3) | 63 ( 39.1) | 32 ( 19.9) |
| NAUSEA | 2 ( 5.7) | 1 ( 2.9) | 22 ( 21.6) | 7 ( 6.9) | 26 ( 20.6) | 7 ( 5.6) | 28 ( 17.4) | 8 ( 5.0) |
| VOMITING | 1 ( 2.9) | 1 ( 2.9) | 20 ( 19.6) | 6 ( 5.9) | 26 ( 20.6) | 6 ( 4.8) | 27 ( 16.8) | 7 ( 4.3) |
| DIARRHOEA | 4 ( 11.4) | 4 ( 11.4) | 12 ( 11.8) | 5 ( 4.9) | 16 ( 12.7) | 6 ( 4.8) | 20 ( 12.4) | 10 ( 6.2) |
| ABDOMINAL PAIN | 1 ( 2.9) | 1 ( 2.9) | 12 ( 11.8) | 3 ( 2.9) | 18 ( 14.3) | 4 ( 3.2) | 19 ( 11.8) | 5 ( 3.1) |
| NEUTROPENIC COLITIS | 4 ( 11.4) | 4 ( 11.4) | 4 ( 3.9) | 3 ( 2.9) | 4 ( 3.2) | 3 ( 2.4) | 8 ( 5.0) | 7 ( 4.3) |
| METABOLISM AND NUTRITION DISORDERS | 13 ( 37.1) | 12 ( 34.3) | 23 ( 22.5) | 15 ( 14.7) | 27 ( 21.4) | 18 ( 14.3) | 40 ( 24.8) | 30 ( 18.6) |
| HYPOKALAEMIA | 6 ( 17.1) | 5 ( 14.3) | 11 ( 10.8) | 9 ( 8.8) | 14 ( 11.1) | 11 ( 8.7) | 20 ( 12.4) | 16 ( 9.9) |
| DECREASED APPETITE | 4 ( 11.4) | 4 ( 11.4) | 10 ( 9.8) | 4 ( 3.9) | 13 ( 10.3) | 6 ( 4.8) | 17 ( 10.6) | 10 ( 6.2) |
| HYPOALBUMINAEMIA | 4 ( 11.4) | 2 ( 5.7) | 6 ( 5.9) | 2 ( 2.0) | 7 ( 5.6) | 2 ( 1.6) | 11 ( 6.8) | 4 ( 2.5) |
| HYPOPHOSPHATAEMIA | 4 ( 11.4) | 4 ( 11.4) | 3 ( 2.9) | 2 ( 2.0) | 5 ( 4.0) | 4 ( 3.2) | 9 ( 5.6) | 8 ( 5.0) |
| INFECTIONS AND INFESTATIONS | 16 ( 45.7) | 16 ( 45.7) | 18 ( 17.6) | 14 ( 13.7) | 22 ( 17.5) | 17 ( 13.5) | 38 ( 23.6) | 33 ( 20.5) |
| SEPSIS | 9 ( 25.7) | 9 ( 25.7) | 7 ( 6.9) | 7 ( 6.9) | 8 ( 6.3) | 8 ( 6.3) | 17 ( 10.6) | 17 ( 10.6) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 0 | 0 | 28 ( 27.5) | 13 ( 12.7) | 35 ( 27.8) | 17 ( 13.5) | 35 ( 21.7) | 17 ( 10.6) |
| PYREXIA | 0 | 0 | 10 ( 9.8) | 5 ( 4.9) | 16 ( 12.7) | 7 ( 5.6) | 16 ( 9.9) | 7 ( 4.3) |
| FATIGUE | 0 | 0 | 9 ( 8.8) | 0 | 13 ( 10.3) | 0 | 13 ( 8.1) | 0 |
| NERVOUS SYSTEM DISORDERS | 5 ( 14.3) | 2 ( 5.7) | 21 ( 20.6) | 9 ( 8.8) | 25 ( 19.8) | 9 ( 7.1) | 30 ( 18.6) | 11 ( 6.8) |
| HEADACHE | 2 ( 5.7) | 2 ( 5.7) | 11 ( 10.8) | 6 ( 5.9) | 14 ( 11.1) | 6 ( 4.8) | 16 ( 9.9) | 8 ( 5.0) |

- *Dasatinib-related Adverse Events of Special Interest*

**Table 37 Summary of On-treatment Dasatinib-related Adverse Events of special interest - All Treated Subjects in the pooled Population- CA180372**

| AE Special Interest | Discontinuous Dasatinib N = 35 | | Continuous Dasatinib Tablet Only N = 102 | | Continuous Dasatinib N = 126 | | All Treated N = 161 | |
|---|---|---|---|---|---|---|---|---|
| | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) |
| FLUID RETENTION | 0 | 0 | 13 ( 12.7) | 8 ( 7.8) | 15 ( 11.9) | 8 ( 6.3) | 15 ( 9.3) | 8 ( 5.0) |
| SUPERFICIAL EDEMA | 0 | 0 | 7 ( 6.9) | 3 ( 2.9) | 8 ( 6.3) | 3 ( 2.4) | 8 ( 5.0) | 3 ( 1.9) |
| PLEURAL EFFUSION | 0 | 0 | 6 ( 5.9) | 4 ( 3.9) | 7 ( 5.6) | 4 ( 3.2) | 7 ( 4.3) | 4 ( 2.5) |
| OTHER FLUID RELATED | 0 | 0 | 5 ( 4.9) | 4 ( 3.9) | 6 ( 4.8) | 4 ( 3.2) | 6 ( 3.7) | 4 ( 2.5) |
| GENERALIZED EDEMA | 0 | 0 | 2 ( 2.0) | 1 ( 1.0) | 3 ( 2.4) | 1 ( 0.8) | 3 ( 1.9) | 1 ( 0.6) |
| ASCITES | 0 | 0 | 3 ( 2.9) | 2 ( 2.0) | 3 ( 2.4) | 2 ( 1.6) | 3 ( 1.9) | 2 ( 1.2) |
| PERICARDIAL EFFUSION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION | 0 | 0 | 1 ( 1.0) | 1 ( 1.0) | 1 ( 0.8) | 1 ( 0.8) | 1 ( 0.6) | 1 ( 0.6) |
| PULMONARY EDEMA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PULMONARY HYPERTENSION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RESPIRATORY DISORDERS | 1 ( 2.9) | 0 | 4 ( 3.9) | 0 | 7 ( 5.6) | 0 | 8 ( 5.0) | 0 |
| CHEST PAIN | 0 | 0 | 0 | 0 | 1 ( 0.8) | 0 | 1 ( 0.6) | 0 |
| NON-PRODUCTIVE COUGH | 0 | 0 | 3 ( 2.9) | 0 | 5 ( 4.0) | 0 | 5 ( 3.1) | 0 |
| SHORTNESS OF BREATH | 1 ( 2.9) | 0 | 2 ( 2.0) | 0 | 4 ( 3.2) | 0 | 5 ( 3.1) | 0 |
| CARDIAC DISORDERS | 1 ( 2.9) | 0 | 5 ( 4.9) | 0 | 8 ( 6.3) | 0 | 9 ( 5.6) | 0 |
| PULMONARY ARTERIAL HYPERTENSION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DIARRHEA | 4 ( 11.4) | 4 ( 11.4) | 12 ( 11.8) | 5 ( 4.9) | 16 ( 12.7) | 6 ( 4.8) | 20 ( 12.4) | 10 ( 6.2) |
| NAUSEA/VOMITING | 3 ( 8.6) | 2 ( 5.7) | 28 ( 27.5) | 9 ( 8.8) | 34 ( 27.0) | 9 ( 7.1) | 37 ( 23.0) | 11 ( 6.8) |
| FATIGUE | 0 | 0 | 10 ( 9.8) | 0 | 14 ( 11.1) | 0 | 14 ( 8.7) | 0 |
| MYALGIAS/ARTHRALGIAS | 0 | 0 | 7 ( 6.9) | 2 ( 2.0) | 9 ( 7.1) | 2 ( 1.6) | 9 ( 5.6) | 2 ( 1.2) |
| RASH | 3 ( 8.6) | 1 ( 2.9) | 12 ( 11.8) | 0 | 16 ( 12.7) | 0 | 19 ( 11.8) | 1 ( 0.6) |
| HEMORRHAGE | 2 ( 5.7) | 2 ( 5.7) | 15 ( 14.7) | 6 ( 5.9) | 18 ( 14.3) | 7 ( 5.6) | 20 ( 12.4) | 9 ( 5.6) |
| GI BLEEDING | 1 ( 2.9) | 1 ( 2.9) | 9 ( 8.8) | 3 ( 2.9) | 11 ( 8.7) | 4 ( 3.2) | 12 ( 7.5) | 5 ( 3.1) |
| CNS BLEEDING | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| OTHER HEMORRHAGE | 1 ( 2.9) | 1 ( 2.9) | 9 ( 8.8) | 3 ( 2.9) | 12 ( 9.5) | 3 ( 2.4) | 13 ( 8.1) | 4 ( 2.5) |

Program Source: /projects/bms235555/stats/SCS/prog/tables/rt-ae-specint.sas 29SEP2017:04:38:21

- *All-causality Adverse Events of Special Interest*

**Table 38 Summary of On-treatment Adverse Events of Special Interest - All Causality - All treated Subjects in the Pooled population**

| | Discontinuous Dasatinib N = 35 | | Continuous Dasatinib Tablet Only N = 102 | | Continuous Dasatinib N = 126 | | All Treated N = 161 | |
|---|---|---|---|---|---|---|---|---|
| AE Special Interest | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) | Any Grade | Severe (3-4) |
| FLUID RETENTION | 0 | 0 | 48 ( 47.1) | 14 ( 13.7) | 56 ( 44.4) | 16 ( 12.7) | 56 ( 34.8) | 16 ( 9.9) |
| SUPERFICIAL EDEMA | 0 | 0 | 35 ( 34.3) | 5 ( 4.9) | 39 ( 31.0) | 5 ( 4.0) | 39 ( 24.2) | 5 ( 3.1) |
| PLEURAL EFFUSION | 0 | 0 | 17 ( 16.7) | 7 ( 6.9) | 21 ( 16.7) | 8 ( 6.3) | 21 ( 13.0) | 8 ( 5.0) |
| OTHER FLUID RELATED | 0 | 0 | 24 ( 23.5) | 5 ( 4.9) | 28 ( 22.2) | 6 ( 4.8) | 28 ( 17.4) | 6 ( 3.7) |
| GENERALIZED EDEMA | 0 | 0 | 16 ( 15.7) | 1 ( 1.0) | 18 ( 14.3) | 1 ( 0.8) | 18 ( 11.2) | 1 ( 0.6) |
| ASCITES | 0 | 0 | 7 ( 6.9) | 2 ( 2.0) | 7 ( 5.6) | 2 ( 1.6) | 7 ( 4.3) | 2 ( 1.2) |
| PERICARDIAL EFFUSION | 0 | 0 | 6 ( 5.9) | 0 | 7 ( 5.6) | 1 ( 0.8) | 7 ( 4.3) | 1 ( 0.6) |
| CONGESTIVE HEART FAILURE/CARDIAC DYSFUNCTION | 0 | 0 | 2 ( 2.0) | 2 ( 2.0) | 2 ( 1.6) | 2 ( 1.6) | 2 ( 1.2) | 2 ( 1.2) |
| PULMONARY EDEMA | 0 | 0 | 4 ( 3.9) | 3 ( 2.9) | 5 ( 4.0) | 3 ( 2.4) | 5 ( 3.1) | 3 ( 1.9) |
| PULMONARY HYPERTENSION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| RESPIRATORY DISORDERS | 1 ( 2.9) | 0 | 69 ( 67.6) | 12 ( 11.8) | 85 ( 67.5) | 13 ( 10.3) | 86 ( 53.4) | 13 ( 8.1) |
| CHEST PAIN | 0 | 0 | 18 ( 17.6) | 4 ( 3.9) | 21 ( 16.7) | 4 ( 3.2) | 21 ( 13.0) | 4 ( 2.5) |
| NON-PRODUCTIVE COUGH | 0 | 0 | 63 ( 61.8) | 1 ( 1.0) | 78 ( 61.9) | 2 ( 1.6) | 78 ( 48.4) | 2 ( 1.2) |
| SHORTNESS OF BREATH | 1 ( 2.9) | 0 | 23 ( 22.5) | 8 ( 7.8) | 28 ( 22.2) | 8 ( 6.3) | 29 ( 18.0) | 8 ( 5.0) |
| CARDIAC DISORDERS | 2 ( 5.7) | 1 ( 2.9) | 40 ( 39.2) | 10 ( 9.8) | 51 ( 40.5) | 11 ( 8.7) | 53 ( 32.9) | 12 ( 7.5) |
| PULMONARY ARTERIAL HYPERTENSION | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| DIARRHOEA | 4 ( 11.4) | 4 ( 11.4) | 70 ( 68.6) | 20 ( 19.6) | 84 ( 66.7) | 29 ( 23.0) | 88 ( 54.7) | 33 ( 20.5) |
| NAUSEA/VOMITING | 6 ( 17.1) | 5 ( 14.3) | 83 ( 81.4) | 26 ( 25.5) | 100 ( 79.4) | 30 ( 23.8) | 106 ( 65.8) | 35 ( 21.7) |
| FATIGUE | 0 | 0 | 48 ( 47.1) | 2 ( 2.0) | 61 ( 48.4) | 2 ( 1.6) | 61 ( 37.9) | 2 ( 1.2) |
| MYALGIAS/ARTHRALGIAS | 0 | 0 | 42 ( 41.2) | 5 ( 4.9) | 48 ( 38.1) | 6 ( 4.8) | 48 ( 29.8) | 6 ( 3.7) |
| RASH | 5 ( 14.3) | 2 ( 5.7) | 61 ( 59.8) | 7 ( 6.9) | 76 ( 60.3) | 8 ( 6.3) | 81 ( 50.3) | 10 ( 6.2) |
| HEMORRHAGE | 5 ( 14.3) | 4 ( 11.4) | 56 ( 54.9) | 16 ( 15.7) | 67 ( 53.2) | 19 ( 15.1) | 72 ( 44.7) | 23 ( 14.3) |
| GI BLEEDING | 2 ( 5.7) | 2 ( 5.7) | 21 ( 20.6) | 7 ( 6.9) | 25 ( 19.8) | 9 ( 7.1) | 27 ( 16.8) | 11 ( 6.8) |
| CNS BLEEDING | 0 | 0 | 3 ( 2.9) | 0 | 3 ( 2.4) | 0 | 3 ( 1.9) | 0 |
| OTHER HEMORRHAGE | 4 ( 11.4) | 3 ( 8.6) | 53 ( 52.0) | 10 ( 9.8) | 62 ( 49.2) | 11 ( 8.7) | 66 ( 41.0) | 14 ( 8.7) |

- *Safety in Ph+ ALL paediatric vs. adult*

**Table 39 Selected >=10% Drug-related Non-Hematologic AE**

| System Organ Class Preferred Term | Pooled Paediatric Ph+ALL (N=161) | | Adult START-L study[i] (N=46) | | Adult Ph+ ALL population CA180-035 study[ii] | | | |
|---|---|---|---|---|---|---|---|---|
| | Combination w/chemo | | Monotherapy | | Monotherapy | | | |
| | % of Subjects | | | | | | | |
| Drug-related AE | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 | QD (N=40) | | BID (N=44) | |
| | | | | | Any Grade | Grade 3-4 | Any Grade | Grade 3-4 |
| **Gastrointestinal Disorders** | | | | | | | | |
| Diarrhea | 12.4 | 6.2 | 33 | 9 | 35 | 5 | 27.3 | 4.5 |
| Nausea | 17.4 | 5 | 22 | 0 | 27.5 | 2.5 | 25 | 4.5 |
| Vomiting | 16.8 | 4.3 | 11 | 0 | 20 | 0 | 18.2 | 2.3 |
| Abdominal Pain | 11.8 | 3.1 | 2 | 0 | 0 | 0 | 2.3 | 2.3 |
| **General Disorders** | | | | | | | | |
| Pyrexia | 9.9 | 4.3 | 22 | 2 | 15 | 0 | 15.9 | 0 |
| Asthenia | 1.2 | 0 | 15 | 7 | 10 | 0 | 6.8 | 2.3 |
| Fatigue | 8.1 | 0 | | | 10 | 0 | 13.6 | |
| Peripheral edema | 3.1 | 1.2 | 13 | 0 | 17.5 | 2.5 | 31.8 | 13.6 |
| **Skin and Subcutaneous Tissue Disorders** | | | | | | | | |
| Rash | 6.8 | 0 | 15 | 2 | 2.5 | 0 | 6.8 | 0 |
| **Nervous System Disorders** | | | | | | | | |
| Headache | 9.9 | 5 | 13 | 0 | 10 | 0 | 6.8 | 2.3 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | | | |
| Pleural effusion | 4.3 | 2.5 | 24 | 7 | 17.5 | 5 | 31.8 | 13.6 |
| Dyspnoea | 2.5 | 0 | 15 | 4 | 10 | 2.5 | 20.5 | 0 |
| **Investigations** | | | | | | | | |
| Weight Decreased | 3.7 | 0 | 13 | 2 | 5 | 0 | 2.3 | 0 |
| **Blood and Lymphatic system disorders** | | | | | | | | |
| Febrile Neutropenia | 32.3 | 31.7 | 8.7 | 8.7 | 12.5 | 12.5 | 6.8 | 6.8 |

## *Serious adverse event / deaths / other significant events*

### Serious Adverse Events (SAEs)

- *Study CA180372*

**Table 40 Dasatinib-related Serious Adverse Event Summary by CTC Grade in Study CA180372 - All Treated Subjects**

| System Organ Class (%) / Preferred Term (%) | All Treated Subjects (N=106) | | | | | |
|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Total |
| TOTAL SUBJECTS WITH AN EVENT | 1 ( 0.9) | 1 ( 0.9) | 22 (20.8) | 20 (18.9) | 0 | 44 (41.5) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 1 ( 0.9) | 0 | 12 (11.3) | 14 (13.2) | 0 | 27 (25.5) |
| FEBRILE NEUTROPENIA | 1 ( 0.9) | 0 | 21 (19.8) | 1 ( 0.9) | 0 | 23 (21.7) |
| NEUTROPENIA | 0 | 0 | 0 | 12 (11.3) | 0 | 12 (11.3) |
| ANAEMIA | 0 | 0 | 5 ( 4.7) | 1 ( 0.9) | 0 | 6 ( 5.7) |
| THROMBOCYTOPENIA | 0 | 0 | 1 ( 0.9) | 4 ( 3.8) | 0 | 5 ( 4.7) |
| LEUKOPENIA | 0 | 0 | 0 | 3 ( 2.8) | 0 | 3 ( 2.8) |
| HAEMORRHAGIC ANAEMIA | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PANCYTOPENIA | 0 | 0 | 0 | 1 ( 0.9) | 0 | 1 ( 0.9) |
| GASTROINTESTINAL DISORDERS | 1 ( 0.9) | 2 ( 1.9) | 10 ( 9.4) | 0 | 0 | 13 (12.3) |
| COLITIS | 0 | 2 ( 1.9) | 3 ( 2.8) | 0 | 0 | 5 ( 4.7) |
| DIARRHOEA | 2 ( 1.9) | 0 | 3 ( 2.8) | 0 | 0 | 5 ( 4.7) |
| LOWER GASTROINTESTINAL HAEMORRHAGE | 0 | 1 ( 0.9) | 2 ( 1.9) | 0 | 0 | 3 ( 2.8) |
| VOMITING | 1 ( 0.9) | 1 ( 0.9) | 1 ( 0.9) | 0 | 0 | 3 ( 2.8) |
| ABDOMINAL PAIN | 0 | 1 ( 0.9) | 1 ( 0.9) | 0 | 0 | 2 ( 1.9) |
| ASCITES | 0 | 0 | 2 ( 1.9) | 0 | 0 | 2 ( 1.9) |
| NAUSEA | 1 ( 0.9) | 0 | 1 ( 0.9) | 0 | 0 | 2 ( 1.9) |
| ANAL HAEMORRHAGE | 1 ( 0.9) | 0 | 0 | 0 | 0 | 1 ( 0.9) |
| ENTEROCOLITIS | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| GASTRIC HAEMORRHAGE | 0 | 1 ( 0.9) | 0 | 0 | 0 | 1 ( 0.9) |
| GASTRITIS | 0 | 1 ( 0.9) | 0 | 0 | 0 | 1 ( 0.9) |
| GASTROINTESTINAL HAEMORRHAGE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PANCREATITIS ACUTE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| RECTAL HAEMORRHAGE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 3 ( 2.8) | 1 ( 0.9) | 8 ( 7.5) | 1 ( 0.9) | 0 | 13 (12.3) |
| PYREXIA | 3 ( 2.8) | 2 ( 1.9) | 4 ( 3.8) | 1 ( 0.9) | 0 | 10 ( 9.4) |
| LOCALISED OEDEMA | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| MUCOSAL INFLAMMATION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| OEDEMA | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| OEDEMA PERIPHERAL | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| INFECTIONS AND INFESTATIONS | 0 | 0 | 6 ( 5.7) | 3 ( 2.8) | 0 | 9 ( 8.5) |
| SEPSIS | 0 | 0 | 1 ( 0.9) | 3 ( 2.8) | 0 | 4 ( 3.8) |
| CLOSTRIDIUM DIFFICILE COLITIS | 0 | 0 | 2 ( 1.9) | 0 | 0 | 2 ( 1.9) |
| HERPES ZOSTER | 0 | 0 | 2 ( 1.9) | 0 | 0 | 2 ( 1.9) |
| DEVICE RELATED INFECTION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| ENTEROCOLITIS INFECTIOUS | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| LUNG INFECTION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| OTITIS MEDIA | 0 | 1 ( 0.9) | 0 | 0 | 0 | 1 ( 0.9) |
| PNEUMONIA | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PNEUMONIA VIRAL | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| SKIN INFECTION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| URINARY TRACT INFECTION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| INVESTIGATIONS | 0 | 0 | 1 ( 0.9) | 7 ( 6.6) | 0 | 8 ( 7.5) |
| NEUTROPHIL COUNT DECREASED | 0 | 0 | 0 | 4 ( 3.8) | 0 | 4 ( 3.8) |
| ALANINE AMINOTRANSFERASE INCREASED | 0 | 0 | 0 | 2 ( 1.9) | 0 | 2 ( 1.9) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 0 | 0 | 1 ( 0.9) | 1 ( 0.9) | 0 | 2 ( 1.9) |
| BLOOD BILIRUBIN INCREASED | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PLATELET COUNT DECREASED | 0 | 0 | 0 | 1 ( 0.9) | 0 | 1 ( 0.9) |
| URINE OUTPUT DECREASED | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| WHITE BLOOD CELL COUNT DECREASED | 0 | 0 | 0 | 1 ( 0.9) | 0 | 1 ( 0.9) |
| METABOLISM AND NUTRITION DISORDERS | 0 | 0 | 4 ( 3.8) | 1 ( 0.9) | 0 | 5 ( 4.7) |
| HYPOALBUMINAEMIA | 0 | 0 | 2 ( 1.9) | 0 | 0 | 2 ( 1.9) |
| HYPOKALAEMIA | 0 | 0 | 1 ( 0.9) | 1 ( 0.9) | 0 | 2 ( 1.9) |
| DECREASED APPETITE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| DEHYDRATION | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| HYPONATRAEMIA | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| NERVOUS SYSTEM DISORDERS | 1 ( 0.9) | 1 ( 0.9) | 2 ( 1.9) | 0 | 0 | 4 ( 3.8) |
| DEPRESSED LEVEL OF CONSCIOUSNESS | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| FACIAL PARESIS | 0 | 1 ( 0.9) | 0 | 0 | 0 | 1 ( 0.9) |
| HEADACHE | 1 ( 0.9) | 0 | 0 | 0 | 0 | 1 ( 0.9) |
| PERIPHERAL MOTOR NEUROPATHY | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PERIPHERAL SENSORY NEUROPATHY | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 0 | 0 | 3 ( 2.8) | 0 | 0 | 3 ( 2.8) |
| PLEURAL EFFUSION | 0 | 0 | 3 ( 2.8) | 0 | 0 | 3 ( 2.8) |
| CHYLOTHORAX | 0 | 1 ( 0.9) | 0 | 0 | 0 | 1 ( 0.9) |
| HAEMOTHORAX | 1 ( 0.9) | 0 | 0 | 0 | 0 | 1 ( 0.9) |
| PSYCHIATRIC DISORDERS | 0 | 0 | 2 ( 1.9) | 0 | 0 | 2 ( 1.9) |
| DELIRIUM | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| PERSONALITY CHANGE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| VASCULAR DISORDERS | 0 | 1 ( 0.9) | 0 | 1 ( 0.9) | 0 | 2 ( 1.9) |
| HYPOTENSION | 0 | 1 ( 0.9) | 0 | 1 ( 0.9) | 0 | 2 ( 1.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| CARDIAC DISORDERS | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| CARDIAC FAILURE | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| RENAL AND URINARY DISORDERS | 1 ( 0.9) | 0 | 0 | 0 | 0 | 1 ( 0.9) |
| ACUTE KIDNEY INJURY | 1 ( 0.9) | 0 | 0 | 0 | 0 | 1 ( 0.9) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |
| OEDEMA GENITAL | 0 | 0 | 1 ( 0.9) | 0 | 0 | 1 ( 0.9) |

- *Study CA180204*

**Table 41 Summary of SAEs by CTCAE Category regardless of relationship to Dasatinib in study CA180204 - All Treated Paediatric and Adult Subjects**

| | | Number (%) of Dasatinib-treated Subjects | | |
|---|---|---|---|---|
| CTCAE Category | SAE | Discontinuous N = 40 | Continuous N = 22 | Total N = 62 |
| **Blood and Lymphatic System Disorders** | | | | |
| | Febrile neutropenia | 0 | 1 (4.5) | 1 (1.6) |
| **Cardiac** | | | | |
| | Hypotension | 1 (2.5) | 0 | 1 (1.6) |
| | Left Ventricular Systolic Dysfunction | 0 | 1 (4.5) | 1 (1.6) |
| | QTc Prolongation | 1 (2.5) | 0 | 1 (1.6) |
| **Dermatology/Skin** | | | | |
| | Rash (Hand-foot skin reaction) | 1 (2.5) | 0 | 1 (1.6) |
| **Gastrointestinal** | | | | |
| | Colitis | 2 (5.0) | 2 (9.1) | 4 (6.5) |
| | Dehydration | 1 (2.5) | 0 | 1 (1.6) |
| | Diarrhea | 1 (2.5) | 0 | 1 (1.6) |
| | Nausea | 0 | 1 (4.5) | 1 (1.6) |
| **General Disorders and Administration Site Conditions** | | | | |
| | Infusion related reaction | 0 | 1 (4.5) | 1 (1.6) |
| **Hemorrhage, Bleeding** | | | | |
| | Abdominal Hemorrhage | 1 (2.5) | 0 | 1 (1.6) |
| **Immune System Disorder** | | | | |
| | Allergic reaction | 1 (2.5) | 1 (4.5) | 2 (3.2) |
| **Infections and Infestations** | | | | |
| | Cellulitis | 1 (2.5) | 0 | 1 (1.6) |
| | Colitis, infectious | 1 (2.5) | 0 | 1 (1.6) |
| | Febrile neutropenia | 2 (5.0) | 0 | 2 (3.2) |
| | Neutrophil decreased | 2 (5.0) | 0 | 2 (3.2) |
| | Periorbital infection | 1 (2.5) | 0 | 1 (1.6) |
| | Upper airway infection | 1 (2.5) | 0 | 1 (1.6) |
| | Sepsis | 1 (2.5) | 0 | 1 (1.6) |
| **Investigations** | | | | |
| | Blood bilirubin increased | 1 (2.5) | 0 | 1 (1.6) |
| | Creatinine increased | 0 | 1 (4.5) | 1 (1.6) |
| **Lymphatics** | | | | |
| | Edema limb | 0 | 1 (4.5) | 1 (1.6) |

| | | | | |
|---|---|---|---|---|
| **Metabolic, Laboratory** | | | | |
| | Albumin - serum low | 1 (2.5) | 1 (4.5) | 2 (3.2) |
| | Hypokalemia | 0 | 2 (9.1) | 2 (3.2) |
| | Hyponatremia | 0 | 1 (4.5) | 1 (1.6) |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| | Back Pain | 0 | 1 (4.5) | 1 (1.6) |
| **Nervous System Disorder** | | | | |
| | Ifosfamide neurotoxicity | 1 (2.5) | 0 | 1 (1.6) |
| | Mood alteration - agitation | 1 (2.5) | 0 | 1 (1.6) |
| | Neurology - Motor | 1 (2.5) | 1 (4.5) | 2 (3.2) |
| | Neurology - Sensory | 0 | 1 (4.5) | 1 (1.6) |
| | Personality/Behavioral | 1 (2.5) | 0 | 1 (1.6) |
| | Seizure | 2 (5.0) | 0 | 2 (3.2) |
| **Pain** | | | | |
| | Headache | 1 (2.5) | 0 | 1 (1.6) |
| **Pulmonary, Upper Respiratory** | | | | |
| | Dyspnea | 0 | 1 (4.5) | 1 (1.6) |
| | Hypoxia | 1 (2.5) | 0 | 1 (1.6) |
| **Renal/Genitourinary** | | | | |
| | Renal Dysfunction | 1 (2.5) | 0 | 1 (1.6) |
| **Vascular** | | | | |
| | Hypertension | 1 (2.5) | 0 | 1 (1.6) |
| | Superior vena cava syndrome | 1 (2.5) | 0 | 1 (1.6) |
| | Thrombosis/thrombus/embolism | 2 (5.0) | 0 | 2 (3.2) |

***Deaths***

- *Study CA180372*

As of the 26 July 2017 DBL, 15 (14.2%) treated subjects died, with most on-study deaths occurring post HR3 (12 subjects, 11.3%). No deaths were considered related to dasatinib.

**Table 42 Summary of Deaths - All Treated Subjects**

| | Number of Subjects Treated (%) | | | |
|---|---|---|---|---|
| | During Induction n (%) | During HR1-3 n (%) | On-study Post HR3 n (%) | Across the Study n (%) |
| **All Treated Subjects (N=106)** | | | | |
| N OF DEATHS | 0 | 3 ( 2.8) | 12 (11.3) | 15 (14.2) |
| PRIMARY REASON OF DEATH | | | | |
| DISEASE | 0 | 0 | 2 ( 1.9) | 2 ( 1.9) |
| HSCT | 0 | 0 | 2 ( 1.9) | 2 ( 1.9) |
| OTHER | 0 | 3 ( 2.8) | 8 ( 7.5) | 11 (10.4) |
| N OF DEATHS IN SUBJECTS IN CCR | 0 | 3 ( 2.8) | 6 ( 5.7) | 9 ( 8.5) |
| N DEATHS WITHIN 30 DAYS FROM LAST DASATINIB DOSE | 0 | 3 ( 2.8) | 2 ( 1.9) | 5 ( 4.7) |
| PRIMARY REASON OF DEATH | | | | |
| OTHER | 0 | 3 ( 2.8) | 2 ( 1.9) | 5 ( 4.7) |
| **Tablet Only (N=82)** | | | | |
| N OF DEATHS | 0 | 2 ( 2.4) | 9 (11.0) | 11 (13.4) |
| PRIMARY REASON OF DEATH | | | | |
| DISEASE | 0 | 0 | 1 ( 1.2) | 1 ( 1.2) |
| HSCT | 0 | 0 | 2 ( 2.4) | 2 ( 2.4) |
| OTHER | 0 | 2 ( 2.4) | 6 ( 7.3) | 8 ( 9.8) |
| N OF DEATHS IN SUBJECTS IN CCR | 0 | 2 ( 2.4) | 4 ( 4.9) | 6 ( 7.3) |
| N DEATHS WITHIN 30 DAYS FROM LAST DASATINIB DOSE | 0 | 2 ( 2.4) | 1 ( 1.2) | 3 ( 3.7) |
| PRIMARY REASON OF DEATH | | | | |
| OTHER | 0 | 2 ( 2.4) | 1 ( 1.2) | 3 ( 3.7) |
| **PFDS Used (N=24)** | | | | |
| N OF DEATHS | 0 | 1 ( 4.2) | 3 (12.5) | 4 (16.7) |
| PRIMARY REASON OF DEATH | | | | |
| DISEASE | 0 | 0 | 1 ( 4.2) | 1 ( 4.2) |
| OTHER | 0 | 1 ( 4.2) | 2 ( 8.3) | 3 (12.5) |
| N OF DEATHS IN SUBJECTS IN CCR | 0 | 1 ( 4.2) | 2 ( 8.3) | 3 (12.5) |
| N DEATHS WITHIN 30 DAYS FROM LAST DASATINIB DOSE | 0 | 1 ( 4.2) | 1 ( 4.2) | 2 ( 8.3) |
| PRIMARY REASON OF DEATH | | | | |
| OTHER | 0 | 1 ( 4.2) | 1 ( 4.2) | 2 ( 8.3) |

CCR=Continued Complete Remission
On-study post-HR3: subjects on or off treatment who had not died, withdrawn consent or were lost to follow-up by the end of HR3.

- *Study CA180204*

Among all treated paediatric subjects in Study CA180204 (N = 55), 7 (12.7%) deaths were reported, including 3 (8.6%) in Cohort 1 (N = 35) and 4 (20.0%) in Cohort 2 (N =20). No death was reported within 30 days of the last dose of treatment, and none was related to dasatinib treatment. Overall, 2 deaths were due to disease progression, and the remaining 5 were due to 'other cause': cardiac failure, acute critical upper airway obstruction, MLL-rearranged therapy-related acute myeloid leukemia, injuries resulting from being hit by a school bus, and infection due to complication of graft vs host disease following HSCT.

## *Laboratory findings*

- *Haematology*

**Table 43 Summary of Grade 3-4 Hematology Laboratory Test Results at Baseline, any Time on Treatment, Beyond Induction, and Beyond Consolidation - All Treated Subjects - Study CA180372**

| Lab Test Description<br>Toxicity Grade | Worst Toxicity Grade (n/N subjects, %)<br>At Baseline | Any Time on Treatment | Beyond Induction | Beyond Consolidation |
|---|---|---|---|---|
| **Leukocytes** | | | | |
| GRADE 3 | 34/106 (32.1) | 17/106 (16.0) | 15/104 (14.4) | 12/93 (12.9) |
| GRADE 4 | 46/106 (43.4) | 83/106 (78.3) | 79/104 (76.0) | 13/93 (14.0) |
| **Absolute Neutrophil Count** | | | | |
| GRADE 3 | 14/103 (13.6) | 9/106 ( 8.5) | 11/104 (10.6) | 11/92 (12.0) |
| GRADE 4 | 73/103 (70.9) | 94/106 (88.7) | 85/104 (81.7) | 13/92 (14.1) |
| **Platelet Count** | | | | |
| GRADE 3 | 26/106 (24.5) | 13/106 (12.3) | 11/104 (10.6) | 5/93 ( 5.4) |
| GRADE 4 | 14/106 (13.2) | 80/106 (75.5) | 74/104 (71.2) | 12/93 (12.9) |
| **Hemoglobin** | | | | |
| GRADE 3 | 19/106 (17.9) | 88/106 (83.0) | 80/104 (76.9) | 15/93 (16.1) |

| | | | | | |
|---|---|---|---|---|---|
| **Leukocytes** | | | | | |
| FROM ANY GRADE AT: | Baseline | Baseline | End of Induction | Baseline | End of Consolidation |
| Grade 3-4 | 100/106 (94.3) | 94/104 (90.4) | 94/104 (90.4) | 25/93 (26.9) | 25/93 (26.9) |
| **Absolute Neutrophil Count** | | | | | |
| FROM ANY GRADE AT: | Baseline | Baseline | End of Induction | Baseline | End of Consolidation |
| Grade 3-4 | 101/103 (98.1) | 94/101 (93.1) | 96/104 (92.3) | 23/89 (25.8) | 24/92 (26.1) |
| **Platelet Count** | | | | | |
| FROM ANY GRADE AT: | Baseline | Baseline | End of Induction | Baseline | End of Consolidation |
| Grade 3-4 | 93/106 (87.7) | 85/104 (81.7) | 85/104 (81.7) | 17/93 (18.3) | 17/93 (18.3) |
| **Hemoglobin** | | | | | |
| FROM ANY GRADE AT: | Baseline | Baseline | End of Induction | Baseline | End of Consolidation |
| Grade 3-4 | 88/106 (83.0) | 80/104 (76.9) | 80/104 (76.9) | 15/93 (16.1) | 15/93 (16.1) |

Toxicity Scale: CTC version 4.0
Note: Grade 3 is the highest possible toxicity grade for hemoglobin test results.

- *Serum chemistry*

**Table 44 Summary of Grade 3-4 Serum Chemistry Laboratory Abnormalities at any Time on Treatment – Any grade at Baseline - All Treated Subjects - Study CA180372**

| Lab Test Category<br>Lab Test | FROM ANY RESULT AT BASELINE<br>n/N subjects (%) |
|---|---|
| **Liver Function** | |
| ALT (high) | |
| GRADE 3-4 | 53/105 (50.5) |
| AST (high) | |
| GRADE 3-4 | 28/100 (28.0) |
| Total bilirubin (high) | |
| GRADE 3-4 | 9/105 (8.6) |
| **Renal Function** | |
| Serum creatinine (high) | |
| GRADE 3-4 | 2/106 (1.9) |
| **Electrolytes** | |
| Calcium (low) | |
| GRADE 3-4 | 18/104 (17.3) |
| Phosphorus (low) | |
| GRADE 3-4 | 13/104 (12.5) |
| Potassium (low) | |
| GRADE 3-4 | 43/106 (40.6) |

Toxicity Scale: CTC version 4.0

- *Liver function tests*

**Table 45 Serum Liver Function Test Summary of Worst Toxicity Grade on Treatments Relative to Baseline ( Any Grade) - All Treated Subjects**

| N of subjects (%) | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| **ALT** | | | |
| ANY GRADE AT BASELINE | | | |
| GRADE 0 | 3 ( 3.7) | 0 | 3 ( 2.9) |
| GRADE 1-2 | 40 (49.4) | 9 (37.5) | 49 (46.7) |
| GRADE 3-4 | 38 (46.9) | 15 (62.5) | 53 (50.5) |
| TOTAL | 81(100.0) | 24(100.0) | 105(100.0) |
| **AST** | | | |
| ANY GRADE AT BASELINE | | | |
| GRADE 0 | 7 ( 8.9) | 0 | 7 ( 7.0) |
| GRADE 1-2 | 51 (64.6) | 14 (66.7) | 65 (65.0) |
| GRADE 3-4 | 21 (26.6) | 7 (33.3) | 28 (28.0) |
| TOTAL | 79(100.0) | 21(100.0) | 100(100.0) |
| **Total bilirubin** | | | |
| ANY GRADE AT BASELINE | | | |
| GRADE 0 | 54 (66.7) | 21 (87.5) | 75 (71.4) |
| GRADE 1-2 | 18 (22.2) | 3 (12.5) | 21 (20.0) |
| GRADE 3-4 | 9 (11.1) | 0 | 9 ( 8.6) |
| TOTAL | 81(100.0) | 24(100.0) | 105(100.0) |

Toxicity Scale: CTC version 4.0

**Table 46 Dasatinib-related Grade 3-4 AEs of Elevated ALT, AST, GGT, or Total Bilirubin Investigations - All Treated Subjects - Study CA180372**

| Preferred Term | Number of subjects (%) (N = 106) Grade 3 | Grade 4 |
|---|---|---|
| ALANINE AMINOTRANSFERASE INCREASED | 16 (15.1) | 7 ( 6.6) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 9 ( 8.5) | 2 ( 1.9) |
| BLOOD BILIRUBIN INCREASED | 3 ( 2.8) | 1 ( 0.9) |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | 0 | 1 ( 0.9) |

MedDRA: 20.0
Subjects may have more than 1 event within a class.

- *Kidney function*

**Table 47 Serum Kidney Function Test Summary of Worst Toxicity Grade on Treatment Relative to Baseline ( Any Grade) All Treated Subjects**

| N of subjects (%) | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| **BUN/Urea** | | | |
| ANY RESULT AT BASELINE | | | |
| <= ULN | 49 (59.8) | 17 (70.8) | 66 (62.3) |
| > ULN | 33 (40.2) | 7 (29.2) | 40 (37.7) |
| TOTAL | 82(100.0) | 24(100.0) | 106(100.0) |
| <= ULN AT BASELINE | | | |
| <= ULN | 31 (77.5) | 11 (78.6) | 42 (77.8) |
| > ULN | 9 (22.5) | 3 (21.4) | 12 (22.2) |
| TOTAL | 40(100.0) | 14(100.0) | 54(100.0) |
| > ULN AT BASELINE | | | |
| <= ULN | 18 (42.9) | 6 (60.0) | 24 (46.2) |
| > ULN | 24 (57.1) | 4 (40.0) | 28 (53.8) |
| TOTAL | 42(100.0) | 10(100.0) | 52(100.0) |
| **Serum creatinine** | | | |
| ANY GRADE AT BASELINE | | | |
| GRADE 0 | 58 (70.7) | 22 (91.7) | 80 (75.5) |
| GRADE 1-2 | 22 (26.8) | 2 ( 8.3) | 24 (22.6) |
| GRADE 3-4 | 2 ( 2.4) | 0 | 2 ( 1.9) |
| TOTAL | 82(100.0) | 24(100.0) | 106(100.0) |
| GRADE 0 AT BASELINE | | | |
| GRADE 0 | 57 (70.4) | 22 (95.7) | 79 (76.0) |
| GRADE 1-2 | 22 (27.2) | 1 ( 4.3) | 23 (22.1) |
| GRADE 3-4 | 2 ( 2.5) | 0 | 2 ( 1.9) |
| TOTAL | 81(100.0) | 23(100.0) | 104(100.0) |
| GRADE 1-2 AT BASELINE | | | |
| GRADE 0 | 1(100.0) | 0 | 1 (50.0) |
| GRADE 1-2 | 0 | 1(100.0) | 1 (50.0) |
| GRADE 3-4 | 0 | 0 | 0 |
| TOTAL | 1(100.0) | 1(100.0) | 2(100.0) |

Toxicity Scale: CTC version 4.0
ULN = upper normal limit, LLN = lower normal limit

- *Vital signs*

**Table 48 Electrocardiogram Summary of Categories - All treated Subjects**

| ECG Measurement (Units) Category (%) | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| Maximal QTc[F] Intervals (msec) | | | |
| <450 | 80 (97.6) | 24 (100.0) | 104 (98.1) |
| 450 - 500 | 1 ( 1.2) | 0 | 1 ( 0.9) |
| >500 | 0 | 0 | 0 |
| NOT REPORTED | 1 ( 1.2) | 0 | 1 ( 0.9) |
| TOTAL | 82 (100.0) | 24 (100.0) | 106 (100.0) |
| QTc[F] changes from baseline (msec) | | | |
| < -60 | 0 | 0 | 0 |
| -60-<-30 | 0 | 0 | 0 |
| -30-<0 | 0 | 0 | 0 |
| 0-30 | 66 (80.5) | 19 (79.2) | 85 (80.2) |
| >30-60 | 9 (11.0) | 5 (20.8) | 14 (13.2) |
| >60 | 2 ( 2.4) | 0 | 2 ( 1.9) |
| NOT REPORTED | 5 ( 6.1) | 0 | 5 ( 4.7) |
| TOTAL | 82 (100.0) | 24 (100.0) | 106 (100.0) |

**Table 49 Summary of Echocardiogram Results on Treatment - All Treated Subjects**

| | Tablet Only N=82 | PFOS Used N=24 | Total N=106 |
|---|---|---|---|
| INTERPRETATION (%) | | | |
| NORMAL | 61 (74.4) | 18 (75.0) | 79 (74.5) |
| AT LEAST ONE ABNORMAL | 8 ( 9.8) | 1 ( 4.2) | 9 ( 8.5) |
| NOT REPORTED | 13 (15.9) | 5 (20.8) | 18 (17.0) |

## *Safety in special populations*

### Intrinsic factors

- *Age*

**Table 50 Summary of On Treatment Dasatinib-related Serious Adverse Events by Age (years) in ≥ 2 Subjects - All Treated Subjects in Study CA180372**

| System Organ Class (%)<br>Preferred Term (%) | < 7<br>N = 36 | >= 7 and < 12<br>N = 35 | >= 12 and < 18<br>N = 35 |
|---|---|---|---|
| TOTAL SUBJECTS WITH AN EVENT | 9 ( 25.0) | 17 ( 48.6) | 18 ( 51.4) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 5 ( 13.9) | 12 ( 34.3) | 10 ( 28.6) |
| FEBRILE NEUTROPENIA | 4 ( 11.1) | 11 ( 31.4) | 8 ( 22.9) |
| NEUTROPENIA | 1 ( 2.8) | 7 ( 20.0) | 4 ( 11.4) |
| ANAEMIA | 1 ( 2.8) | 3 ( 8.6) | 2 ( 5.7) |
| THROMBOCYTOPENIA | 1 ( 2.8) | 4 ( 11.4) | 0 |
| LEUKOPENIA | 1 ( 2.8) | 2 ( 5.7) | 0 |
| GASTROINTESTINAL DISORDERS | 2 ( 5.6) | 5 ( 14.3) | 6 ( 17.1) |
| COLITIS | 1 ( 2.8) | 3 ( 8.6) | 1 ( 2.9) |
| DIARRHOEA | 0 | 3 ( 8.6) | 2 ( 5.7) |
| LOWER GASTROINTESTINAL HAEMORRHAGE | 0 | 2 ( 5.7) | 1 ( 2.9) |
| VOMITING | 0 | 2 ( 5.7) | 1 ( 2.9) |
| ABDOMINAL PAIN | 0 | 1 ( 2.9) | 1 ( 2.9) |
| ASCITES | 0 | 1 ( 2.9) | 1 ( 2.9) |
| NAUSEA | 0 | 1 ( 2.9) | 1 ( 2.9) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 2 ( 5.6) | 7 ( 20.0) | 4 ( 11.4) |
| PYREXIA | 2 ( 5.6) | 5 ( 14.3) | 3 ( 8.6) |
| INFECTIONS AND INFESTATIONS | 3 ( 8.3) | 5 ( 14.3) | 1 ( 2.9) |
| SEPSIS | 0 | 3 ( 8.6) | 1 ( 2.9) |
| CLOSTRIDIUM DIFFICILE COLITIS | 0 | 1 ( 2.9) | 1 ( 2.9) |
| HERPES ZOSTER | 0 | 2 ( 5.7) | 0 |
| INVESTIGATIONS | 2 ( 5.6) | 2 ( 5.7) | 4 ( 11.4) |
| NEUTROPHIL COUNT DECREASED | 1 ( 2.8) | 0 | 3 ( 8.6) |
| ALANINE AMINOTRANSFERASE INCREASED | 1 ( 2.8) | 0 | 1 ( 2.9) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 1 ( 2.8) | 0 | 1 ( 2.9) |
| METABOLISM AND NUTRITION DISORDERS | 0 | 3 ( 8.6) | 2 ( 5.7) |
| HYPOALBUMINAEMIA | 0 | 1 ( 2.9) | 1 ( 2.9) |
| HYPOKALAEMIA | 0 | 1 ( 2.9) | 1 ( 2.9) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 0 | 0 | 3 ( 8.6) |
| PLEURAL EFFUSION | 0 | 0 | 3 ( 8.6) |
| VASCULAR DISORDERS | 1 ( 2.8) | 1 ( 2.9) | 0 |
| HYPOTENSION | 1 ( 2.8) | 1 ( 2.9) | 0 |

MedDRA: 20.0
Subjects may have more than 1 event within a class.

- *Gender*

**Table 51 Summary of On Treatment Dasatinib-related Serious Adverse Events by Gender in ≥ 2 Subjects - All Treated Subjects in Study CA180372**

| System Organ Class (%)<br>Preferred Term (%) | Female<br>N = 49 | Male<br>N = 57 |
|---|---|---|
| TOTAL SUBJECTS WITH AN EVENT | 22 ( 44.9) | 22 ( 38.6) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 13 ( 26.5) | 14 ( 24.6) |
| FEBRILE NEUTROPENIA | 10 ( 20.4) | 13 ( 22.8) |
| NEUTROPENIA | 4 ( 8.2) | 8 ( 14.0) |
| ANAEMIA | 1 ( 2.0) | 5 ( 8.8) |
| THROMBOCYTOPENIA | 1 ( 2.0) | 4 ( 7.0) |
| LEUKOPENIA | 1 ( 2.0) | 2 ( 3.5) |
| GASTROINTESTINAL DISORDERS | 6 ( 12.2) | 7 ( 12.3) |
| COLITIS | 3 ( 6.1) | 2 ( 3.5) |
| DIARRHOEA | 1 ( 2.0) | 4 ( 7.0) |
| LOWER GASTROINTESTINAL HAEMORRHAGE | 1 ( 2.0) | 2 ( 3.5) |
| VOMITING | 1 ( 2.0) | 2 ( 3.5) |
| ABDOMINAL PAIN | 0 | 2 ( 3.5) |
| ASCITES | 0 | 2 ( 3.5) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 5 ( 10.2) | 8 ( 14.0) |
| PYREXIA | 3 ( 6.1) | 7 ( 12.3) |
| INFECTIONS AND INFESTATIONS | 5 ( 10.2) | 4 ( 7.0) |
| SEPSIS | 2 ( 4.1) | 2 ( 3.5) |
| INVESTIGATIONS | 2 ( 4.1) | 6 ( 10.5) |
| NEUTROPHIL COUNT DECREASED | 1 ( 2.0) | 3 ( 5.3) |
| ALANINE AMINOTRANSFERASE INCREASED | 0 | 2 ( 3.5) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 0 | 2 ( 3.5) |
| METABOLISM AND NUTRITION DISORDERS | 2 ( 4.1) | 3 ( 5.3) |
| HYPOALBUMINAEMIA | 0 | 2 ( 3.5) |
| HYPOKALAEMIA | 2 ( 4.1) | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 1 ( 2.0) | 2 ( 3.5) |
| PLEURAL EFFUSION | 1 ( 2.0) | 2 ( 3.5) |

MedDRA: 20.0
Subjects may have more than 1 event within a class.

- *Race*

**Table 52 Summary of On Treatment Dasatinib-related Serious Adverse Events by Race in ≥ 2 Subjects - All Treated Subjects in Study CA180372**

| System Organ Class (%)<br>Preferred Term (%) | White<br>N = 85 | Black or African American<br>N = 13 | Asian<br>N = 5 | Other<br>N = 3 |
|---|---|---|---|---|
| TOTAL SUBJECTS WITH AN EVENT | 36 ( 42.4) | 3 ( 23.1) | 3 ( 60.0) | 2 ( 66.7) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 22 ( 25.9) | 3 ( 23.1) | 1 ( 20.0) | 1 ( 33.3) |
| FEBRILE NEUTROPENIA | 18 ( 21.2) | 3 ( 23.1) | 1 ( 20.0) | 1 ( 33.3) |
| NEUTROPENIA | 10 ( 11.8) | 1 ( 7.7) | 1 ( 20.0) | 0 |
| ANAEMIA | 4 ( 4.7) | 1 ( 7.7) | 1 ( 20.0) | 0 |
| THROMBOCYTOPENIA | 4 ( 4.7) | 1 ( 7.7) | 0 | 0 |
| LEUKOPENIA | 2 ( 2.4) | 1 ( 7.7) | 0 | 0 |
| GASTROINTESTINAL DISORDERS | 12 ( 14.1) | 0 | 1 ( 20.0) | 0 |
| COLITIS | 5 ( 5.9) | 0 | 0 | 0 |
| DIARRHOEA | 4 ( 4.7) | 0 | 1 ( 20.0) | 0 |
| LOWER GASTROINTESTINAL HAEMORRHAGE | 3 ( 3.5) | 0 | 0 | 0 |
| VOMITING | 3 ( 3.5) | 0 | 0 | 0 |
| ABDOMINAL PAIN | 2 ( 2.4) | 0 | 0 | 0 |
| NAUSEA | 2 ( 2.4) | 0 | 0 | 0 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 11 ( 12.9) | 0 | 2 ( 40.0) | 0 |
| PYREXIA | 9 ( 10.6) | 0 | 1 ( 20.0) | 0 |
| INFECTIONS AND INFESTATIONS | 7 ( 8.2) | 2 ( 15.4) | 0 | 0 |
| SEPSIS | 4 ( 4.7) | 0 | 0 | 0 |
| CLOSTRIDIUM DIFFICILE COLITIS | 2 ( 2.4) | 0 | 0 | 0 |
| INVESTIGATIONS | 7 ( 8.2) | 0 | 1 ( 20.0) | 0 |
| NEUTROPHIL COUNT DECREASED | 3 ( 3.5) | 0 | 1 ( 20.0) | 0 |
| ALANINE AMINOTRANSFERASE INCREASED | 2 ( 2.4) | 0 | 0 | 0 |
| ASPARTATE AMINOTRANSFERASE INCREASED | 2 ( 2.4) | 0 | 0 | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 2 ( 2.4) | 0 | 1 ( 20.0) | 0 |
| PLEURAL EFFUSION | 2 ( 2.4) | 0 | 1 ( 20.0) | 0 |
| VASCULAR DISORDERS | 2 ( 2.4) | 0 | 0 | 0 |
| HYPOTENSION | 2 ( 2.4) | 0 | 0 | 0 |

MedDRA: 20.0
Subjects may have more than 1 event within a class.

**Extrinsic factors**

- *Geographic region*

Though most subjects on treatment were in North America, and fewer subjects were in Europe or Rest of World. AEs and SAEs, AEs leading to discontinuation of study treatment were observed at comparable frequencies across geographic region subgroups of the pooled or CA180372 Ph+ ALL study population.
In Study CA180372, most subjects on treatment were in North America (N = 78), and fewer subjects were in Europe (N = 25) or Rest of World (N = 3). In the pooled population from Studies CA180372 and CA180204, most subjects on treatment were in North America (N = 130), and fewer subjects were in Europe (N = 25) or Rest of World (N = 6).

- *ECOG*

**Table 53 Summary of On Treatment Dasatinib-related Serious Adverse Events by Performance Status in ≥ 2 Subjects - All Treated Subjects in Study CA180372**

| System Organ Class (%)<br>Preferred Term (%) | ECOG = 0<br>N = 39 | ECOG = 1<br>N = 50 | ECOG = 2<br>N = 14 |
|---|---|---|---|
| TOTAL SUBJECTS WITH AN EVENT | 11 ( 28.2) | 24 ( 48.0) | 7 ( 50.0) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 9 ( 23.1) | 13 ( 26.0) | 3 ( 21.4) |
| FEBRILE NEUTROPENIA | 8 ( 20.5) | 11 ( 22.0) | 2 ( 14.3) |
| NEUTROPENIA | 3 ( 7.7) | 7 ( 14.0) | 2 ( 14.3) |
| ANAEMIA | 4 ( 10.3) | 1 ( 2.0) | 1 ( 7.1) |
| THROMBOCYTOPENIA | 2 ( 5.1) | 2 ( 4.0) | 1 ( 7.1) |
| LEUKOPENIA | 2 ( 5.1) | 1 ( 2.0) | 0 |
| GASTROINTESTINAL DISORDERS | 3 ( 7.7) | 7 ( 14.0) | 3 ( 21.4) |
| COLITIS | 1 ( 2.6) | 2 ( 4.0) | 2 ( 14.3) |
| DIARRHOEA | 2 ( 5.1) | 1 ( 2.0) | 2 ( 14.3) |
| LOWER GASTROINTESTINAL HAEMORRHAGE | 0 | 1 ( 2.0) | 2 ( 14.3) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 5 ( 12.8) | 4 ( 8.0) | 4 ( 28.6) |
| PYREXIA | 5 ( 12.8) | 3 ( 6.0) | 2 ( 14.3) |
| INFECTIONS AND INFESTATIONS | 3 ( 7.7) | 2 ( 4.0) | 3 ( 21.4) |
| SEPSIS | 0 | 1 ( 2.0) | 3 ( 21.4) |
| CLOSTRIDIUM DIFFICILE COLITIS | 0 | 0 | 2 ( 14.3) |
| INVESTIGATIONS | 3 ( 7.7) | 3 ( 6.0) | 2 ( 14.3) |
| NEUTROPHIL COUNT DECREASED | 2 ( 5.1) | 1 ( 2.0) | 1 ( 7.1) |
| METABOLISM AND NUTRITION DISORDERS | 2 ( 5.1) | 3 ( 6.0) | 0 |
| HYPOKALAEMIA | 0 | 2 ( 4.0) | 0 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 2 ( 5.1) | 1 ( 2.0) | 0 |
| PLEURAL EFFUSION | 2 ( 5.1) | 1 ( 2.0) | 0 |

MedDRA: 20.0
Karnofsky/Lansky scores collected in study CA180372 were mapped to ECOG scores per Appendix 8 in the CA180372 protocol.
Subjects may have more than 1 event within a class.

## *Safety related to drug-drug interactions and other interactions*

No new information in paediatric subjects is available.

## *Discontinuation due to adverse events*

### Study CA180372

*All-causality AEs leading to discontinuation*

In Study CA180372, AEs that led to treatment discontinuation were reported in 7 (6.6%) out of 106 subjects. All subjects who discontinued treatment took dasatinib tablet only, and no subject who took dasatinib PFOS at least once discontinued treatment due to an AE.

Grade 3-5 AEs leading to treatment discontinuation were reported in 4 (3.8%) out of 106 subjects and included Grade 4 enteritis, Grade 5 fungal sepsis, Grade 3 lung infection, and Grade 3 thrombocytopenia.

*Dasatinib-related AEs leading to discontinuation*

Dasatinib-related AEs that led to treatment discontinuation occurred in 2 (1.9%) subjects: 1 subject with a Grade 1 AE of drug hypersensitivity, and 1 subject with a Grade 3 AE of thrombocytopenia. These 2 subjects took dasatinib tablet only, and no subjects who took dasatinib PFOS at least once discontinued due to a dasatinib-related AE.

**Study CA180204**

In CA180204, 'action taken' regarding study drug was not collected as part of AE reporting, and therefore no summaries of AEs leading to discontinuation of study treatment were generated. Based on investigator reports after database lock, 2 subjects were identified with on-treatment toxicities or complications leading to discontinuation of treatment: 1 subject with persistent QTc prolonged, and 1 subject with methotrexate-related leukoencephalopathy.

### *Post marketing experience*

Dasatinib was first approved for the treatment of adults with CML or Ph+ ALL who are resistant or intolerant to imatinib on 28 June 2006 by the US FDA. Dasatinib was subsequently approved in other countries and is marketed worldwide for these indications in over 60 international countries including the EU, Japan, and Canada:

- Dasatinib is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including imatinib.
- Dasatinib is indicated for the treatment of adults with Ph+ ALL with resistance or intolerance to prior therapy.
- Dasatinib is indicated for the treatment of adult subjects with newly diagnosed Ph+ CML in chronic phase.

As reported in Periodic Benefit-Risk Evaluation Report No. 5 (28-Jun-2016 through 27-Jun-2017), the cumulative number of patients exposed to dasatinib from 28-Jun-2006 through 31-Mar-2017 is estimated to be 63,960, and the cumulative exposure is estimated to be 127,690 patient-years.13 Cumulatively, of the approximately 6,773 subjects assigned to treatment (ie, assigned to treatment with the investigational medicinal product, active comparator, and/or placebo control) in BMS-sponsored clinical trials, approximately 5,389 subjects have been exposed to dasatinib. Approximately 1,214 total subjects have been exposed to dasatinib under Expanded Access Programs (EAPs; CA180325). Cumulatively, 3,300 subjects have been exposed to dasatinib while participating in an ISR/ISTs supported by BMS. Therefore, in total, approximately 9,903 subjects have been exposed to dasatinib from 04-Nov-2003 through 27-Jun-2017.

## 2.6.1. Discussion on clinical safety

The safety of dasatinib has been characterised in CML patients and appears similar in Ph+ALL in adults and overall in paediatric ALL. The safety results reported in the main and supportive study did not reveal any new concern in combination with poly-chemotherapy backbone.

Dasatinib's characteristic effect of effusions in pleura or pericardium, observed as a dose-dependent adverse event in adult CML, was not observed in the discontinued treatment or PFOS (used) group, and in all grades in 5.9% in the tablet (only) group. Considering the complexity of the disease and treatment this result is acceptable. Pleural effusions were not observed in childhood CML treatment. The incidence of pleural (or pericardial) effusions is not expected to be underestimated as the clinical monitoring of patients was very thorough.

There were two studies in a total of 161 paediatric patients with Ph+ ALL in which Sprycel was administered in combination with chemotherapy. In Study 1, of 55 paediatric patients, 35 received Sprycel in combination with chemotherapy on a discontinuous dosing regimen (two weeks on treatment followed by one to two weeks off) and 20 received Sprycel in combination with chemotherapy on a continuous dosing regimen. In Study 2, 106 paediatric patients received Sprycel in combination with chemotherapy on a continuous dosing regimen. Among the 126 Ph+ ALL paediatric patients treated with Sprycel on a continuous dosing regimen, the median duration of therapy was 23.6 months (range 1.4 to 33 months) (SmPC, section 4.8).

Adverse reactions reported in the two paediatric studies in which Sprycel was administered in combination with chemotherapy were consistent with the known safety profile of Sprycel in adults, and expected effects of chemotherapy. Of the 126 Ph+ ALL paediatric patients on a continuous dosing regimen, 2 (1.6%) experienced adverse reactions leading to treatment discontinuation(SmPC, section 4.8).

The adverse events were less frequently reported in the group of patients treated by "discontinuous" dasatinib, compared to the continuous (tablet only) group. This is in line with a dose relation, which therefore add uncertainty to interpretation of results obtained in the group of PFOS (used, n=24) and PFOS (exclusively, n = 8) group, because the bioavailability is estimated to be 19% less by the 60 mg/m2 dose with PFOS. A new analysis showed a similar exposure distribution between disease types in both adult and paediatric patients. In addition, the results showed that the intestinal permeability did not change between chronic and acute leukaemia (see discussion on clinical pharmacology).

Dasatinib treatment of paediatric ALL-patients appears to have limited clinically significant impact on growth and development, but it is difficult to draw definitive conclusions due to the concomitant treatment of dose-intense combination chemotherapy and without a longer follow-up period.

The adherence to treatment was not optimal, with 25-30% of patients receiving less than 18 dasatinib doses / month. The risk for interaction with concomitant medication and simultaneous AEs e.g. mucositis may be partly responsible..

Cardiac events had an impact on clinically relevant protocol deviations reported in 40 subjects: 40 deviations due to use of concomitant medications with potential to prolong QTc, and two deviations due to subjects with blast-phase CML who were misclassified with Ph+ ALL. Inclusion of these two subjects in analysis did not impact interpretability of study results. Most of the deviations (30 subjects) were subjects who received short-term prophylactic antibiotics with a macrolide, pentamidine or other prohibited medications, which included droperidol, methadone, haloperidol, domepridone and chlorpromazine. The use of the prohibited concomitant therapy did not impact the efficacy of the treatment with dasatinib plus chemotherapy; none of these subjects had a QTc >450msec.

The adverse events affect mainly bone-marrow function, skin and mucosa - in particular in the gastrointestinal tract, manifested as vomiting and diarrhoea. Sepsis and infections may be a consequence of neutropenia and barrier defect, because contagious infections rarely are observed in leukaemia patients. In addition, all may be serious in grade, and in a few cases lead to treatment discontinuation. The number of all-causality related AEs leading to discontinuation was 8.5% (grade 3-

5 was 4.9%) in the tablet (only) group, and 2.4 % (1.2 % grade 3-5) were interpreted as dasatinib-related. No discontinuation were registered due to AE, all causality or dasatinib-related in the PFOS (once) group in the main study.

As of last data-base lock, 15 (14.2%) treated subjects died. Twelve of 15 while on-study deaths occurring post HR3. No deaths were considered related to dasatinib. Nine (8.5%) subjects who were in CCR died and 5 (4.7%) subjects died less than 30 days after discontinuation from dasatinib treatment. Of the 11 deaths reported in the category of "Other," 9 deaths were attributed primarily to infections. However, for a more meaningful comparison, the paediatric Ph+ ALL population was compared with the adult Ph+ ALL population and with the paediatric population studied for the CP-CML indication.

It is acknowledged that even focusing the analyses in the Ph+ ALL population, the setting is different between children and adults. In the paediatric population dasatinib was used in association with chemotherapy and in the adult population it was used as monotherapy in patients with resistance or intolerance to prior therapies. In the heavily pretreated adult population, the overall safety profile was influenced by the advanced stage of the disease and the use of prior therapies. In the paediatric population it was influenced by the concomitant use of chemotherapy. Dasatinib's safety profile is notably consistent across these groups, being in general more favourable in the paediatric population, namely with less pleural effusion and peripheral edema. There is some more abdominal pain (maybe related to age groups) and much more febrile neutropenia (in probable relation with the ALL backbone chemotherapy treatment). Nevertheless, in general, the safety profile of dasatinib in the paediatric Ph+ ALL study population was comparable to that in the adult trials.

The adverse events observed in treatment of acute leukaemia may be related. It is also noted in tables of AEOSI and SAE that patients may have more than one event within a class. A trend has been observed towards more frequent SAEs in the age-group 12-18 years compared to the youngest patients, below the age of 7 years.

In paediatric patients with Ph+ ALL treated with dasatinib in combination with chemotherapy, CBCs should be performed prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, CBCs should be performed every 2 days until recovery (SmPC, section 4.4).

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 (SmPC, section 4.4).

In the paediatric ALL studies, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults, within the context of an acute leukaemia patient receiving a background chemotherapy regimen (SmPC, section 4.8).

The introduction of the oral suspension, PFOS, in ALL will be a great treatment advantage in order to dispense the medication to a young child. Results on safety were pooled with tablet treated patients, and do not indicate specific safety issues or adverse events.

## 2.6.2. Conclusions on clinical safety

The safety profile of Sprycel administered in combination with chemotherapy in paediatric patients with Ph+ ALL was consistent with the known safety profile of Sprycel in adults and the expected effects of chemotherapy, with the exception of a lower pleural effusion rate in paediatric patients as compared to adults.

### 2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.7. Risk management plan*

The CHMP endorsed RMP version 16.1 with the following content:

### *Safety concerns*

**Table 54 Summary of the safety concerns**

| | |
|---|---|
| *Important identified risks* | Myelosuppression<br>Fluid Retention<br>Bleeding Related Events<br>QT Prolongation<br>PAH<br>Pregnancy Related Malformative or Foeto/ Neonatal Toxicity |
| *Important potential risks* | Severe Hepatotoxicities<br>Direct Cardiotoxic Effects (eg, Cardiomyopathy)<br>Growth and development disorders and bone mineral metabolism disorders in the paediatric population<br>Toxic Skin Reactions<br>CYP3A4 Drug Interactions<br>HBV Reactivation<br>Nephrotic Syndrome |
| *Missing information* | Carcinogenicity<br>Paediatric data<br>• Children < 1 year of age<br>Reproductive and lactation data |

### *Pharmacovigilance plan*

No additional pharmacovigilance activities are planned.

### *Risk minimisation measures*

**Table 55 Summary table of risk minimisation measures by safety concern**

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| | **Additional risk minimisation measures:**<br>DHPC issued in EU Apr-2016 | **Additional pharmacovigilance activities:**<br>None |
| Nephrotic Syndrome | **Routine risk minimisation measures:**<br>SmPC Section 4.8 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |
| | **Additional risk minimisation measures:**<br>None | **Additional pharmacovigilance activities:**<br>None |
| Carcinogenicity | **Routine risk minimisation measures:**<br>SmPC Section 5.3 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |
| | **Additional risk minimisation measures:**<br>None | **Additional pharmacovigilance activities:**<br>None |
| Paediatric data: Children < 1 year of age | **Routine risk minimisation measures:**<br>SmPC Section 4.2. | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |
| | **Additional risk minimisation measures:**<br>None | **Additional pharmacovigilance activities:**<br>None |
| Reproductive and lactation data | **Routine risk minimisation measures:**<br>SmPC Sections 4.6 and 5.3 | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br>None |
| | **Additional risk minimisation measures:**<br>None | **Additional pharmacovigilance activities:**<br>None |

### *Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The applicant also removed the text allowing constitution of the powder for oral suspension by patients or caregivers at the end of the Package Leaflet to ensure that constitution is limited to pharmacists or qualified healthcare professionals.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Island.

## 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

The applied indication is as follows:

Sprycel is indicated for the treatment of paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy.

### 3.1.2. Available therapies and unmet medical need

In the EU, imatinib is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.

The survival rate among subjects with Ph+ ALL still lags behind most other cytogenetic subgroups in paediatric ALL. Until recently, HSCT in first complete remission offered the best opportunity for long-term EFS for children with Ph+ ALL, with an improvement in disease free survival of up to 65% and OS 72%. This strategy is limited by the availability of a suitably matched donor, by the risk of post-transplant–related morbidity and mortality and by relapses after HSCT, particularly in those who are MRD positive prior to transplantation. Paediatric patients with no suitable donor for HSCT have an even more critical unmet need for disease management.

### 3.1.3. Main clinical studies

The clinical package of Sprycel for the paediatric ALL indication was primarily supported by data from a Phase II, open-label, multi-centre, single-arm, historically-controlled study of dasatinib added to standard chemotherapy in paediatric patients with newly diagnosed philadelphia chromosome positive acute lymphoblastic leukemia (Study CA180372).

## *3.2. Favourable effects*

In study CA180372 the 3-year binomial EFS rate with dasatinib plus chemotherapy was 66.0% (90% CI: 57.7, 73.7). As an indirect comparison, to the EFS rate was 49.2% (90% CI: 38.0, 60.4) with chemotherapy alone in AIEOP-BFM 2000 and to 59.1% (90% CI: 51.8, 66.2) with continuous imatinib plus chemotherapy in the amended EsPhALL trial in all treated subjects.

Regarding the secondary endpoints, the OS rate was 91.5% (95% CI: 84.2 - 95.5) at 3 years and the CR was 93.4% (99/106) after consolidation chemotherapy. In addition, the MRD negativity rate assessed by Ig/TCR rearrangement was 71.7% by the end of consolidation in all treated patients. When this rate was based on the 85 patients with evaluable Ig/TCR assessments, the estimate was 89.4%. The MRD-negativity rates at the end of induction and consolidation as measured by flow cytometry were 66.0% and 84.0%, respectively.

In the supportive study CA180204, the 3-year EFS rate was 80.8% (95% CI: 70.2, 91.4) in the 52 paediatric patients considered evaluable for efficacy and 68.4% (95% CI: 48.3, 88.6) in the 19 subjects on continuous dasatinib.

## 3.3. Uncertainties and limitations about favourable effects

For CP-CML a PFOS dose of 90 mg/m$^2$ has been proposed and endorsed by CHMP, but bioequivalence will be investigated in a PK window study in CP-CML conducted post-approval. As the PK, including bioavailability, of dasatinib appear to be comparable across disease status, the PFOS dose used in CP-CML has also been endorsed for the Ph+ ALL indication. The MAH was committed to provide the results of this PK-window study post-approval. In relation to this it needs to stressed that although (based on the mechanistic understanding, the analysis of efficacy versus GI toxicity, formulation and patient populations, and the analysis of PK in the different patient populations) the PBPK model is considered to provide reassuring data on the extrapolation of PK across the patient populations, the PBPK model is not fully validated. The CHMP recommended the MAH to confirm (post-approval) that the post-approval analysis will be conducted to demonstrate that the PBPK model adequately captures the effects of chemotherapy on absorption in line with the existing guideline on Reporting and Qualification of PBPK models..

## 3.4. Unfavourable effects

Dasatinib-related AEs were reported in 86.3% and 72.2% had grade 3-4 AEs in the studied population. No new concerns were observed. Similar manifestations are observed treating ALL paediatric patients with PFOS.

The pattern of AEs are similar to treatment by dasatinib in paediatric and adult CML and adult ALL, dominated by all grade myelosuppression, mucositis / gastrointestinal manifestations and infections – but not any particular microbiological agent.

The pattern of SAEs in general follows the same manifestations. The AEs and SAEs are recognized in this patient population and manageable, and the pattern also reflects the lack of co-morbidity in the paediatric patient population.

No deaths have been related to dasatinib treatment.

## 3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties and limitations about unfavourable effects.

## 3.6. Effects Table

**Table 56 Effects Table for dasatinib in paediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy (Study CA180372- data cut-off: 26 July 2017)**

| Effect | Short description | Unit | Treatment | Historical control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| 3-Year binom | number of pts without event | % | 66 | - AIEOP-BFM 2000: 49.2 | - Study CA180372 | See ‘‘clinical efficacy’’ |

| Effect | Short description | Unit | Treatment | Historical control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| ial EFS rate | after 3 years since the start of dasatinib divided by the number of treated subjects | | | - EsPhALL : 59.1 | 90% CI: 57.7, 73.7<br>- AIEOP-BFM 2000: 90% CI: 38.0, 60.4<br>- EsPhALL : 90% CI: 51.8, 66.2 | section |
| **Unfavourable Effects** | | | | | | |
| ADRs | Grade 3-4 | % | 72.2 | - | | See ''clinical safety'' section |
| Febrile neutropaenia | Grade 3-4 | % | 26.2 | - | | |
| Nausea | Grade 3-4 | % | 5.6 | - | | |
| Vomiting | Grade 3-4 | % | 4.8 | - | | |
| Abdominal pain | Grade 3-4 | % | 3.2 | - | | |
| Diarrhoea | Grade 3-4 | % | 4.8 | - | | |
| Pyrexia | Grade 3-4 | % | 5.6 | - | | |
| Headache | Grade 3-4 | % | 4.8 | - | | |
| Decreased appetite | Grade 3-4 | % | 4.8 | - | | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

In study CA180372 the 3-year binomial EFS rate with dasatinib plus chemotherapy was 66.0% (90% CI: 57.7, 73.7). As an indirect comparison, to the EFS rate was 49.2% (90% CI: 38.0, 60.4) with chemotherapy alone in AIEOP-BFM 2000 and to 59.1% (90% CI: 51.8, 66.2) with continuous imatinib plus chemotherapy in the amended EsPhALL trial in all treated subjects.

Further, the safety profile of dasatinib is acceptable, manifestations manageable and without new concerns. Pleural effusions were unusual, no pericardial effusions were reported, and likewise very serious potential complications like cerebral haemorrhage, pulmonary oedema or pulmonary hypertension was not observed.

### 3.7.2. Balance of benefits and risks

Clinically meaningful results have been observed with the use of dasatinib combination with chemotherapy in the treatment of paediatric patients with newly diagnosed Ph+ ALL which outweighs the ADRs that are considered manageable, despite the combination with intensive chemotherapy.

### 3.7.3. Additional considerations on the benefit-risk balance

N/A.

### *3.8. Conclusions*

The overall B/R of Sprycel is positive.

# 4. Recommendations

### *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of Indication to include a paediatric indication for Philadelphia chromosome positive acute lymphoblastic leukaemia for Sprycel; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated.
The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the product information.
The RMP version 16.1 has also been submitted.

### *Conditions and requirements of the marketing authorisation*

### Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) ) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

### Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0042/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

### *Similarity with authorised orphan medicinal products*

The CHMP by consensus is of the opinion that Sprycel is not similar to Xaluprine, Blincyto, Iglusig and Besponsa within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

## 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Extension of Indication to include a paediatric indication for Philadelphia chromosome positive acute lymphoblastic leukaemia for Sprycel; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated.
The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the product information.
The RMP version 16.1 has also been submitted.

### *Summary*

Please refer to Scientific Discussion ‘‘Sprycel-H-C-709-II-59’’

## Attachments

1. SmPC, Package Leaflet (changes highlighted) of Sprycel as adopted by the CHMP on 13 December 2018.

## Appendix

1. CHMP AR on similarity dated 13 December 2018.

## REFERENCES


1. Steliarova E et al. Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991-2010 (Automated Childhood Cancer Information System): a population-based study. Lancet Oncol. 2018 Sep; 19(9):1159-1169.

2. Biondi A et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. Lancet Oncol. 2012 Sep;13(9):936-45.

3. Heerema NA. Secondary cytogenetic aberrations in childhood Philadelphia chromosome positive acute lymphoblastic leukemia are nonrandom and may be associated with outcome. Leukemia. 2004 Apr;18(4):693-702.

4. Giles FJ et al. Class effects of tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia. Leukemia. 2009 Oct;23(10):1698-707.

5. Chiaretti S and Foa R. Management of adult Ph-positive acute lymphoblastic leukemia. ASH Educ Book 2015. 2015 Dec; 406-413.

6. Schultz KR et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. 2014 Jul;28(7):1467-71.

7. Bernbeck B. Symptoms of childhood acute lymphoblastic leukemia: red flags to recognize leukemia in daily practice. Klin Padiatr. 2009 Nov-Dec;221(6):369-73.

8. Bacher et al. Additional clonal abnormalities in Philadelphia-positive ALL and CML demonstrate a different cytogenetic pattern at diagnosis and follow different pathways at progression. Cancer Genetics and Cytogenetics. Volume 157, Issue 1, February 2005, Pages 53-61

9. Chang B et al. Imatinib resistant *BCR-ABL1* mutations at relapse in children with Ph+ALL: a Children's Oncology Group (COG) study. Br J Haematol. 2012 May; 157(4): 507–510.

10. Cortes JE et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016 Jul 10;34(20):2333-40.

11. Rousselot P et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood. 2016 Aug 11;128(6):774-82.

12. Ravandi F et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood. 2010 Sep 23;116(12):2070-7.


[i] Final Clinical Study Report for CA180015: A Phase 2 Study of BMS-354825 in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate. Bristol-Myers Squibb; 2007. Document Control Number 930025471.

[ii] Clinical Study Report for Study CA180035: A Randomized, Two-arm, Multicenter, Open-label Phase III Study of BMS-354825 Administered Orally at a Dose of 70 mg Twice Daily or 140 mg Once Daily in Subjects with Chronic Myeloid Leukemia in Accelerated Phase or in Myeloid or Lymphoid Blast Phase or with Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia who are Resistant or Intolerant to Imatinib Mesylate. Bristol-Myers Squibb; 2008. Document Control Number 930029431.