SCIENTIFIC DISCUSSION

1. Introduction

Chronic myeloid leukaemia represents 7-20% of all leukaemia cases, with a worldwide incidence projected at less than one to two per 100.000 people. Approximately 85% of patients are diagnosed with chronic-phase chronic myeloid leukaemia. The overall 5-year survival rate (1992-1998) was approximately 35%. Acute lymphoblastic leukaemia is predominantly a disease of childhood and the incidence in adults is less than one per 100.000 people. Of these approximately 20-25% produces the Philadelphia chromosome, long-term survival at 10 years in adults is in the range of 25-35%.

Chronic myeloid leukaemia is a haematopoietic stem cell disorder associated with a reciprocal translocation between chromosomes 9 and 22 to produce the Philadelphia chromosome. This chromosomal translocation results in a chimeric protein product BCR-ABL, which is a constitutively active form of the ABL tyrosine kinase. CML is a progressive disease, which evolves through chronic, accelerated, and blast crisis phases. Blast phase is the most advanced stage of CML and is highly refractory to therapy. The blast phase phenotype is myeloblastic in two-thirds of patients and lymphoblastic in the remaining one-third.

Both imatinib, an oral inhibitor of the ABL kinase, and interferon, an injectable immune modulator, produce durable responses in patients with CML. Based on high rates of both haematologic and cytogenetic responses, imatinib is currently approved for use in newly diagnosed CML patients as well as in CML blast phase patients previously treated with interferon. Imatinib is most effective in patients with chronic phase CML, in whom the complete haematologic response (CHR) rate is 95% and the complete cytogenetic response (CCyR) rate is 39%. In patients with accelerated, myeloid, or lymphoid blast phase CML, or Ph+ ALL, imatinib is less effective.

Although imatinib is effective in treating newly diagnosed CML, resistance to imatinib has emerged. The 2-year incidence of resistance is estimated to be 80% in blast phase, 40% to 50% in accelerated phase, and at least 10% in chronic phase.

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.

2. Quality aspects

Introduction
SPRYCEL is presented as a film-coated tablets containing 20 mg, 50 mg and 70 mg of Dasatinib as active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, cascarmellose sodium, hydroxypropyl cellulose, magnesium stearate and purified water. The film coat consists of hypromellose, titanium dioxide, polyethylene glycol and purified Water.

The film-coated tablets are marketed either in aluminum/aluminum blisters or high-density polyethylene (HDPE) bottles with two piece child resistant closures having an aluminum-foil induction seal and containing silica gel desiccant canister.

Active Substance
The active substance is dasatinib and its chemical name is *N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate according to the IUPAC nomenclature.
Dasatinib is a crystalline white powder and exhibits pH dependent aqueous solubility (from 18.4 mg/ml at pH 2.6 to 0.008mg/ml at pH 6.0). It is very slightly soluble in acetone and acetonitrile and slightly soluble in ethanol, methanol, polyethyleneglycol 400 and propyleneglycol. It is practically insoluble in corn oil.

- **Manufacture**

Dasatinib is synthesised in two reactions steps with three solid isolations followed by purification (Crystallisation).

The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.

Specifications for starting materials, reagents, and solvents have been provided. Adequate control of critical steps and intermediates has been presented.

Structure elucidation has been performed by ultraviolet spectroscopy, infrared absorption spectroscopy, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy and ^{15}N-NMR spectroscopy and the molecular weight as determined by mass spectroscopy is in agreement with the expected molecular weight. The results of the elemental analysis are consistent with the proposed molecular formula. Unambiguous proof of structure was provided by X-ray crystallography.

- **Specification**

The active substance specifications include tests for appearance, color, identification (IR or Raman and HPLC), assay (97.5-102.0% HPLC), Impurities/Degradants (HPLC) and water content (Karl Fisher).
The specifications reflect all relevant quality attributes of the active substance. The analytical methods which were used in the routine controls were described and their validations are in accordance with the ICH Guidelines.
Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified. Impurity limits in the specification are justified by toxicology studies.
Residual solvents were satisfactorily controlled in the active substance. All limits are in accordance with ICH requirements. Certificates of analyses for the active substances issued by the finished product manufacturer were provide and all batch analysis results comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies were completed according to ICH guidelines demonstrated adequate stability of the active substance. It was confirmed that the active substance is very stable when exposed to a variety of stressed conditions such as, thermal, humidity and light exposure. The results of the long-term and accelerated studies support the retest period.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients are sufficiently justified.
Dasatinib tablets were developed in 5 and 50-mg strengths to cover a dose range of 15 - 180 mg for Phase I clinical studies. These tablets were manufactured using a wet granulation process. For Phase II clinical studies and commercialization, a wet granulation process was developed to cover a potential tablet strength of 20 - 150 mg. 20 and 50-mg tablets were developed using the 25% w/w drug load granulation for Phase II clinical studies to cover a dose range of 20 - 100 mg (twice a day). This same formulation (i.e., same drug load granulation) was used to manufacture 150-mg tablets for long-term stability studies (LTSS) to provide a bracket for any intermediate strengths (i.e., between 20 and 150 mg). Additionally, 70-mg tablets developed for commercialization using the same drug load granulation.
In fact the proposed commercial tablets, 20, 50, and 70 mg, will be manufactured from the same drug load granulation and use similar processes that were used to manufacture tablets for Phase II clinical studies and LTSS. However the only difference between the Phase II/LTSS and the proposed commercial tablets is in their debossing. This difference in debossing is not expected to have any impact on the quality or performance of the finished product.
The Phase II/LTSS/commercial formulation has the same qualitative composition as the Phase I formulations with the exception of the film coat.

The manufacturing process of major unit operations (i.e., granulation, drying, and lubrication) was characterized at both laboratory and pilot scales using statistical experimental designs. Coating parameters were chosen based on prior experience with similar coating materials.

Dasatinib is characterized as a low solubility/high permeability (BCS II) compound according to the Biopharmaceutics Classification System (BCS). In this context, dissolution of dasatinib can potentially be rate-limiting for absorption. The dissolution of a poorly soluble drug can be influenced by its particle size distribution. After several studies it was concluded that the active substance with particle size D[90] ranging from 4 to 130 microns has been shown to have no impact on blend flow, *in-vitro* tablet dissolution and content uniformity, and has produced tablets with satisfactory hardness. Results of the study demonstrated the ruggedness of the formulation and manufacturing process with respect to active substance particle size.
The MAH intends to market 20, 50, and 70-mg strength tablets. The proposed commercial tablets, 20 and 50 mg, are qualitatively and quantitatively identical to the 20 and 50-mg tablets used in Phase II studies with the exception of debossing. The results of a bioequivalence study demonstrated that the 70-mg tablet is bioequivalent to the combination of 20-mg plus 50-mg tablets.
In conclusion, statistical experimental designs, in combination with characterization of functional excipients and active substance, have been used to understand the tablet formulation and manufacturing process. Results of formulation and process development studies demonstrate that the tablet formulation and the manufacturing process are robust.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing processes such as wet granulation, drying, milling, blending, compression and film-coating unit operations. Furthermore, the equipment used is commonly available in the pharmaceutical industry.
The major steps to prepare dasatinib tablets are the granulation and drying processes for the manufacture of the granules, the blending/lubrication process for the manufacture of the final blend, and the tablet compression process.

The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The medicinal product specifications were established according the ICH guidelines and include the following tests: appearance, identification (HPLC and Raman or ATR:IR), assay, impurities/degradants (HPLC), uniformity of dosage units, dissolution and microbial limits (Ph Eur). All analytical procedures which were used for testing the medicinal product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.

- **Stability of the Product**

The stability studies were conducted according to the current ICH guideline. Three production scale batches of each strength have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was stored under elevated temperature and humidity conditions for 3 months and at ICH conditions and another production batch per strength was stored for photostability at ICH conditions.
Based on the available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects
Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.
At the time of the CHMP opinion, there were two minor unresolved quality issues which do not have any impact on the benefit/risk ratio of the medicinal product. The applicant gave a letter of undertaking and committed to resolve these as follow up measures after the opinion, within an agreed timeframe.

3. Non-clinical aspects

Introduction
The non-clinical toxicity studies were conducted according to GLP. The safety pharmacology studies were GLP-compliant with exception of the hERG and Purkinje fibre evaluations (conducted before the release of the ICH S7B guideline).

Pharmacology
Pharmacology studies included in vitro and in vivo studies to determine dasatinib's kinase inhibition selectivity spectrum, potency versus BCR-ABL kinase activity, mode of binding to BCR-ABL, leukemic cell-killing potency, and activity against multiple forms of imatinib resistance. These studies defined a pharmacological profile for dasatinib that has some distinct aspects as compared to imatinib and provide a rationale for the development of dasatinib for the treatment of CML and ALL.

- Primary pharmacodynamics

In vitro pharmacology
X-ray crystal structure analysis of the ABL kinase domain in complex with dasatinib revealed that, like imatinib, dasatinib binds in the ATP-binding site of the ABL kinase. Dasatinib binds to the active or "opened" conformation of the BCR-ABL kinase domain and is predicted, based on modeling studies, to also bind to the inactive or "closed" conformation.
The inhibitory activity of dasatinib was evaluated *in vitro* on five tyrosine kinase families SRC family kinases (SRC, LCK, YES, FYN), BCR-ABL, KIT, EPHA2 and PDGFβ.

Results demonstrated, that dasatinib is a potent inhibitor of selected protein tyrosine kinases of which SRC, BCR-ABL, KIT, PDGF receptor and EPH receptor have been linked to various forms of human malignancies.
Moreover, dasatinib killed or inhibited the proliferation of three human BCR-ABL dependent CML cell lines and one human BCR-ABL dependent ALL cell line. Dasatinib exhibited a high growth inhibitory potential in the four tested leukaemia cell lines with IC_{50} values ≤1 nM. Imatinib was considerably less potent in this cellular assay with a 300-655 fold difference in potency.
Both imatinib and dasatinib induced erythroid differentiation and cell death in the erythromyeloblastoid K-562 CML cell line although dasatinib appeared to be at least 150-fold more potent than imatinib in inducing this response.
Dasatinib demonstrated antiproliferative activity in human umbilical vein endothelial cells (HUVEC) treated with VEGF or bFGF. IC_{50} values of 42 nM and 248 nM were obtained under conditions with VEGF-stimulated and bFGF-stimulated growth, respectively. Additionally, dasatinib attenuated VEGF and bFGF stimulated HUVEC endothelial cell migration *in vitro* (IC_{50}<5 nM).

In vivo pharmacology
The tumour inhibiting activity of dasatinib was evaluated in human CML xenograft models grown SC in SCID mice. Cures were defined as the absence of detectable tumour at a time greater than ten times the tumour volume doubling time after the cessation of treatment.
Dasatinib was curative in mice bearing K562 human CML tumours over a range of dose levels (8-50 mg/kg) when administered PO once a day for 10 days using a "5-days-on and 2-days off" treatment regimen. Treatment was initiated when the tumours reached a size of 200 to 500 mg. High doses of imatinib failed to produce a comparative response. The minimum effective dose for dasatinib was determined as 2.5 mg/kg. In addition, dasatinib was highly efficient in this model when administered IV. Dasatinib was curative in mice bearing large KU812 tumours (up to > 1g tumour) when treated with 50 mg/kg/day for 5 days.
The SRC phosphorylation was investigated in peripheral mononuclear cell (PBMCs) collected from human prostate cancer cell (PC-3) bearing mice administered 1, 5, 15 or 50 mg/kg dasatinib. Dasatinib treatment resulted in a dose-dependent inhibition of SRC phosphorylation with an almost complete inhibition within 5 hours following administration of 15 and 50 mg/kg. Administration of 5 mg/kg resulted in 44% inhibition of SRC phosphorylation whereas 1 mg/kg was almost inactive. Based on $AUC_{0\text{-}24h}$ values, the animal:human plasma exposure ratios were 0.8 and 1.9 for the 5 mg/kg and 15 mg/kg dose groups, respectively. Based on pharmacokinetic data it was estimated that the dasatinib plasma concentration required to inhibit 50% of phospho-SRC was 91 nM in PBMCs.

Dasatinib treatment (10 mg/kg/day) increased survival in mice inoculated intracranially with K562 CML cells and the survival efficacy was superior to what was observed with imatinib (300 mg/kg/day). In a similar study, increased survival was observed following treatment with 10 and 30 mg/kg/day dasatinib whereas 200 mg/kg/day imatinib failed to inhibit intracranial tumour growth. Thus dasatinib appears to have a therapeutic advantage over imatinib in the treatment of intracranial CML.
Dasatinib was equally active against a human CML model in mice whether treatment was administered daily for ten consecutive days or if a short treatment break (5-days-on and 2-days off) was introduced into the dosing regimen. Moreover, a twice-daily dosing regimen produced efficacy that was superior to the once daily dosing regimen. Consequently, in mice bearing K562 human CML tumours, a superior anti-tumour activity (cure) was observed in the twice-daily 1.25 mg/kg dose group when compared to the dose group administered 2.5 mg/kg dasatinib on a once-daily schedule (growth inhibition).

Cellular activity of human dasatinib metabolites
In cancer patients, the systemic exposure of the metabolites represented 1-13% of the drug-related material. Furthermore, BMS-582691, the pharmacologically most potent metabolite, represented maximally 4% of dasatinib-related radioactivity in the *in vitro* and *in vivo* metabolism studies conducted with humans or human liver microsomes. Therefore, the dasatinib metabolites are not expected to contribute significantly to the pharmacological activity of dasatinib.

- Secondary pharmacodynamics

Dasatinib affinity towards 42 different receptors and channels was evaluated in a competitive binding assay. Dasatinib had no significant effect (all assays were ≤46% inhibition at 10 μM) on the binding of any of the receptor or ion-channel ligands evaluated and no effect on acetylcholinesterase activity (930003305).

Dasatinib proved less potent against selected non-target protein tyrosine kinases and serine/threonine kinases. An IC_{50} value of at least 5,000 nM was obtained for FAK, IGF1 receptor, insulin receptor, PKA, PKC, GSK-3, MET, EMT/ZAP-70, SYK and CAMKII. Moreover, IC_{50} values were obtained for VEGF receptor-2 (>2,000 nM), FGF receptor (880 nM), MEK kinase (1700 nM), HER1 receptor (180 nM), HER2 receptor (710 nM) and p38 (103 nM) (930003300).

The three major dasatinib metabolites, BMS-573188 (carboxylic acid), BMS-582691 (N-dealkylated), and BMS-606181 (N-oxide), were evaluated *in vitro* for their ability to inhibit or stimulate the binding of appropriate radioligands to 34 different receptors or ion channels and to inhibit the activities of 4 different enzymes (acetylcholinesterase, monamine oxidases A and B, and phosphodiesterase-3). BMS-573188, and BMS-606181 at 10 μM had no biologically relevant effect on binding of any of these ligands to their receptors or ion channels or on any enzyme activities evaluated. BMS-582691 at 10 μM had ≥ 50% effects on 7 of the 34 receptors/channels evaluated (adrenergic β2, non-selective adrenergic α2, non-selective serotonin 5-HT1, serotonin 5-HT1A, norepinephrine transporter, and dopamine transporter receptors, and the sodium channel) (930011274).

- Safety pharmacology programme

When tested in HEK cells stably transfected with the human hERG/IKr channel, dasatanib inhibited the hERG currents by 6, 37 and 77% at 3, 10 and 30 μM, respectively. The calculated IC50 was 14.3 μM. In accordance with these findings, 30 μM dasatinib prolonged APD_{50} by 26% and APD_{90} by 11% in the rabbit Purkinje fibre assay. The recorded action potential prolongations were ≤ 5% at 3 and 10 μM (non-GLP, 920018211). Nevertheless no changes in ECG parameters were observed up to 22 hours following administration of 10 mg/kg dasatinib to six instrumented conscious monkeys. Treatment-related findings consisted of increases in systolic (5 -15%) and diastolic (8-21%) blood pressure for approximately two hours following dasatinib administration when compared to vehicle control (GLP, 930005453). In addition, no effect on ECG following single-dose administration to monkeys at plasma exposure levels up to 27 times higher than what is seen in patients administered 70 mg/kg BID (n=2) (930003271). Moreover, no effect on heart rate or ECG (anesthetized animals) was observed in a one-month intermittent oral toxicity study in monkeys.

Evaluation of the potential effects of dasatinib on CNS and respiratory system were conducted as part of single- and repeat-dose toxicity studies in monkeys. Nervous system evaluations were conducted as part of comprehensive physical examinations and included assessments of temperament or behaviour, movement, coordination or balance/muscle tone, peripheral reflexes, proprioception, and functions of cranial nerves II through XII. These evaluations did not demonstrate any dasatinib-related changes in neurologic function at exposures approximately 3- to 28-fold greater than exposures in humans at the recommended clinical dose.

Respiratory system evaluations included assessments of lung sounds by thoracic auscultation and respiratory rate. These evaluations did not demonstrate any dasatinib-related changes in respiratory function at exposures approximately 3- to 28-fold greater than exposures in humans at the recommended clinical dose.

The major dasatinib metabolites were tested in hERG and Purkinje fibre assays for their potential effects on cardiac function. BMS-573188 inhibited IKr currents by approximately 6 and 11% at 10 and 30 μM; BMS-582691 inhibited IKr currents by 24, 72, and 95% at 3, 10 and 30 μM; and BMS-606181 inhibited IKr currents by 8 and 12% at 10 and 30 μM, respectively. In the Purkinje-fibre assay at 30 μM, BMS-573188 and BMS-606181 had no biologically relevant effects on action potential duration, whereas BMS-582691 prolonged APD50 and APD90 by 10 and 9%, respectively (non-GLP, 930010945).

- Pharmacodynamic drug interactions

It is possible that the onset of acquired drug resistance will be minimized by combining imatinib and dasatinib treatment. The effect of concomitant imatinib and dasatinib treatment was investigated applying assays for cellular proliferation and BCR-ABL phosphorylation on Ba/F3 expressing wild-type BCR-ABL and four common imatinib-resistant mutants (Y253F, E255K, T315I, and M351T).

The studies showed that dasatinib retains its inhibitory capacity when coadministered with imatinib at concentrations several-fold above typical clinical levels. In fact, co-administering imatinib with dasatinib resulted in lower cell proliferation IC_{50} values than observed with the single-treatments, suggesting an additive antiproliferative effect. As expected, cells expressing the BCR-ABL mutant T315I were not sensitive to neither imatinib nor dasatinib treatment (O'Hare et al., 2005).

Pharmacokinetics
Plasma samples collected from rats, rabbits, and monkeys in GLP toxicokinetic studies were analysed with validated liquid chromatography with tandem mass spectrometry methods to determine concentrations of dasatinib. Adequate precision and accuracy were obtained with the analytical methods. The toxicokinetic method validation studies were not GLP-compliant; however the toxicokinetic evaluations performed in the course of the toxicity studies were compliant with GLP regulations.

Dasatinib was rapidly absorbed following oral administration to mice, rats, dogs and monkeys with T_{max} ranging from 0.6 to 2.3 hours. The oral bioavailability was rather low with values ranging from 14% to 34%. The steady state volume of distribution of dasatinib in mice, rats, dogs, and monkeys were greater than the volume of total body water, suggesting extravascular distribution of the drug. Based on a Caco-2 permeability assay and *in vivo* data, dasatinib does not appear to be a P-glycoprotein substrate.

The serum protein binding of dasatinib was determined by equilibrium dialysis at 10 μM and was found to be 92%, 97%, 96%, 97%, and 94% in mouse, rat, dog, monkey, and human, respectively. The largest percentages of the radioactive dose were associated with tissues of the gastrointestinal tract and liver following a single PO administration of ^{14}C-dasatinib to Long-Evans rats. These findings are consistent with the oral route of dasatinib administration and major route of elimination in the faeces. At 168 h post-dose, radioactivity was only detected in 4 of the 22 sampled tissues (adrenal glands, eyes, kidneys, and liver). Dasatinib displayed melatonin affinity and absorbs light in the 290 to 700 nm range thus a phototoxicity study has been conducted by the Applicant.

The metabolism of ^{14}C-dasatinib was investigated *in vivo* in rats, monkeys, and humans following PO administration. Unchanged dasatinib was the most abundant drug-related component in the plasma of rats (34-55% at 1-8 h), monkeys (32% at 4 h), and humans (26% at 2 h). Still, the studies showed that dasatinib undergoes extensive oxidative metabolism and conjugation thus in total 29 metabolites were detected the samples collected from rats, monkeys, and humans. CYP3A4 appears to play a major role in dasatinib metabolism. In addition, FMO3 seems involved. Multiple glucuronide conjugates of dasatinib were detected, however the uridine diphosphate-glucuronosyltransferase enzymes responsible for the direct glucuronidation of dasatinib have not been identified. Dasatinib treatment did not increase CYP enzyme activity or expression in primary human hepatocytes whereas it inhibited the activites of liver microsome CYP2C8 (Ki of 3.6 μM) and CYP3A4 (Ki = 1.9 μM). A C_{max} value of 0.12 μM has been reported in humans and accordingly, there is a possibility of interactions between dasatinib and drugs that are CYP3A4 and CYP2C8 substrates. A clinical drug interaction study showed that coadministration with the CYP3A4 substrate simvastatin increased the exposures of simvastatin and simvastatin acid with approximately 20% and 27%, respectively. Warnings are given in the SPC on the risk for pharmacokinetic drug interactions when dasatinib is coadministered with other CYP3A4 substrates. However, the risk for interactions with CYP2C8 substrates (e.g. the cancer drug paclitaxel, glitazones, torsemide) has not been evaluated.

Biliary excretion was the predominant route for dasatinib elimination in rats, monkeys and humans following oral administration whereas urinary excretion only played a minor role.

Toxicology
Dasatinib was administered PO in all the toxicological studies since this is the intended clinical way of administration.

- Single dose toxicity

Single-dose toxicity was evaluated in rats and monkeys. Mortalities were observed in rats administered 100 mg/kg. All monkeys were sacrificed due to a moribund condition following

administration of 45 mg/kg; a dose resulting in dasatinib plasma exposure levels 27 times higher than is observed in patients administered 70 mg/kg BID. The major target tissues appeared to be skin (haemorrhage), immune system (lymphoid depletion and decrease in lymphocytes), gastrointestinal tract (ulceration, haemorrhage), kidney (kidney tubule dilatation) and heart (haemorrhage and/or necrosis). In addition, bone resorption was inhibited leading to decreased plasma calcium and phosphorus levels. The majority of the findings were reversible or partially reversible within the 14 Days recovery period.
Based on toxicokinetic analysis performed in monkeys, dasatinib plasma exposure (AUC) was on average 2493, 4587 and 8258 for both sexes following administration of 15, 25 and 45 mg/kg, respectively. The obtained exposure levels were approximately 8, 15 and 27 times higher than what is seen in patients administered 70 mg/kg BID.

- Repeat dose toxicity (with toxicokinetics)

Repeat-dose toxicity studies were conducted in Sprague-Dawley rats and Cynomolgus monkeys. All doses and concentrations were corrected for free base content and drug purity. The vehicle consisted either of sodium acetate buffer or sodium citrate buffer.
An exploratory repeat-dose toxicity study conducted in two dogs was discontinued after two days due to gastrointestinal toxicity (930003268). Dasatinib treatment (5 mg/kg) induced emesis and bloody vomitus and liquid, mucous and bloody faeces within two hours post-dosing. Additional findings consisted of red discolouration of the mesenteric lymph node and mucosae of the stomach, small intestine and colon. Microscopically, thymic lymphoid depletion was observed in the female. Decreases in total protein, albumin, and globulins were observed.
The gastrointestinal, haematopoietic and lymphoid systems were the major target organs in the repeat-dose toxicity studies. The major dose-limiting event was gastrointestinal toxicity and in the 9-month monkey study, animals were euthanized due to GI toxicity when exposed to clinically relevant dasatinib plasma levels. In rats, mortalities were observed in studies of 4 weeks duration or longer at plasma exposure levels (AUC) four-fold higher than observed in patients (70 mg BID). The predominant causes of death in rats were GI and lymphoid toxicity. Consistent GI findings were dose-related enteropathy, faecal abnormalities, vomiting, distension of the GI tract with gas/fluid/digesta and GI tract haemorrhage. Microscopic evaluations performed in rats detected dose-related villus alterations in the small intestine along with epithelial hyperplasia and fibrosis. In addition, small intestine villous blunting and inflammation were recorded in monkeys. The haematology and clinical chemistry findings suggested inflammation, blood loss, poor food consumption and electrolyte loss. The GI toxicity findings occurred at clinically relevant AUC levels. Diarrhoea, nausea and vomiting are very common findings in the clinical setting while e.g. GI haemorrhage, stomatitis, colitis and abdominal pain are common findings in patients undergoing dasatinib treatment. Bleeding is exacerbated by treatment since dasatinib prolongs bleeding time via an effect on platelet function and bleeding-related events have been reported in patients taking dasatinib. Erythroid toxicity was observed in the form of reduced erythrocytes, haemoglobin and haematocrit counts. Moreover, a reduction in the number of erythroid cells was observed in the bone marrow of monkeys without safety margin. Anaemia is a common finding in dasatinib-treated patients. Lymphoid toxicity was observed in the form of lymphoid depletion of the thymus and spleen and an accompanying reduction in thymus and spleen weight. In addition, reductions in plasma lymphocytes and splenic T-cells and B-cells were observed in rats. Hypocellularity of the bone marrow was observed in rats at a dose giving rise to 4 to 6-fold higher AUC values than observed in patients. Infections were not observed in the non-clinical studies but are common in the clinical setting. Dasatanib potently inhibits osteoclastic bone resorption and reduced plasma calcium and/or phosphorus levels were frequent findings in the repeat-dose toxicity studies. Increases in liver weight and aspartate aminotransferase were observed in rats without correlative microscopic findings. Furthermore, increased heart weight (no microscopic findings), increased ovary weight and an increase in corpora lutea were observed in dasatinib-treated rats. These findings were also observed in a long-term toxicity study conducted with imatinib. Dasatinib administration caused an increase in the incidence and severity of kidney mineralization in the monkey 9-month toxicity study. In addition, an increase in prerenal or renal azotemia was observed. No signs of renal function impairment were detected in the other non-clinical studies. All dasatinib-related changes were generally reversible in surviving animals except for the increase in kidney mineralization.

- Genotoxicity

The genotoxic potential of dasatinib was evaluated in a standard battery of *in vitro* and *in vivo* tests.
Moderate to marked cytotoxicity was observed in the *Salmonella* and *E. coli* strains cultured at dasatinib concentrations of 400 and 1600 μg/plate, respectively. Dasatinib was tested for its ability to induce chromosomal aberrations in CHO cells in the presence and absence of metabolic activation (S9) and with treatment period of 4 or 20 hours. Under the conditions tested, dasatinib was clastogenic at the highest concentrations evaluated with 12-31% structural aberrations versus 0% for the vehicle control. Cytotoxicity was observed at these concentrations levels. At lower dasatinib concentrations, the percentage of cells with structural aberrations (1.5-5%) were within the historical control range although a significant increase was detected when compared to vehicle control. No chromosomal aberrations were observed at 2.5 μg/mL following 20 h incubation in the absence of metabolic activation. There was no significant increase in the incidence of numerical aberrations. Dasatinib did not increase the frequency of polychromatic erythrocytes (PCE) with micronuclei when compared with to the vehicle control values. Bone marrow toxicity was observed at the 20 and 40 mg/kg dose levels with PCE reductions of approximately 20 and 45%, respectively.

- Carcinogenicity

No studies have been performed.

- Reproduction Toxicity

Dasatanib's potential effects on embryo-foetal development were evaluated in pregnant rats and rabbits.
In rats, administration of dasatinib during the period of organogenesis induced embryolethality at all doses with 17%, 77%, 100% and 100% resorbed conceptuses per litter at 2.5, 5, 10, or 20 mg/kg, respectively. Foetal skeletal alterations at 2.5 and 5 mg/kg/day (mean maternal AUC values ≤ 239 ng·hr/mL) included bent scapula or humerus and reduced ossification of the sternebrae and thoracic vertebral centra. Besides skeletal findings, foetal abnormalities at 5 mg/kg/day included fluid-filled thoracic and abdominal cavities, oedema and small liver. There were no surviving foetuses at 10 or 20 mg/kg/day (mean maternal AUC values of 1270 to 1490 ng·hr/mL). Maternal toxicity was observed in rats at doses ≥ 10 mg/kg/day; mortality occurred at 20 mg/kg/day.
Embryolethality with associated decreases in litter size was observed at 10 mg/kg/day dasatinib in a rabbit dose-finding study, whereas lower doses did not give rise to embryo-foetal findings. In the pivotal rabbit study, dasatinib induced foetal skeletal alterations in the absence of maternal toxicity at all doses (0.5, 2, or 6 mg/kg/day, mean AUC values ≥ 44 ng·hr/mL). The skeletal abnormalities consisted of delays in ossification of foetal lumbar vertebrae and pelvis. At 6 mg/kg, dasatinib also caused irregular ossification of the hyoid. Thus, dasatinib caused foetal alterations in rats and rabbits at doses that did not produce maternal toxicity.

- Local tolerance

No studies were conducted.

- Other toxicity studies

Dasatinib was phototoxic in a neutral red uptake phototoxicity assay performed in BALB/c 3T3 mouse fibroblast (in duplicate trials, PIF values were 12 and 37 and MPE values were 0.2 and 0.4).

Immunotox
Dasatinib at daily doses of 20 and 50 mg/kg for 3 days inhibited the proliferation of murine splenic T-cells in a dose-dependent manner. In the cardiac transplant study, dasatinib given twice daily at 25 mg/kg for up to 30 days inhibited graft rejection in mice. The observed immunosuppression appeared comparable to that of cyclosporine. However, 15 mg/kg given twice daily (continuous daily dosing) or 25 mg/kg given twice daily (5-days on and 2-days off schedule) for 30 days did not extend graft survival time.

Immunotoxicity was observed in the standard toxicity studies in the form of lymphoid depletion of the thymus and spleen and an accompanying reduction in thymus and spleen weight at clinically relevant doses in long-term studies. Hypocellularity of the bone marrow was observed in rats at a dose giving rise to 4 to 6-fold higher AUC values than observed in patients. In addition, reductions in plasma lymphocytes and splenic T-cells and B-cells were observed in rats administered 15 mg/kg dasatinib

for two weeks (rat:human AUC exposure margin around 3). Despite the decreases in splenic lymphocyte subpopulations and weights at 15 mg/kg, dasatinib treatment did not have any adverse effect on the T-cell dependent antibody response to the antigen Keyhole Limpet Hemocyanin (KLH).

Other
Dasatanib potently inhibited osteoclastic bone resorption. Dasatinib dose-dependently inhibited PTH-stimulated release of ^{45}Ca into the medium by fetal rat long bones *in vitro* with an apparent IC_{50} of 2 nM. At 5 nM dasatinib completely blocked PTH-stimulated bone resorption *in vitro*. Moreover, dasatinib blocked the normalization of plasma calcium in the thyro-parathyroidectomized rat model after PTH infusion.
In vitro, dasatinib inhibited agonist-induced platelet aggregation in human, monkey, and rat platelet-rich plasma at concentrations of 0.5 and 5 µg/mL, but no effect was observed at 0.05 µg/mL (0.1 µM). Dasatinib produced near-complete (94%) inhibition of shear-induced platelet aggregation of human platelets at 5 µg/mL, with 46% inhibition at 0.5 µg/mL, and no effect at 0.05 µg/mL. The effect of dasatinib on human whole blood clot formation was limited to a 29% reduction in clot strength at 5 µg/mL, with no effect at 0.5 µg/mL. *In vivo*, dasatinib at mean plasma concentrations ≥ 144 ng/mL in rats prolonged cuticle bleeding time, but did not cause spontaneous bleeding. Bleeding time was not extended at a plasma exposure of 61 ng/mL.

Ecotoxicity/environmental risk assessment
In the calculations of PEC_{SW}, the market penetration factor (normally default 1%) was calculated to 0.006 µg/L. Studies were performed including an acute toxicity study in green algae, a full life-cycle toxicity test in Daphnia magna and an acute toxicity study in rainbow trout. In addition, dasatinib was evaluated with respect to activated sludge respiration inhibition and the biodegradation and adsorption of dasatinib was determined under aerobic conditions in an activated sludge respiration inhibition study. Altogether, the evaluation of PEC/PNEC ratios for surface water, groundwater and wastewater treatment microorganisms all gave ratios well below 1.

- **Discussion on the non-clinical aspects**

With IC_{50} values in the lower nM range, dasatinib is a potent inhibitor of members of five tyrosine kinase families: SRC family kinases (SRC, LCK, YES, FYN), BCR-ABL, KIT, EPHA2 and PDGFβ.
The pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.
Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUC_{τ}) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg BID. The overall mean terminal half-life of dasatinib is approximately 5-6 hours in patients.
Data from healthy subjects administered a single, 100 mg dose of dasatinib 30 minutes following a high-fat meal indicated a 14% increase in the mean AUC of dasatinib. A low-fat meal 30 minutes prior to dasatinib resulted in a 21% increase in the mean AUC of dasatinib. The observed food effects do not represent clinically relevant changes in exposure.
In patients, dasatinib has a large apparent volume of distribution (2,505 l) suggesting that the medicinal product is extensively distributed in the extravascular space. At clinically relevant concentrations of dasatinib, binding to plasma proteins was approximately 96% on the basis of *in vitro* experiments.
Dasatinib is extensively metabolized in humans with multiple enzymes involved in the generation of the metabolites. In healthy subjects administered 100 mg of [^{14}C]-labelled dasatinib, unchanged dasatinib represented 29% of circulating radioactivity in plasma. Plasma concentration and measured *in vitro* activity indicate that metabolites of dasatinib are unlikely to play a major role in the observed pharmacology of the product. CYP3A4 is a major enzyme responsible for the metabolism of dasatinib.
Elimination is predominantly in the faeces, mostly as metabolites. Following a single oral dose of [^{14}C]-labelled dasatinib, approximately 89% of the dose was eliminated within 10 days, with 4% and 85% of the radioactivity recovered in the urine and faeces, respectively. Unchanged dasatinib accounted for 0.1% and 19% of the dose in urine and faeces, respectively, with the remainder of the dose as metabolites.
Dasatinib and its metabolites are minimally excreted via the kidney. Exposure to dasatinib may be expected to increase if liver function is impaired.

The gastrointestinal, haematopoietic and lymphoid systems were the major target organs in the repeat-dose toxicity studies. The major dose-limiting event was gastrointestinal toxicity and in the 9-month monkey study, animals were euthanized due to GI toxicity when exposed to clinically relevant dasatinib plasma levels. In rats, mortalities were observed in studies of 4 weeks duration or longer at plasma exposure levels (AUC) four-fold higher than observed in patients (70 mg BID). The predominant causes of death in rats were GI and lymphoid toxicity. Consistent GI findings were dose-related enteropathy, faecal abnormalities, vomiting, distension of the GI tract with gas/fluid/digesta and GI tract haemorrhage

The haematology and clinical chemistry findings suggested inflammation, blood loss, poor food consumption and electrolyte loss. The GI toxicity findings occurred at clinically relevant AUC levels. Bleeding is exacerbated by treatment since dasatinib prolongs bleeding time via an effect on platelet function erythroid toxicity was observed in the form of reduced erythrocytes, haemoglobin and haematocrit counts. Anaemia is a common finding in dasatinib-treated patients. Lymphoid toxicity was observed in the form of lymphoid depletion of the thymus and spleen and an accompanying reduction in thymus and spleen weight. In addition, reductions in plasma lymphocytes and splenic T-cells and B-cells were observed in rats. Hypocellularity of the bone marrow was observed in rats at a dose giving rise to 4 to 6-fold higher AUC values than observed in patients. All dasatinib-related changes were generally reversible in surviving animals except for an increase in kidney mineralization.

Dasatinib was clastogenic in CHO cells. The lowest nonclastogenic concentration of 2.5 µg/mL is approximately 50-fold greater than the maximum plasma concentration (C_{max}) measured in humans given the recommended clinical dose of 70 mg BID. According to ICH S1A, long-term carcinogenicity studies are not required when the life-expectancy in the indicated population is short (i.e. less than 2-3 years). Consequently, the lack of carcinogenicity studies for dasatinib is justified.

Considering the indication the lack of a fertility study is acceptable. Administration of dasatinib to rats during the period of organogenesis induced embryolethality at clinically relevant maternal plasma exposures (AUC). In addition, dasatinib induced foetal skeletal alterations in the absence of maternal toxicity in rats and rabbits at clinically relevant maternal plasma exposures.

The lack of a prenatal and postnatal development study is acceptable when considering the life-threatening indication.

Dasatinib was phototoxic in the neutral red uptake phototoxicity assay and this is stated in the SPC section 5.3. Dasatinib treatment inhibits T-cell activation and proliferation and causes reductions in plasma lymphocytes and splenic T-cells and B-cells. Immunotoxicty studies demonstrated that a threshold exists for the dasatinib-induced immunosuppressive effect but based on the non-clinical studies some immunotoxicity findings are expected in the clinic. Dasatinib inhibited platelet aggregation in human, monkey, and rat platelet-rich plasma *in vitro*. The no-effect concentration of 0.05 µg/mL is equivalent to the plasma C_{max} measured in humans given the clinical dose of 70 mg BID. *In vivo*, dasatinib in rats prolonged cuticle bleeding time, but did not cause spontaneous bleeding.

In accordance with what has been reported for other SRC tyrosine kinase inhibitors, dasatanib potently inhibits osteoclastic bone resorption when tested *in vitro* and *in vivo* at clinically relevant concentrations.

Dasatinib is unlikely to represent a risk to the environment.

4. Clinical aspects

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.

Pharmacokinetics

PK data have been studied in healthy volunteers and in the target population. The studies pertinent to clinical pharmacology are tabulated below:

Clinical Pharmacology Studies

Study Number	Study Characteristics	Dasatinib Dose Formulation Strength Type	Number of Subjects Evaluable for PK Analysis/Total Number of Subjects Treated
CA180002	Single and multiple ascending dose study in subjects with leukemia	15, 30, 50, 75, 105, 140, 180 mg 5 days on and 2 days off QD regimen (Q5D) 25, 35, 50, 70 mg 5 days on and 2 days off q12h regimen (B5D) 35, 50, 70, 90, 120 mg q12h regimen (B7D) 5 and 50 mg Phase 1 clinical tablet	84/91
CA180009[a]	Food effect study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	49/54
CA180016[a]	Formulation comparability study in healthy subjects	100 mg 50 mg Phase 1 clinical tablet 100 mg 5 mg Phase 1 clinical tablet 100 mg 20 mg Phase 2 clinical tablet[b] 100 mg 50 mg Phase 2 clinical tablet[b]	74/75
CA180019	^{14}C ADME study in healthy subjects	100 mg Solution	8/8
CA180020	Famotidine/antacid interaction study in healthy subjects	50 mg Phase 2 clinical tablet[b]	22/24
CA180022	Simvastatin interaction study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	48/48
CA180032	Rifampin interaction study in healthy subjects	100 mg 50 mg Phase 2 clinical tablet[b]	20/20
CA180037[a]	Bioequivalence study in healthy subjects	70 mg 20 mg + 50 mg Phase 2 clinical tablet[b] 70 mg 70 mg Phase 2 clinical tablet[b]	61/64

The principal PK parameters from across-trial results in healthy volunteers and in the target population are summarized below:

Summary of Pharmacokinetic Parameters of Dasatinib in Healthy Subjects and Leukemia Subjects

Dasatinib Dose on Day 1 (Regimen)	Population (N)	Cmax (ng/mL) Geom. Mean (CV%)	AUC(0-T) (ng•h/mL) Geom. Mean (CV%)[a]	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)
50 mg	Healthy (N = 22)	41.52 (54)	101.67 (45)[b]	1.00 (0.50, 3.00)	4.01 (0.99)
50 mg (B5D)	Leukemia (N = 3)	34.71 (80)	109.09 (68)	1.00 (0.50, 3.00)	5.20 (1.03)
50 mg (B7D)	Leukemia (N = 8)[c]	17.15 (75)	101.18 (47)	2.33 (1.00, 5.07)	3.87 (1.01)
50 mg (Q5D)	Leukemia (N = 3)	34.55 (40)	111.38 (46)	1.00 (0.92, 1.08)	3.65 (1.11)
70 mg	Healthy (N = 61)	66.83 (40)	204.48 (37)	1.00 (0.50, 3.00)	3.77 (1.38)
70 mg (B5D/B7D)	Leukemia (N = 22)	33.44 (82)	129.77 (74)	1.38 (0.50, 6.00)	3.77 (1.39)
75 mg (Q5D)	Leukemia (N = 3)	56.50 (59) [52.73][d]	219.19 (60) [204.58]	1.18 (0.50, 2.08)	2.23 (0.58)
100 mg	Healthy (N = 88)	83.49 (50)	275.13 (48)	1.00 (0.50, 4.00)	4.73 (1.99)
90 mg (B7D)	Leukemia (N = 11)	63.17 (84) [70.19]	219.25 (80) [243.61]	1.22 (0.50, 3.13)	3.56 (1.39)
105 mg (Q5D)	Leukemia (N = 3)	37.92 (20) [36.11]	201.65 (22) [192.05]	3.05 (1.97, 3.17)	3.71 (2.63)
120 mg (B7D)	Leukemia (N = 7)	73.64 (118) [61.37]	290.11 (118) [241.76]	1.52 (0.42, 4.00)	4.26 (1.84)

[a] AUC(0-T) = AUC up to 12 or 24 hours
[b] AUC corrected for residual AUC from the PM dose
[c] N = 7 for AUC(0-T) and T-HALF
[d] Values in square brackets represent geometric mean values normalized to a 70 or a 100 mg dose
B5D = every 12 hours (q12h), 5 days on and 2 days off schedule; B7D = q12h continuous schedule; Q5D = once daily (QD) 5 days on and 2 days off schedule; NC = not calculated
Source: Tables 2.1.1 and 3.1.1.1, Appendix 2, and CA180002

- Absorption

Dasatinib is rapidly absorbed in subjects following oral administration. The oral bioavailability was low with values ranging from 14% to 34%. The steady state volume of distribution of dasatinib in mice, rats, dogs and monkeys was greater than the volume of total body water, suggesting extravascular distribution of the drug. Mean peak concentrations at the suggested clinical dose regimen of 70 mg twice daily were observed between median Tmax of 1.00 to 1.42 hours either in healthy subjects or in leukaemia patients.

- Distribution

On the basis of in vitro studies at clinically relevant concentrations (100 and 500 ng/mL), binding of dasatinib to serum proteins was approximately 96%. Dasatinib distributes freely in human red blood cells; the blood to plasma concentration ratio was 1.8. The Vz/F after multiple dosing with the proposed therapeutic dose of 70 mg q12h for 5 or 8 days was 2505 L. In animals, the absolute bioavailability of dasatinib ranged from 14% to 34%. Assuming the most conservative value of F in humans (15.2%), Vz corrected for oral bioavailability is calculated (0.152•Vz/F) to be approximately 381 L. The apparent volume of distribution is about 9-fold greater than total body water suggesting an extensive extravascular distribution in humans.

- Metabolism

In human liver microsomes, dasatinib inhibited CYP2A6 (IC_{50} = 35 μM), CYP2C8 (IC_{50} = 12 μM), CYP2C9 (IC_{50} = 50 μM), and CYP3A4 (IC_{50} values of 18 and 10 μM for midazolam and testosterone substrates, respectively).CYP2C8 inhibition by dasatinib followed a competitive inhibition model with a Ki of 3.6 μM. While none of the other enzymes tested showed any signs of time-dependent CYP inhibition, CYP3A4 inhibition by dasatinib was time-dependent with a K_I = 1.9μM. Dasatinib has little potential to induce CYP3A4 and, at concentrations ≤ 25 μM, dasatinib did not induce CYP1A2, 2B6, 2C9, and 3A4 in primary cultures of human hepatocytes.
The metabolism of ^{14}C-dasatinib was investigated *in vivo* in rats, monkeys, and humans following PO administration. Unchanged dasatinib was the most abundant drug-related component in the plasma of rats (34-55% at 1-8 h), monkeys (32% at 4 h), and humans (26% at 2 h). Nevertheless studies demonstrated, that dasatinib undergoes extensive oxidative metabolism and conjugation. In total 29 metabolites were detected. CYP3A4 appears to play a major role in dasatinib metabolism. Dasatinib treatment inhibited the activites of liver microsome CYP2C8 (Ki of 3.6 μM) and CYP3A4 (Ki = 1.9 μM). A C_{max} value of 0.12 μM has been reported in humans.

- Elimination

Following repeated doses of 70 mg orally administered dasatinib in the target population, the terminal elimination half-life was 5.4 hours (SD3.5), and apparent oral clearance was 578 L/h (SD 537).

Subjects eliminated radioactivity primarily in faeces. Mean total recoveries of total radioactivity through 9 days post-dose were approximately 4% and 85% in urine and faeces, respectively, with a mean total of approximately 89%. Negligible amounts of dasatinib and BMS-606181 were excreted in the urine (≤ 1% of dose) and approximately 19% of the dose was recovered in the faeces as dasatinib.

- Dose proportionality and time dependencies

Dose proportionality was examined in an open-label, Phase 1, dose-escalation study administered orally to patients with chronic, accelerated, or blast phase chronic myelogenous leukaemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukaemia who have primary or acquired haematologic resistance to or intolerance of imatinib mesylate. Patients received the following dosing regimens of dasatinib in the fasted state:

- 15, 30, 50, 75, 105, 140, or 180 mg once daily (15-180 mg/day) for 5 consecutive days followed by 2 non-treatment days every week (Q5D Regimen)
- 25, 35, 50, or 70 mg twice daily (50-140 mg/day) for 5 consecutive days followed by 2 non-treatment days every week (B5D Regimen)
- 35, 50, 70, 90, or 120 mg twice daily (70-240 mg/day) continuous dosing schedule (B7D Regimen)

The AUC of dasatinib is approximately dose proportional in the dose range of 15 to 240 mg/day. The 90% CIs are wide, indicating that the variability in AUC is high. Similar results were obtained when AUC(TAU) was analyzed separately for the q12h and QD regimens.

For the suggested clinical dosing regimen of 70mg twice daily, the geometric means for accumulation index ranged between 1.60 and 1.73 on day 8 and between 0.78 to 1.53 on Day 29.

- Special populations

The PK of dasatinib has not been studied in patients with impaired renal or hepatic function.

No PK studies have been performed in children.

No marked gender, race (Caucasian vs. other) or age (<65, >65) differences in the PK parameters of dasatinib in healthy subjects have been detected.

- Pharmacokinetic interaction studies

In vivo
The potential for clinically relevant drug-drug interactions has been subject to clinical drug interaction studies with rifampin, simvastatine, famotinine and an antacid.

Rifampin:

Rifampicin decreases mean Cmax and AUC of dasatinib by 81% and 82%, respectively.

Simvastatine:
Mean Cmax and AUC (INF) of simvastatin were increased by 37% and 20%, respectively, and the mean Cmax and AUC (INF) of simvastatin acid were increased by 41% and 27%, respectively, when simvastatin was administered in combination with a single 100 mg dose of dasatinib.

When 30 mL of aluminium hydroxide/magnesium hydroxide-containing antacid was administered to the same subjects concomitantly with a 50 mg dose of dasatinib, a 55% reduction in dasatinib AUC, and a 58% reduction in Cmax were observed. When a single 50 mg dose of dasatinib was administered to 24 healthy subjects 10 hours following famotidine, the AUC and Cmax of dasatinib were reduced by 61% and 63%, respectively.

Pharmacodynamics
No clinical Pharmacodynamic studies have been performed.

Clinical efficacy

- Dose response study(ies)

Determination of the recommended dose was developed based upon:
1) Non-clinical pharmacology and clinical pharmacokinetic information
2) Efficacy in subjects with chronic, accelerated, or blast phase CML resistant or intolerant to imatinib
The in vitro inhibitory concentration (IC50) against imatinib-naive strains ranged from 0.7 nM - 1.8 nM, and the IC50 against imatinib-resistant strains ranged from 1 nM - 2.1 nM. After adjusting for protein binding, the IC50 of dasatinib in vivo is estimated to be in the range of 17.5 to 52.5 nM. On the proposed 70 mg BID dosing regimen, the geometric mean Cmax for dasatinib on day 5/8 is 2.4- to 7.4-fold higher than the in vivo protein binding adjusted IC50, and mean concentration is above the protein-binding adjusted IC50 for 10 of 12 hours in each dosing interval. This compares with a mean concentration that is above the target concentration for 4 of 12 hours on the 50 mg BID regimen, and for 12 of 24 hours on the 140 mg QD regimen.
In study CA180002 (40 subjects were in chronic phase and 44 subjects had advanced disease), intra-subject dose escalation and schedule escalation were allowed in order to optimize an individual subject's haematologic, cytogenetic, and molecular response while maintaining and evaluating safety, tolerability, pharmacokinetics, BCR-ABL mutation status, and dasatinib's effect on specific biomarkers. In this study, the majority (83%) of subjects were resistant to imatinib, and doses were escalated from 15 mg QD to 180 mg QD (chronic phase), 25 mg BID to 90 mg BID (chronic phase), and 35 mg BID to 120 mg BID (advanced phases). In all cohorts, haematologic and cytogenetic responses were reported.
Pharmacokinetic information showed that doses greater than 50 mg BID produced serum concentrations of dasatinib above the level of the IC50 of in vitro growth inhibition assays. Pharmacodynamic information showed that phosphorylated CRKL, a substrate of BCR-ABL, was inhibited over a greater period of time with the BID regimen than the QD regimen and provided a rationale for the BID dosing regimen. Although this study was not powered for a comparison between dosing schedules, the BID and QD schedules in chronic phase showed no difference in efficacy despite the pharmacodynamic data showing more prolonged BCR-ABL inhibition with the BID regimen.
A review of each subject's dosing and the date a haematologic and cytogenetic response were noted shows that most subjects (9 of 14 with CCyR) in chronic phase CML achieved a CCyR at doses of 100 - 140 mg total daily dose of dasatinib. One subject achieved a CCyR at 50 mg QD of dasatinib who was previously imatinib intolerant. Three subjects achieved a CCyR at 70 - 75 mg total daily dose. No one achieved a CCyR at 15 or 30 mg QD.
CHR was achieved across doses ranging from 15 - 180 mg QD and from 25 - 70 mg BID. In accelerated phase CML, CHR was achieved at all dose levels ranging from 50 - 120 mg BID and CCyR was achieved at the 70 mg BID (1 subject) and 120 mg BID (1 subject) dose levels only. In blast phase CML, CHR and NEL were achieved in all dose levels ranging from 35 - 90 mg BID but in no subject at 120 mg BID. In blast phase CML, CCyR was reported at doses ranging from 50 - 90 mg BID. No CCyR was noted at 35 mg BID, 120 mg BID nor the majority of the 50 mg BID doses.

Although this trial was not designed to determine responses at each dose level and the majority of subjects (40 out of 84) began treatment with dasatinib at a total daily dose of 100 - 140 mg/day, haematologic responses were noted in subjects taking 15 – 180 mg/day and most complete cytogenetic responses occurred in subjects taking dasatinib doses in the 100 - 140 mg/day range, thus, a dose of 70 mg BID was concluded as a reasonable dose for Phase 2 studies.

- Main study(ies)

The claimed efficacy is based upon 6 studies, one Phase 1 and five pivotal Phase 2, in subjects with chronic, accelerated, myeloid blast, and lymphoid blast chronic myeloid leukaemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) resistant or intolerant to imatinib. Safety and efficacy data collected on 481 treated subjects with leukaemia from 5 pivotal Phase 2 studies (CA180005, CA180006, CA180013, CA180015, and CA180017) comprise the primary efficacy and safety analyses for the current application.

Primary Studies Supporting the Safety and Efficacy of Dasatinib in Subjects with CML or Ph+ ALL

Study (Phase)	Population	Accrual Target	CTD Cohort[a]		Total Enrolled[a]
			Enrolled	Treated	
CA180002 (Phase 1)	**Chronic, accelerated, blast phase CML and Ph+ ALL** (IM-R or IM-I)	60 - 100	85	84	92
CA180013 (Phase 2)	**Chronic phase CML** (IM-R or IM-I)	100 IM-R	198	186	424
CA180017 (Phase 2)	**Chronic phase CML**, Randomized, dasatinib vs. imatinib (IM-R or IM-I)	150	36[b]	36[b]	166
CA180005 (Phase 2)	**Accelerated phase CML** (IM-R or IM-I)	60 IM-R	120	107	197
CA180006 (Phase 2)	**Myeloid blast phase CML** (IM-R or IM-I)	60 IM-R	80	74	124
CA180015 (Phase 2)	**Ph+ ALL or lymphoid phase CML** (IM-R or IM-I)	60 IM-R	81	78	101
Total			600	565	1,104

IM-R: imatinib-resistant subjects; IM-I: imatinib-intolerant subjects

[a] Additional subjects were enrolled until other dasatinib studies could be initiated. The total number of enrolled subjects reflects the enrolment number in the interactive voice response system. All treated subjects were counted once. However, some subjects were counted twice in enrolment numbers because disease status necessitated rolling over from one study to a different study.

[b] In CA180017, the first 36 randomized and treated (with dasatinib [N = 22] or imatinib [N = 14]) subjects were included in the interim analysis.

Study CA180013: A Phase 2 Study (open-label) to Determine the Activity of BMS-354825 in Subjects with Chronic Phase Philadelphia Chromosome Positive Chronic Myeloid Leukemia who have Disease that is Resistant to High Dose Imatinib or who are Intolerant of Imatinib

METHODS

Study Participants

Subjects of either gender, at least 18 years of age, who signed informed consent and who have **chronic phase CML** and imatinib resistant/intolerant criteria were included.

Resistance or intolerance to imatinib defined as 1 of the following:

a) developed progressive disease while being treated with imatinib > 600 mg/day with acquired or primary resistance defined as follows:

i) acquired resistance to imatinib. Subjects who achieved MCyR or CHR on imatinib at any dose prior to progression, defined by 1 of the following:
- loss of MCyR: achieved a confirmed MCyR and subsequently no longer met the MCyR criteria, and had a ≥ 30% increase in Ph+ metaphases on 2 cytogenetic analyses performed at least 4 weeks apart while receiving imatinib
- loss of CHR: achieved a confirmed CHR and subsequently no longer met the CHR criteria consistently on all assessments over a consecutive 2 week period while receiving imatinib
- an increasing white-cell count: defined as a doubling of the count from the nadir to more than 20,000 per cubic millimeter or an increase by more than 50,000 per cubic millimeter on 2 occasions at least 2 weeks apart in the subject who had never strictly had a CHR despite receiving maximally tolerated doses of therapy

ii) primary resistance to imatinib. Subjects who never achieved MCyR or CHR at any dose, and met one of the following continuously increasing white blood cell count on at least 2 consecutive evaluations at least 2 weeks apart with the final assessment showing a doubling of WBC from the nadir to ≥ 20,000/mm3 or an absolute increase in WBC by more than 50,000/ mm3 above lowest count after starting imatinib no CHR after 3 months, no cytogenetic response (CyR) after 6 months and no MCyR after 12 months

b) CML with resistance to imatinib ≤ 600 mg/d with genetic mutation in the BCR-ABL gene that was associated with a high level of resistance to imatinib.
(L248V, G250E, Q252H/R, Y253H/F, E255K/V, T315I/D, F317L, H369P/R).

c) intolerant of imatinib at any dose. Subjects intolerant to imatinib 800 mg must have demonstrated progressive disease or lack of CyR at doses ≤ 600 mg. Intolerance was defined as:
i) Grade 3 or greater non-hematologic toxicity that is imatinib-related
ii) Grade 4 hematologic toxicity that is imatinib-related lasting more than 7 days

Subjects were excluded if they suffer from uncontrolled or significant cardiovascular disease, had a history of a significant bleeding disorder unrelated to CML, previous diagnosis of accelerated phase or blast crisis CML or concurrent incurable malignancy other than CML.

Treatments
Dasatinib was administered continuous daily at an oral dose of 70 mg BID. Dose modifications were allowed for management of disease progression or toxicity. Subjects with evidence of disease progression could have their dose increased to 90 mg BID, in the absence of prohibitive toxicity.

Objectives
The primary objective of this study was to estimate the MCyR rate to dasatinib in subjects with chronic phase CML who had disease that was resistant to imatinib.
Secondary objectives were to estimate the MCyR rate in the imatinib-intolerant subjects and to assess the durability of MCyR and time to MCyR in the imatinib-resistant and the imatinib-intolerant groups

Outcomes/endpoints
Determination of cytogenetic response was based on the prevalence of Ph+ metaphases among cells with metaphases in a bone marrow sample. If possible at least 20 metaphases were evaluated, please refer to the following table:

Cytogenetic Response Criteria

	Ph+ Cells in Metaphase in Bone Marrow
Complete Cytogenetic Response (CCyR)[a]	0%
Partial Cytogenetic Response (PCyR)[a]	1% to 35%
Minor Cytogenetic Response	36% to 65%
Minimal Cytogenetic Response	66% to 95%
No Cytogenetic Response	96% to 100%

Source: Appendix 1.1

[a] Major Cytogenetic Response (MCyR) is the combination of CCyR and PCyR.

CHR was defined as:
1) WBC ≤ institutional ULN
2) platelets < 450,000/mm3
3) no blasts or promyelocytes in peripheral blood
4) < 5% myelocytes plus metamyelocytes in peripheral blood
5) peripheral blood basophils < 20%
6) no extramedullary involvement (including no hepatomegaly or splenomegaly).
Response, as defined, must be maintained for at least 4 weeks after first documented. A CHR could begin only 14 days after dosing start date.

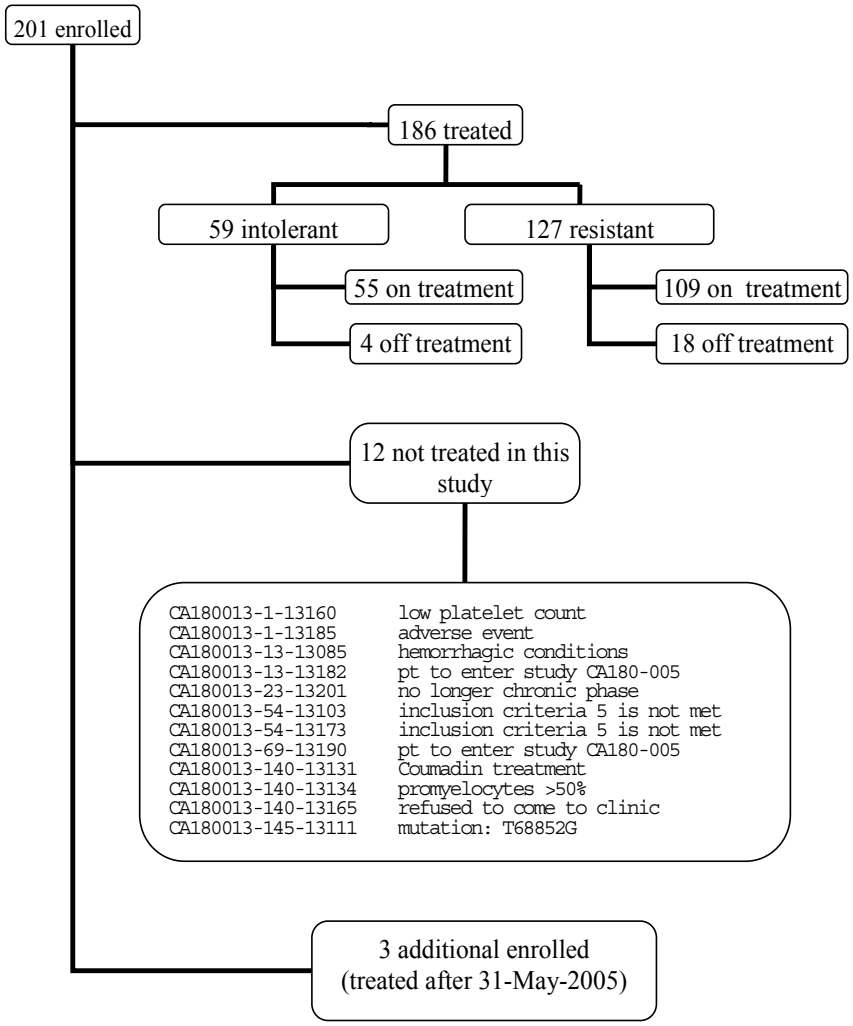
Sample size
With a minimum accrual of 100 imatinib-resistant treated subjects, the maximum width of the exact 2-sided 95% confidence interval (CI) would have been 19% if the MCyR rate was in the expected 5% to 30% range.

Randomisation and Blinding (masking)
Not applicable since this study had an unblinded single-arm design.

Statistical methods
Frequency tables were used to summarize categorical variables. Continuous and other numeric variables were summarized with the number of observations, mean, standard deviation, median, minimum and maximum. Response rates (haematologic and cytogenetic) were estimated along with their 95% exact CIs based on the Clopper-Pearson method. Kaplan-Meier estimates of the median time-to and durations of MCyR and CHR were provided along with their 95% CIs. The Kaplan-Meier estimate of the probability curve was also provided.

RESULTS

Participant flow



Recruitment

The study population for this interim analysis is subjects who were enrolled by 12-May-2005 and received their first dose of study drug by 31-May-2005. A total of 201 subjects were enrolled in the study by May 12, 2005.

Conduct of the study

Major changes incorporated in this amendment were eliminating the possible use of anagrelide in case of thrombocytosis in subjects with CML, as this is not an approved indication for the use of anagrelide in Europe (28-Apr-2005).

Baseline data

The median time from initial diagnosis of CML to first dosing with dasatinib was 64 months (5.3 years, range = 4 to 251 months). Notably, this duration was longer in the imatinib-resistant subjects (median 77 months or 6.4 years, range 4 – 251 months) than the imatinib-intolerant subjects (median 26 months or 2.2 years, range 4 - 145 months).

A majority of imatinib-resistant subjects (72%) had received more than 3 years of prior therapy with imatinib; the highest dose of imatinib was > 600 mg/day in 72% of subjects.

A majority of imatinib-intolerant subjects (54%) had received less than 1 year of prior therapy with imatinib; the highest dose of imatinib was 400-600 mg/day in 92% of subjects.

Fifty-nine subjects in this study were determined to be imatinib-intolerant. The primary reasons included rash, hepatotoxicity, arthralgia, gastrointestinal symptoms, oedema, haematologic toxicity,

and “other”. The “other” reasons included: pulmonary toxicity, fatigue, weight gain, anaphylaxis, and renal failure.

Numbers analysed
All over 186 subjects have been treated. The evaluable for cytogenetic response data set consisted of 169 subjects and for cytogenetic response based on ≥ 20 metaphases consisted of 151 subjects. 226 subjects have been additionally enrolled.

Outcomes and estimation
At a median follow-up of 6 months, the MCyR was 45% (83/186) (*52% in updated analysis at 8 months median follow-up)* in the total population, 31% (40/127) (*39% in update)* in the imatinib-resistant subjects, and 73% (43/59) (*80% in update)* in the imatinib-intolerant subjects.
The median time for imatinib-resistant and imatinib-intolerant subjects to achieve MCyR was 85 days.
The complete haematologic response (CHR) rate was 90% in the total population including 87% in the primary target population of imatinib-resistant subjects and 97% in the imatinib-intolerant subjects.
The median time for imatinib-resistant subjects to achieve CHR was 16 days.

Cytogenetic Response in Chronic Phase CML - Treated Subjects (Study CA180013)

Imatinib Status	**Number of Subjects (%)**		
	Intolerant N = 59	**Resistant N = 127**	**Total N = 186**
Best Cytogenetic Response			
Complete (0%)	33 (55.9)	28 (22.0)	61 (32.8)
Partial (>0% - 35%)	10 (16.9)	12 (9.4)	22 (11.8)
Minor (>35% - 65%)	1 (1.7)	8 (6.3)	9 (4.8)
Minimal (>65% - 95%)	2 (3.4)	17 (13.4)	19 (10.2)
No Response (>95% - 100%)	6 (10.2)	43 (33.9)	49 (26.3)
Unable to determine	7 (11.9)	19 (15.0)	26 (14.0)

A table demonstrating combined efficacy outcomes for all phase II studies is shown under ‘Analysis performed across trials’.

Study CA180017 is an open-label, randomised, non-comparative multicenter study that was conducted in patients who failed initial treatment with 400 or 600 mg imatinib. They were randomised (2:1) to either dasatinib (70 mg BID) or imatinib (400 mg BID). Crossover to the alternative treatment arm was allowed if patients showed evidence of disease progression or intolerance that could not be managed by dose modification. *Updated results are available for 150 patients*: 101 were randomised to SPRYCEL and 49 to imatinib (all imatinib-resistant). The median time from diagnosis to randomisation was 64 months in the dasatinib group and 52 months in the imatinib group. All subjects were extensively pretreated. Prior complete haematologic response (CHR) to imatinib was achieved in 91% of the overall patient population. A prior MCyR to imatinib was achieved in 28% and 29% of the patients in the dasatinib and imatinib arms, respectively.
Median duration of treatment was 5.5 months for dasatinib (with 38% of patients treated for > 6 months to date) and 3.2 months for imatinib (with 6% of patients treated for > 6 months to date). In the dasatinib arm, 92% of patients achieved a CHR prior to cross-over, 82% of the patients in the imatinib arm achieved a CHR prior to cross-over. At a median follow-up of 3 months, a MCyR occurred more often in the dasatinib arm (35%) than in the imatinib arm (29%). Notably, 21% of patients reported a complete cytogenetic response (CCyR) in the dasatinib arm while only 8% achieved a CCyR in the imatinib arm.
A total of 15% of the patients in the dasatinib arm, and 76% in the imatinib arm had treatment failure, defined as disease progression or cross-over to the other treatment (lack of response, study drug intolerance).

Study CA180005: A Phase 2 Study of Dasatinib in Subjects with Accelerated Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

Methods

- Study Participants

Subjects of either gender, at least 18 years of age, who signed informed consent and who suffered from Ph+ (or BCR-ABL) accelerated phase CML and met the imatinib resistant/intolerant criteria, were included.

Primary or acquired hematologic resistance or intolerance to imatinib:

a) hematologic resistance defined as any of the following:

i) initial diagnosis of chronic phase CML that progressed to accelerated phase while on treatment with imatinib ≥ 400 mg/day (primary or acquired resistance)

ii) initial diagnosis of accelerated phase CML and failure to achieve a hematologic response after ≥ 4 weeks (or ≥ 2 weeks for subjects showing rapid disease progression) of imatinib ≥ 600 mg/day; the required prior imatinib dose was 400 to < 600 mg/day if the subject was intolerant to ≥ 600 mg/day (primary resistance)

iii) initial diagnosis of accelerated or blast phase CML that progressed to accelerated phase CML following an initial hematologic response to imatinib ≥ 600 mg/day (acquired resistance). The required prior imatinib dose was 400 to < 600 mg/day if the subject was intolerant of ≥ 600 mg/day

b) imatinib intolerance defined as either:

i) toxicity that was considered at least possibly related to imatinib ≤ 400 mg/day that led to a discontinuation of imatinib therapy

ii) ability to tolerate only < 400 mg/day imatinib. A subject who tolerated 400 mg/day imatinib, but was intolerant of higher doses, was not considered imatinib-tolerant

Similar exclusion criteria as in study **CA180013** were applied please refer to study **CA180013** above**.**

- Treatments

Dasatinib was administered daily at an oral dose of 70 mg BID. Dose modifications were allowed for the management of disease progression or toxicity. Subjects with evidence of disease progression could have their dose increased to 100 mg BID in the absence of prohibitive toxicity.

- **Objectives**

The primary objective of this study was to estimate the major hematologic response (MaHR) and overall hematologic response (OHR) rates to dasatinib in accelerated phase CML subjects with primary or acquired resistance to imatinib.

Secondary Objectives included the assessment of the: durability of hematologic response and time to hematologic response (overall and major) in the imatinib-resistant and imatinib-tolerant groups separately, the cytogenetic and molecular responses in the imatinib-resistant group and the assessment of the hematologic, cytogenetic, and molecular responses in the imatinib-intolerant group.

- **Outcomes/endpoints**

Hematologic Response Criteria

Major Hematologic Response (MaHR)

Complete Hematologic Response (CHR)

1) White blood cell (WBC) ≤ institutional upper limit of normal (ULN)
2) Absolute neutrophil count (ANC) ≥ 1000/mm^3
3) Platelets ≥ 100,000/mm^3
4) No blasts or promyelocytes in peripheral blood
5) Bone marrow blasts ≤ 5%
6) < 5% myelocytes plus metamyelocytes in peripheral blood
7) Peripheral basophils < 20%
8) No extramedullary involvement (including no hepatomegaly or splenomegaly)

No Evidence of Leukemia (NEL)

1) WBC ≤ ULN
2) Bone marrow blasts ≤ 5%
3) No blasts or promyelocytes in peripheral blood
4) < 5% myelocytes plus metamyelocytes in peripheral blood
5) No extramedullary involvement (including no hepatomegaly or splenomegaly)
6) Peripheral basophils < 20% and at least one of the following:
   - 20,000/mm^3 ≤ platelets and < 100,000/mm^3
   - 500/mm^3 ≤ ANC < 1000/mm^3

Minor Hematologic Response (MiHR)

1) < 15% blasts in bone marrow and in peripheral blood
2) < 30% blasts plus promyelocytes in bone marrow and < 30% blasts plus promyelocytes in peripheral blood
3) < 20% basophils in peripheral blood
4) No extramedullary disease other than spleen and liver

Cytogenetic Response Criteria
Similar criteria as in study **CA180013** were applied, please refer to study **CA130013**.

Molecular Response
A major molecular response was defined as the proportion of subjects with a CCyR who achieved a 3-log reduction of BCR-ABL transcripts from a standardized baseline value of BCR-ABL to BCR ratio.

- **Sample size**

With a minimum accrual of 60 treated subjects, the maximum width of the exact 2-sided 95% confidence interval (CI) was 25% when the hematologic response rate was in the expected 5% to 30% range.

- **Randomisation and Blinding (masking)**

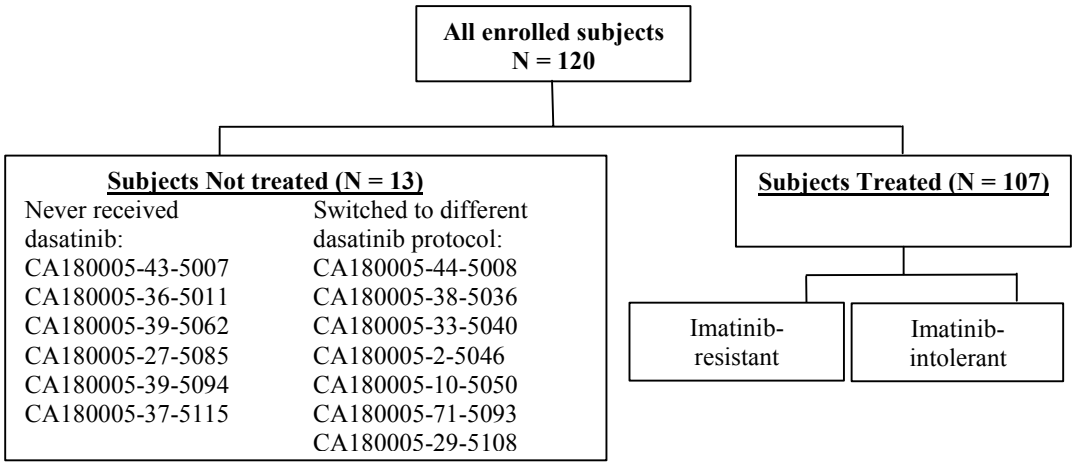
Not applicable since this study had an unblinded single-arm design.

- **Statistical methods**

Similar statistical methods as in study CA180013 were applied please refer to study CA130013.

Results

- *Participant flow*



- *Recruitment*

This study was designed to enroll a minimum of 60 subjects with a history of imatinib-resistant accelerated phase CML. This interim efficacy summary includes results collected on subjects enrolled on or before 12-May-2005 and received the first dose of study drug on or before 22-May-2005 with a data cutoff date of 10-Nov-2005.
As of the data cutoff date for this interim analysis, a total of 120 subjects were enrolled and 107 (99 imatinib-resistant, 8 imatinib-intolerant) received at least 1 dose of dasatinib.

- *Conduct of the study*

A similar amendment regarding the use of anagrelide was made as in study **CA180013.**

On (18-Aug-2005) a modification of the hematologic response criteria has been amanded.
The changes to the hematologic response criteria for advanced subjects introduces the concept of a "major hematologic response." This groups CHR and NEL under 1 general category. This change was introduced to highlight the observation that subjects achieving NEL have a durability of response similar to CHR but may have some degree of neutropenia or thrombocytopenia due to a long history of previous treatments for CML or ALL and thus do not meet the full criteria of CHR. The definition of return to chronic phase was renamed "minor hematologic response" to separate this category from CHR and NEL as the duration of response was expected to be shorter for this cohort.

- *Baseline data*

Gender was well balanced. About 47% of patients had an ECOG performance status of 0, 39% of patients had an ECOG-PS of 1 and 14% ECOG-PS of 2. The distribution of performance status corresponded to the advanced stage of disease compared to chronic CML . The vast majority of patients were of white race. Most patients had been treated with imatinib for more than 3 years (68,2%) and with highest imatinib doses > 600mg daily. Approximately 30% of patients had a MCyR as best cytogenetic response to imatinib. Only 8 patients were defined as Imatinib intolerant.

- *Numbers analysed*

All over 107 subjects have been treated. The evaluable for cytogenetic response data set consisted of 98 subjects and for cytogenetic response based on ≥ 20 metaphases consisted of 85 subjects. 77 subjects have been additionally enrolled.

- *Outcomes and estimation*

After follow-up of ≥ 6 months, the MaHR rate was 59% (63/107) in the total population *(64% in the updated analysis at a median of 8 months follow-up),* 59% (58/99) in the primary target population of imatinib-resistant subjects *(65% in update),*, and 63% (5/8) in imatinib-intolerant subjects *(unchanged*

in update),. The OHR rate was 80% (86/107) in the total population, and 81% (80/99) and 75% (6/8) in imatinib-resistant and imatinib-intolerant subjects, respectively.
The median time for imatinib-resistant subjects to achieve MaHR was 57 days and treatment response seemed to be persistent in the majority of patients. Among the 63 subjects that had achieved MaHR, only 1 imatinib-resistant subject progressed (*In the update 7 out of the 69 imatinib intolerant and imatinib resistant MaHR patients had progressed. The longest duration of MaHR was 12.3+ months).* 8 patients only were defined as imatinib intolerant.

Efficacy Responses in Subjects with Accelerated CML Resistant or Intolerant to Imatinib (Studies CA180005 and CA180002)				
	CA180005			CA180002
	Intolerant N = 8	Resistant N = 99	Total N = 107	Total N = 11
Median Duration of therapy (months)				
All treated subjects	6.0	5.5	5.5	5
Subjects still on treatment	6.4	5.6	5.6	10
Hematologic Response				
OHR (n [%])	6 (75)	80 (81)	86 (80)	6 (55)
MaHR (n [%])	5 (63)	58 (59)	63 (59)	6 (55)
CHR (n [%])	2 (25)	33 (33)	35 (33)	5 (46)
NEL (n [%])	3 (38)	25 (25)	28 (26)	1 (9)
MiHR (n [%])	1 (13)	22 (22)	23 (21)	0
Median time to MaHR (days)	N/A	57.0	57.0	89.5
Cytogenetic Response				
MCyR (n [%])	1 (13)	32 (32)	33 (31)	3 (27)
CCyR (n [%])	0	23 (23)	23 (21)	2 (18)
Duration of Response (months)				
MaHR (range)	1.4 - 8.5	0.9 - 9.5	0.9 - 9.5	1.3 - 11

Secondary outcome. At the time of this analysis, the MCyR was 31% (33/107) in the total population *(33% in update)*, 32% (32/99) in imatinib-resistant subjects (including 23% [23/99] CCyR), and 13% (1/8) in the imatinib-intolerant subjects. Approximately 6% (6/107) of all subjects had minor cytogenetic responses, and 18% (19/107) had minimal cytogenetic responses resulting in an overall cytogenetic response rate of 54% (58/107).

Cytogenetic Response in Accelerated Phase CML - Treated Subjects (Study CA180005)

	All Treated Subjects		
	Number of Subjects (%)		
Imatinib Status	Intolerant N = 8	Resistant N = 99	Total N = 107
Best Cytogenetic Response			
Complete (0%)	0	23 (23.2)	23 (21.5)
Partial (>0% - 35%)	1 (12.5)	9 (9.1	10 (9.3)
Minor (>35% - 65%)	0	6 (6.1)	6 (5.6)
Minimal (>65% - 95%)	3 (37.5)	16 (16.2)	19 (17.8)
No Response (>95% - 100%)	3 (37.5)	34 (34.3)	37 (34.6)
Unable to determine	1 (12.5)	11 (11.1)	12 (11.2)

BCR-ABL mutation analysis:
Out of 107 total enrolled (99 imatinib-resistant, 8 imatinib-intolerant) subjects, 56 (52%) subjects had imatinib-resistant mutations identified at one of 3 central laboratories. Among 56 subjects with mutations, twenty-seven (48%) subjects have mutations located within the P loop of the kinase domain. In addition, 47 (84%) subjects with detectable mutations had a mild to very high level of

imatinib insensitivity. Nine (16%) subjects with detectable mutations had mutations of an unknown sensitivity level

Despite the presence of imatinib-resistant mutations in these subjects with accelerated phase CML, a major hematologic response (MaHR) in 37 (66%) subjects was detected.

Many (18, 67%) of the subjects with mutations within the P loop were able to achieve a MaHR by either achieving a CHR or NEL. Additionally, the majority (30, 64%) of subjects with detectable mutations with mild to very high imatinib insensitivity achieved a MaHR .

A MCyR was also achieved in 17 (30%) subjects with imatinib-resistant mutations. Over a third (6, 35%) of the subjects who achieved a MCyR had detectable mutations within the P loop, and over half (11, 65%) of the subjects who achieved a MCyR had mutations with mild to very high imatinib insensitivity.

Concomitant Therapy

In imatinib-resistant subjects, hydroxyurea use was reported during the study in 17 subjects, and anagrelide use was reported in 4 subjects. These agents were not reported as being used during the study in imatinib-intolerant subjects.

Study CA180006: A Phase 2 Study of Dasatinib in Subjects with Myeloid Blast Phase Chronic Myeloid Leukemia Resistant to or Intolerant of Imatinib Mesylate

Methods

- *Study Participants*

Subjects were enrolled at 35 sites worldwide. Subjects of either gender, at least 18 years of age, who signed informed consent and who suffer from Ph+ (or BCR-ABL+) myeloid blast phase chronic myeloid leukemia whose disease has primary or acquired haematologic resistance to imatinib or who are intolerant of imatinib. Subjects were considered to have myeloid blast phase CML if they met at least 1 of the following criteria:

a) ≥ 30% myeloid blasts in peripheral blood or in bone marrow

b) Extramedullary infiltrates of leukemic cells (other than in spleen or liver) with peripheral blood myeloid blast morphology were included:

Hematologic resistance or intolerance to imatinib was defined as:

a) Hematologic resistance to imatinib defined as any of the following:

i) Subjects initially diagnosed with chronic phase CML who progressed to myeloid phase CML while on treatment with a prescribed imatinib dose of ≥400 mg/day. This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed to myeloid blast phase (acquired resistance).

ii) Subjects initially diagnosed with accelerated phase CML who progressed to myeloid phase CML while on treatment with a prescribed imatinib dose of ≥600 mg/day (or 400 mg to < 600 mg/day if the subject is intolerant of ≥600 mg/day). This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed to myeloid blast phase (acquired resistance).

iii) Subjects initially diagnosed with myeloid blast phase CML who meet the criteria for myeloid phase blast crisis after at least 4 weeks of treatment prescribed at a dose of ≥600 mg/day (or 400 mg to < 600 mg/day if the subject is intolerant of ≥600 mg/day). This 4-week treatment requirement can be shortened to 2 weeks for patients who are rapidly progressing. This includes subjects who had no response to imatinib (primary resistance) and those who responded and subsequently progressed back to myeloid blast phase (acquired resistance).

b) Imatinib intolerance defined as:

i) Toxicity that was considered at least possibly related to imatinib ≤ 400 mg/day that led to a discontinuation of imatinib therapy.

ii) Ability to tolerate only < 400 mg/day imatinib. A subject who tolerated 400 mg/day imatinib, but was intolerant of higher doses was not considered imatinib-intolerant.

Similar exclusion criteria as in study **CA180013** were applied please refer to study **CA180013** above**.**

- *Treatments*

Dasatinib was administered daily at an oral dose of 70 mg BID.
Dose modifications were allowed for the management of disease progression or toxicity. Subjects with evidence of disease progression could have their dose increased to 100 mg BID in the absence of prohibitive toxicity. The following criteria were to be used for dose escalation:
• Rising percent blasts on 2 consecutive haematologic assessments at least 1 week apart
• No CHR within 1 month of starting study therapy
• No CCyR at or after 3 months of study therapy
• Loss of response

- *Objectives*

The primary objective was to estimate the major and overall haematologic response rates to dasatinib in myeloid blast phase CML subjects with primary or acquired resistance to imatinib.
Secondary Objectives included the assessment of: the durability of hematologic response and time to hematologic response (overall and major) in the imatinib-resistant group and imatinib-intolerant groups separately, the cytogenetic and molecular responses in the imatinib-resistant group, the hematologic, cytogenetic, and molecular responses in the imatinib-intolerant group

- *Outcomes/endpoints*

The definition of primary and secondary outcomes are similar to study CA180005, please refer to the definitions presented above.

- *Sample size*

With a minimum accrual of 30 treated subjects in each group, the maximum width of the exact 2-sided 95% confidence interval (CI) was 35% when the hematologic response rate was in the expected 5% to 30% range.

- *Randomisation and Blinding (masking)*

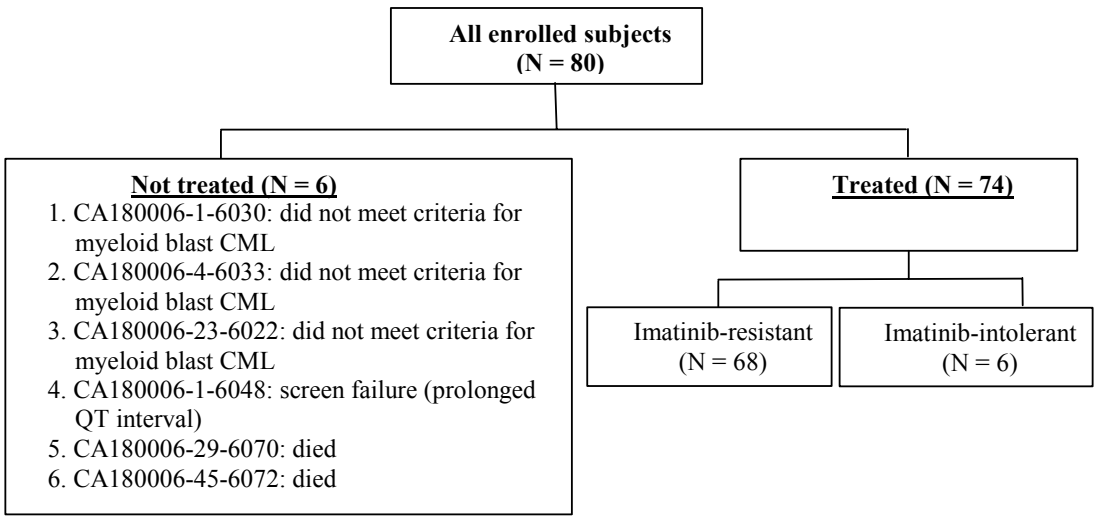
Not applicable, since this study had an unblinded single-arm design.

- *Statistical methods*

Similar statistical methods as in study CA180013 were applied, please refer to study CA130013

Results

- *Participant flow*



- *Recruitment*

The study population for this interim analysis is the first 80 subjects consecutively enrolled up to and including 17-May-2005 and who received the first dose of study drug on or before 18-May-2005.

- *Conduct of the study*

Similar amendments regarding the use of anagrelide and the Modification of the hematologic response criteria were made as in study **CA18005.**

- *Baseline data*

Demographic characteristics of the study population were representative of patients with myeloid blast phase CML. Most subjects in both imatinib-resistant and imatinib-intolerant subsets were between 45 and 65 years of age and 22% were > 65 years. Gender was balanced in this study, patients were predominantly white (76%). 38% of patients had a performance status of 2 at study entry, as defined by the Eastern Cooperative Oncology Group (ECOG).
All subjects had received prior imatinib. Thirty-six (49%) of the subjects had received > 600 mg imatinib daily while the remaining 38 (51%) subjects had received 400-600 mg imatinib daily. Nearly half of the subjects, 35 (47%) had received imatinib for > 3 years, 28 (38%) had received imatinib for 1-3 years, and 11 (15%) had received imatinib for < 1 year.
Twenty-four (32%) subjects, including 22 (32%) imatinib-resistant and 2 (33%) imatinib-intolerant subjects, had CCyR to imatinib.

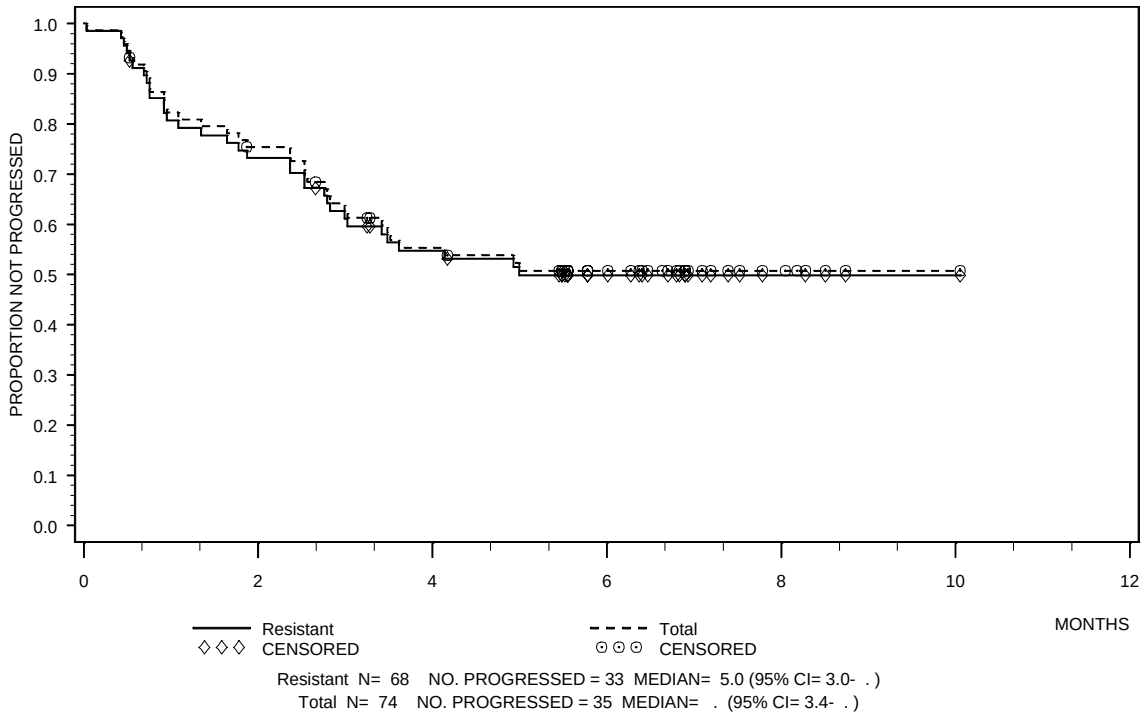
- *Numbers analysed*

All over 74 subjects have been treated. The evaluable for cytogenetic response data set consisted of 71 subjects and for cytogenetic response based on ≥ 20 metaphases consisted of 62 subjects. 44 subjects have been additionally enrolled.

- *Outcomes and estimation*

After follow-up of ≥ 6 months, the MaHR rate was 32% (24/74) *(34% in the updated analysis at a median of 8 months follow-up),* in the total population, 34% (23/68) *(35% in update),* in the primary target population of imatinib-resistant subjects, and 17% (1/7) *(unchanged in update),* in imatinib-intolerant subjects.
The median time for imatinib-resistant subjects to achieve any haematologic response was 30 days. None of the 24 subjects who had achieved MaHR had progressed *(Update: Among 25 MaHR patients 3 progressed. The longest duration of MaHR was 9.9+ months).*

Progression-Free Survival (Study CA180006)



The MCyR rate was 30% (22/74) *(31% in update),* in the total population, 29% (20/68) *(31% in update)* in imatinib-resistant subjects, and 33% (2/6) for imatinib-intolerant subjects *(unchanged in update).*
Approximately 3% (2/74) of all subjects had minor cytogenetic responses, and 10% (7/74) had minimal cytogenetic responses resulting in an OCyR rate of 42% (31/74).

BCR-ABL mutation analysis:
Out of a total of 74 (68 imatinib-resistant, 6 imatinib-intolerant) treated subjects 27 (37%) subjects had imatinib-resistant mutations detected at one of 3 central laboratories.
21 unique imatinib-resistant mutations have been detected, with G250E being the most common one detected in 6 subjects. Among 27 subjects with mutations, over half (15, 56%) of them had mutations located within the P loop of the kinase domain. In addition, the majority (21, 78%) of the subjects had detectable mutations with a mild to very high level of imatinib insensitivity. Six (22%) subjects had detectable mutations of an unknown sensitivity level.
A third (5, 33%) of the subjects with detectable mutations within the P loop were able to achieve a MaHR. Additionally, seven (33%) of the subjects with detectable mutations with mild to very high imatinib insensitivity achieved a MaHR.
A MCyR was also achieved in 6 (22%) of the subjects with detectable imatinib-resistant mutations. Four (67%) of the subjects who achieved a MCyR had detectable mutations within the P loop, and four (67%) of the subjects who achieved a MCyR had detectable mutations with mild to very high imatinib insensitivity.

Concomitant Therapy:
Sixteen subjects received hydroxyurea and 1 subject received anagrelide.

Study CA180015: A Phase 2 Study of Dasatinib in Subjects with Lymphoid Blast Phase Chronic Myeloid Leukemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia Resistant to or Intolerant of Imatinib Mesylate

Methods

- *Study Participants*

Subjects of either gender, at least 18 years of age, who signed informed consent and met the following imatinib-resistant/intolerant disease criteria were included.
1) Subjects with Ph+ (or BCR-ABL+) lymphoid blast phase CML whose disease had primary or acquired resistance to imatinib or who were intolerant of imatinib.
2) Subjects with Ph+ ALL previously treated with standard induction or consolidation chemo therapy *and* who had progression or lack of response to imatinib at a dose of ≥ 600 mg/day (or 400 mg/day to < 600 mg/day if the subject was intolerant of 600 mg/day) after 4 weeks.

Imatinib intolerance was defined as:
Subjects with lymphoid blast phase CML or with Ph+ ALL, with a toxicity considered at least possibly related to imatinib at a dose of 400 mg/ day or lower that led to a discontinuation of therapy.
Note: Subjects were to have had prior exposure to imatinib as defined above. However, imatinib did not need to be their most recent CML treatment prior to coming on this study
Note: A subject who tolerated a dose of imatinib 400 mg/day but was intolerant of higher doses was not considered imatinib-intolerant.

Similar exclusion criteria as in study CA180013 were applied, please refer to study CA180013 above.

- *Treatments*

Dasatinib was administered daily at an oral dose of 70 mg BID. Dose modifications were allowed for the management of disease progression or toxicity. Subjects with evidence of disease progression could have their dose increased to 100 mg BID in the absence of prohibitive toxicity.

- *Objectives*

The primary objective of this study was to estimate the major haematologic response (MaHR) rate and overall haematologic response (OHR) rate to dasatinib in lymphoid blast phase CML subjects and Ph+ ALL subjects with primary or acquired resistance to imatinib.
Secondary Objectives included the assessment of: the durability of hematologic response and time to hematologic response (overall and major) in the imatinib-resistant group, the cytogenetic and molecular responses in the imatinib-resistant group, the hematologic, cytogenetic, and molecular responses in the imatinib-intolerant group

- *Outcomes/endpoints*

The definition of primary and secondary outcomes are similar to study **CA180005,** please refer to the definitions presented above.

- *Sample size*

With a minimum accrual of 30 treated subjects in each group, the maximum width of the exact 2-sided 95% confidence interval (CI) was 35% when the hematologic response rate was in the expected 5% to 30% range.

- *Randomisation and Blinding (masking)*

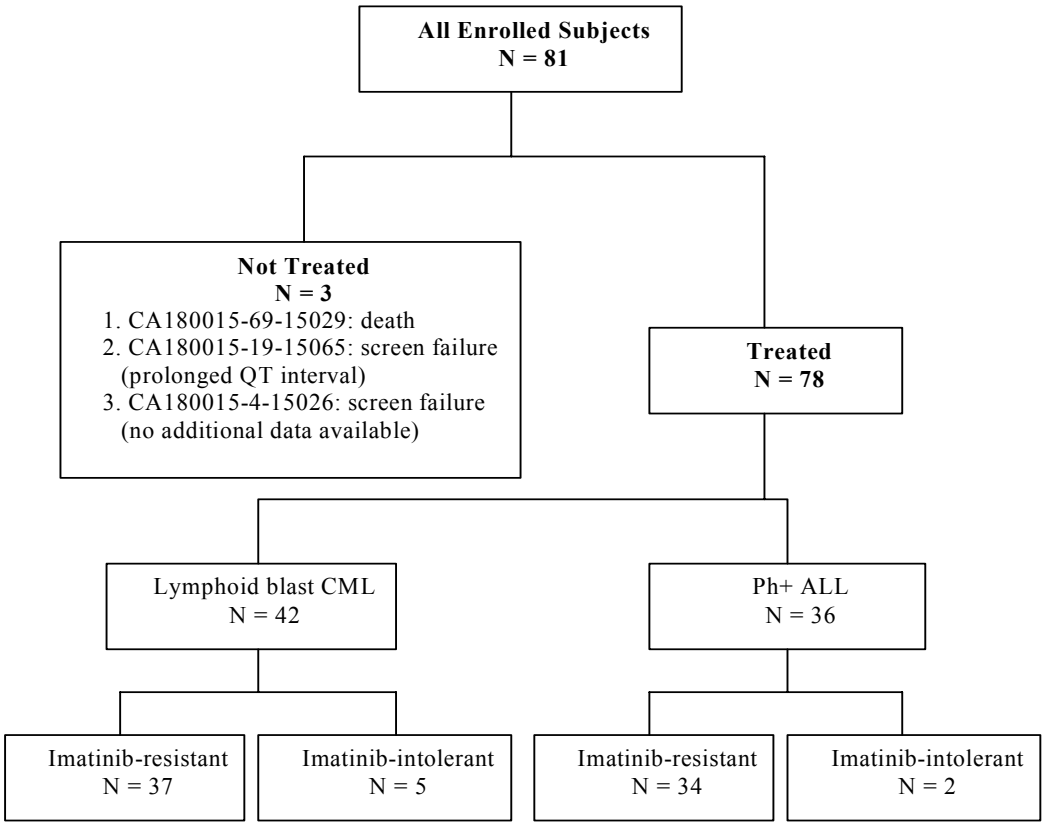
Not applicable, since this study had an unblinded single-arm design.

- *Statistical methods*

Similar statistical methods as in study CA180013 were applied, please refer to study CA130013.

Results

- *Participant flow*



- *Recruitment*

As of the enrollment cutoff date, the first 81 subjects had been enrolled and 78 had received at least 1 dose of dasatinib (42 lymphoid blast CML subjects and 36 Ph+ ALL subjects). Three subjects were enrolled but not treated.

- *Conduct of the study*

Similar amendments regarding the use of anagrelide and the modification of the hematologic response criteria were made as in study **CA18005.**

- *Baseline data*

History of Lymphoid Blast CML and Ph+ ALL

The median time from initial diagnosis to the start of dosing was 28 months for lymphoid blast CML subjects and 20 months for Ph+ ALL subjects. The most common previous therapies received by the subjects in lymphoid blast CML subjects included chemotherapy (79%), interferon (48%), bone marrow transplant (33%), and radiotherapy (19%); and in Ph+ ALL subjects, chemotherapy (92%), bone marrow transplant (42%), radiotherapy (33%), and interferon (8%). The 3 most commonly used prior chemotherapies other than imatinib in lymphoid blast CML subjects were hydroxyurea (79%), vincristine (60%), and cytarabine (50%); in Ph+ ALL subjects they were vincristine (75%), cytarabine (75%), and methotrexate (72%).

Prior Imatinib Therapy

Twentynine percent of lymphoid blast CML subjects and 53% of Ph+ ALL subjects received imatinib for 1 to 3 years. Approximately 50% of the subjects (52% lymphoid blast CML subjects and 47% Ph+ ALL subjects) had received an imatinib dosage > 600 mg/day. In the lymphoid blast CML population, CHR and CCyR to imatinib were reported in 67% and 33% of subjects, respectively; while in the Ph+ ALL population, CHR and CCyR to imatinib were reported in 75% and 42% of subjects, respectively.

Patients with Lymphoid Blast CML had a mean age of 47 years (range 19-72) and patients with Ph+ ALL a mean age of 48 (range 15-85). Subjects treated in this study were mostly male and the vast majority were white (>95%). 17% of Lymphoid Blast CML patients had a performance status of 2 at study entry compared to 31% of Ph+ ALL patients.

- *Numbers analysed*

All over 78 subjects have been treated. The evaluable for cytogenetic response data set consisted of 78 subjects and for cytogenetic response based on ≥ 20 metaphases consisted of 75 subjects. 20 subjects have been additionally enrolled.

- *Outcomes and estimation*

35 (83.3%) subjects with lymphoid blast CML, including 30 that were imatinib-resistant and 5 that were imatinib-intolerant, have discontinued dasatinib at the time of the 6-months interim analysis. The median duration of therapy is 2.8 months (range 0.1 - 6.4 months) for all treated subjects and 25 weeks (range 23.0 - 29.0 weeks) for all treated subjects still on study. Eighty-six percent of all lymphoid blast subjects still on study have had ≥ 24 weeks of therapy.
At the time of this analysis, 24 (67%) Ph+ ALL subjects, all of whom were imatinib resistant, have discontinued dasatinib. The median duration of therapy was 3.2 months (range 0.2 - 8.1 months) for all treated subjects and 25 weeks (range 24.0 - 36.0 weeks) for treated subjects still on study. All 12 Ph+ ALL subjects still on study have had ≥ 24 weeks of therapy.

Lymphoid Blast Phase

At the time of the analysis, the MaHR rate was 31% (13/42) in the total population, 32% (12/37) in the primary target population of imatinib-resistant subjects, and 20% (1/5) in imatinib-intolerant subjects. The OHR rate was 36% (15/42) in the total population, and 38% (14/37) and 20% (1/5) in imatinib-resistant and imatinib-intolerant subjects, respectively.
Among the 13 subjects who had achieved a MaHR, 6 imatinib-resistant subjects had progressed. Subject CA180015-2-15017 progressed after 3.3 months of therapy, subject CA180015-4-15021 progressed after 1.9 months of therapy, subject CA180015-13-15010 progressed after 1.9 months of therapy, subject CA180015-21-15076 progressed after 3.7 months of therapy, subject CA180015-31-15040 progressed after 2.8 months of therapy, and subject CA180015-39-15050 progressed after 3.5 months of therapy.
No imatinib-intolerant subjects who had achieved a MaHR had progressed. The longest duration of response has been 5.4+ months (imatinib-resistant subject) and the shortest duration of response has been 1.6+ months (imatinib-intolerant subject). The median time for these imatinib-resistant subjects to achieve MaHR was 35 days. In the total subject population, the median PFS was 2.8 months (95% CI: 2.0-4.3)

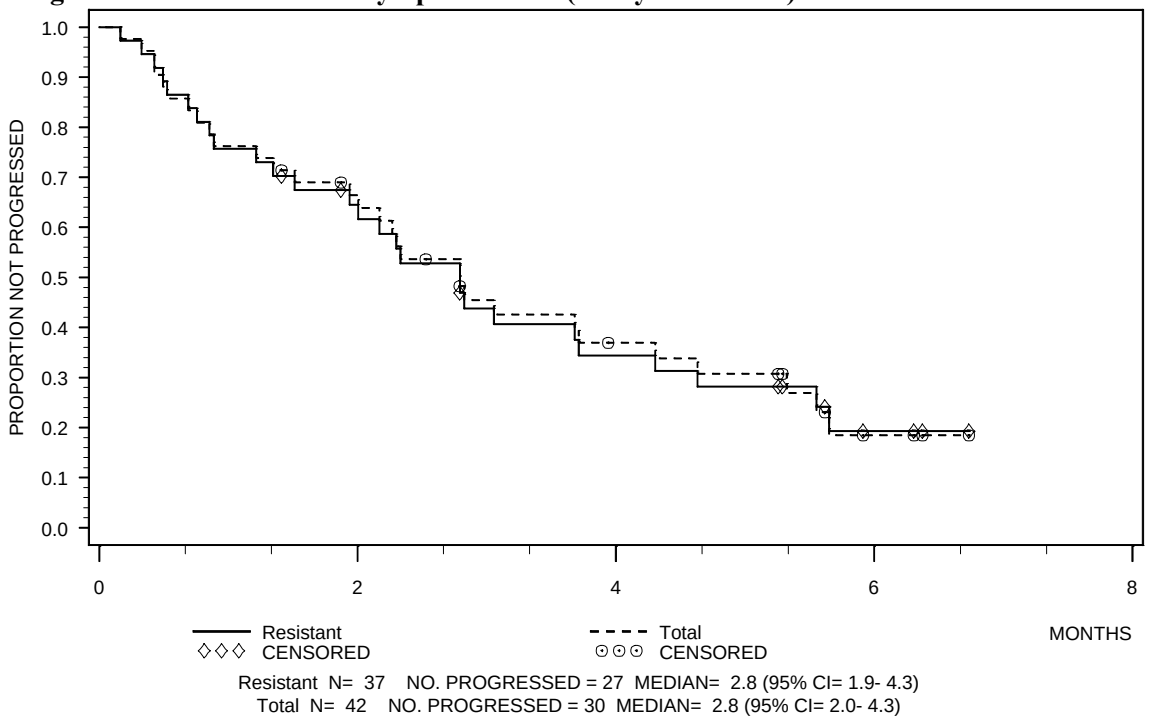
Ph+ ALL

At the time of this analysis, the MaHR rate was 42% (15/36) in the total population, 38% (13/34) in the primary target population of imatinib-resistant subjects, and 100% (2/2) in imatinib-intolerant subjects. In the MaHR group 6/13 and 10/15 remain in remission at the 8.month update does speak in favour of a true clinical benefit.
The OHR rate was 47% (17/36) in the total population, and 44% (15/34) and 100% (2/2) in the imatinib-resistant and imatinib-intolerant subjects, respectively.
At the time of this analysis, among the 15 subjects who had achieved a MaHR, 3 imatinib-resistant subjects had progressed. No imatinib-intolerant subject had progressed.
The longest duration of MaHR has been 5.4+ months (imatinib-resistant subject) and the shortest duration has been 1.9+ months. (*In the 8 month update 7 out of 13 MaHR patients with lymphoid blast crisis had progressed while only 5 out of 15 Ph+ALL responders had progressed).*
The median time for these subjects to achieve MaHR was 57 days.
In the total subject population, the median PFS was 3.3 months (range 1.1-7.2).

Best Confirmed Hematologic Response - Treated Subjects (Study CA180015)

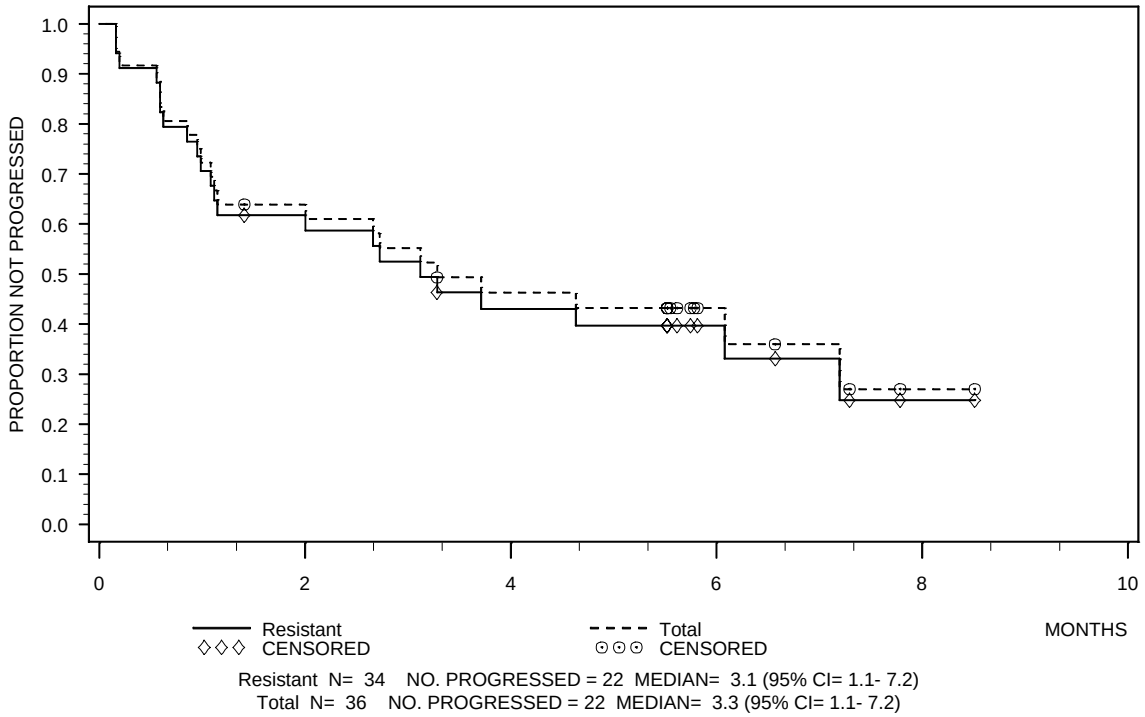
	All Treated Subjects		
	Number of Subjects (%)		
Disease Status: LYMPHOID BLAST	Intolerant N = 5	Resistant N = 37	Total N = 42
Best Hematologic Response			
CHR	1 (20.0)	10 (27.0)	11 (26.2)
NEL	0	2 (5.4)	2 (4.8)
Minor	0	2 (5.4)	2 (4.8)
No Response	4 (80.0)	23 (62.2)	27 (64.3)
Disease Status: PH+ ALL	N = 2	N = 34	N = 36
Best Hematologic Response			
CHR	1 (50.0)	10 (29.4)	11 (30.6)
NEL	1 (50.0)	3 (8.8)	4 (11.1)
Minor	0	2 (5.9	2 (5.6)
No Response	0	19 (55.9)	19 (52.8)

Progression-Free Survival - Lymphoid Blast (Study CA180015)



PROGRAM SOURCE : /wwbdm/clin/proj/ca/180/015/val/stats/SIXMOSXTRA/programs/eff_timeto.sas RUN DATE: 2-Dec-2005 15:35

Progression-Free Survival - Ph+ ALL (Study CA180015)



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Cytogenetic Response

For Lymphoid Blast Phase CML patients the MCyR rate was 50% (21/42) for the total population, 49% (18/37) in imatinib-resistant subjects, and 60% (3/5) for imatinib-intolerant subjects.

For Ph+ ALL patients the MCyR rate was 58% (21/36) for the total population and 56% (19/34) for the imatinib-resistant subjects. Both subjects in the imatinib-intolerant subgroup achieved McyR.

BCR-ABL mutation analysis:

Of the 42 subjects with lymphoid blast CML, 37 are imatinib-resistant and 5 are imatinib-intolerant.

Twenty (48%) subjects had imatinib-resistant mutations detected at one of 3 central laboratories. Of the imatinib resistant subjects, 19 (51%) had detectable mutations versus only 1 (20%) of the imatinib intolerant subjects.

Among the 36 subjects with Ph+ ALL, 34 are imatinib-resistant and 2 are imatinib-intolerant among which 17 (47%) subjects had imatinib-resistant mutations detected. Of the imatinib-resistant subjects, 16 (47%) had detectable mutations, in addition to 1 (50%) of the imatinib-intolerant subjects.

A MaHR was achieved in 6 (30%) of the subjects with lymphoid blast CML and in 7 (41%) of those with Ph+ ALL. Three (33%) of the subjects with lymphoid blast CML and 2 (29%) of the subjects with Ph+ ALL with mutations within the P loop were able to achieve a MaHR. Two (14%) of the subjects with lymphoid blast CML and 5 (36%) of the subjects with Ph+ ALL with detectable mild to very high imatinib insensitive mutations had MaHR.

A MCyR was also achieved in 9 (45%) of the subjects with lymphoid blast CML and in 8 (47%) of the subjects with Ph+ ALL with detectable imatinib-resistant mutations. Nearly half (4, 44%) of the subjects with lymphoid blast CML and 2 (25%) of the subjects with Ph+ ALL who achieved a MCyR had detectable mutations within the P loop.

Concomitant Therapy

1 subject (imatinib-resistant lymphoid blast CML) received anagrelide. Four (10%) lymphoid blast CML subjects (all imatinib-resistant) and 2 Ph+ ALL subjects (both imatinib-resistant) received hydroxyurea. Subjects who required intrathecal chemotherapy during the study period were allowed to continue in the trial and receive dasatinib.

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

Combined efficacy outcomes for all phase II studies are shown in the following table (shaded boxes correspond to the primary outcomes):

Efficacy in Dasatinib Phase 2, Single-arm Studies

	Chronic (N = 186)	Accelerated (N = 107)	Myeloid Blast (N = 74)	Lymphoid Blast (N = 42)	Ph+ ALL (N = 36)
Haematologic Response (%)[a]					
OHR (95% CI)	NA[c]	80 (72 - 87)	53 (41 - 64)	36 (22 - 52)	47 (30 - 65)
MaHR (95% CI)	NA	59 (49 - 68)	32 (22 - 44)	31 (18 - 47)	42 (26 - 59)
CHR	90	33	24	26	31
NEL	NA	26	8	5	11
MiHR (95% CI)	NA	21 (14 - 31)	20 (12 - 31)	5 (0.6 - 16)	6 (0.7 - 19)
Cytogenetic Response (%)[b]					
MCyR (95% CI)	45 (37 - 52)	31 (22 - 41)	30 (20 - 42)	50 (34 - 66)	58 (41 - 75)
CCyR	33	21	27	43	58

[a] ≥ 6-month follow-up. Haematologic response criteria (all confirmed responses were maintained at least 4 weeks): **OHR** = MaHR + MiHR; **MaHR** = CHR + NEL; **CHR (chronic):** WBC ≤ institutional ULN, platelets < 450,000/mm^3, no blasts or promyelocytes in PB, < 5% myelocytes plus metamyelocytes in PB, peripheral basophils < 20%, and no extramedullary involvement; **CHR (advanced):** WBC ≤ institutional ULN, ANC ≥ 1000/mm^3, platelets ≥ 100,000/mm^3, no blasts or promyelocytes in PB, bone marrow (BM) blasts ≤ 5%, <5% myelocytes plus metamyelocytes in PB, peripheral basophils < 20%, and no extramedullary involvement; **NEL**: same criteria as for CHR but 500/mm^3 ≤ ANC <1000/mm^3, and/or 20,000/mm^3 ≤ platelets < 100,000/mm^3; **MiHR**: < 15% blasts in BM and in PB, < 30% blasts plus promyelocytes in BM and < 30% blasts plus promyelocytes in PB, < 20% basophils in PB, and no extramedullary disease other than spleen and liver. Shaded boxes = primary endpoints

[b] ≥ 6-month follow-up. Cytogenetic response criteria: **CCyR** (0% Ph+ metaphases) or PCyR (> 0 % - 35%). **MCyR** = CCyR + PCyR. **Shaded boxes = primary endpoints**

[c] NA: not applicable

- Clinical studies in special populations

Not performed

- Supportive study(ies)

Phase I Dose-escalation Study (CA180002) (Please also see under dose response study)
In this study in which subjects had the longest follow-up (up to 19 months, with treatment and follow-up ongoing), none of the chronic or accelerated phase subjects who achieved a MaHR reported disease progression, and 4 of 11 blast phase and Ph+ ALL responders who achieved MaHR experienced disease progression.

Table 4.3.3: CA180002: Efficacy of Dasatinib in All Phases of CML or Ph+ ALL

Phase of Disease (Dose Schedule)	Hematologic response (%)[a]	Cytogenetic response, MCyR (%)	# Responders[b]	# Progressed
Chronic CML (QD)	95	48	20	0
Chronic CML (BID)	89	42	17	0

Table 4.3.3: CA180002: Efficacy of Dasatinib in All Phases of CML or Ph+ ALL

Phase of Disease (Dose Schedule)	Hematologic response (%)[a]	Cytogenetic response, MCyR (%)	# Responders[b]	# Progressed
Accelerated CML (BID)	55	27	6	0
Myeloid blast CML (BID)	30	35	6	1
Lymphoid blast CML/Ph+ ALL (BID)	50	80	5	3

[a] CHR for subjects with chronic CML or MaHR for subjects with advanced stages of CML or Ph+ ALL

[b] Responders with chronic CML have achieved CHR and responders with advanced CML have achieved MaHR.

Source: CA180002 ISR

- Discussion on clinical efficacy

The demonstration of efficacy in 481 subjects with chronic, accelerated, myeloid blast, and lymphoid blast chronic myeloid leukaemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) resistant or intolerant to imatinib is based upon 6 studies, one Phase I and five pivotal Phase II (CA180005, CA180006, CA180013, CA180015, and CA180017).
The efficacy of Sprycel is based on haematological and cytogenetic response rates observed in all phases of CML and in Ph+ ALL. Combined efficacy outcomes for all phase II studies are shown above in the table presented under 'Analysis performed across trials'.
In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in 84 patients and followed for up to 19 months. Responses were durable across all phases of CML and Ph+ ALL.

Clinical safety

The total dasatinib safety cohort discussed in this document represents **511 subjects**, and a breakdown of subjects is presented in the table below. These are the same 6 clinical studies of dasatinib treatment (one Phase 1 and 5 Phase 2 studies), which provide the primary efficacy data.

Dasatinib-treated Subjects Included in Safety Analyses

	Number of Subjects				
Study	**Chronic CML**	**Accelerated CML**	**Myeloid Blast CML**	**Lymphoid Blast CML/Ph+ ALL**	**Total**
CA180002	NA[a]	11	23	10	**44**
CA180005	0	107	0	0	**107**
CA180006	0	0	74	0	**74**
CA180013	186	0	0	0	**186**
CA180015	0	0	0	78	**78**
CA180017	22	0	0	0	**22**
Total	**208**	**118**	**97**	**88**	**511**

- Patient exposure

Of the total number (511) of patients treated in clinical trials with SPRYCEL that received a starting dose of 70 mg BID, 199 (22%) patients were over 65 years of age, while 33 (4%) patients were over 75 years of age.

The majority of subjects (57%; N = 289) had a duration of between 3 and 6 months of treatment. Thirty-two percent (N = 166) were treated for 3 months or less, and 11% (N = 56) were treated for more than 6 months.

- Adverse events

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade, but treatment was discontinued for adverse reactions in 6% of patients in chronic phase CML, 5% in accelerated phase CML, 11% in myeloid blast phase CML, and 6% in lymphoid blast phase CML or Ph+ ALL.
The most frequently reported adverse reactions were fluid retention (including pleural effusion), diarrhoea, skin rash, headache, haemorrhage, fatigue, nausea, and dyspnoea (Table). Drug-related febrile neutropenia was reported in 4% of patients.
Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as "fluid retention". The use of dasatinib is associated with fluid retention with severe cases in 7% of patients. Severe pleural and pericardial effusion were reported in 4% and < 1% of patients, respectively. Severe ascites and generalised oedema were each reported in < 1%. Less than 1% of patients have had severe non-cardiogenic pulmonary oedema. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.
Bleeding drug-related events, ranging from petechiae and epistaxis to severe gastrointestinal haemorrhage and CNS bleeding, were reported in patients taking SPRYCEL. Severe CNS haemorrhage occurred in < 1% of patients; 3 cases were fatal and two of them were associated with CTC grade 4 thrombocytopenia. Severe gastrointestinal haemorrhage occurred in 5% of patients and generally required treatment interruption and transfusions. Other severe haemorrhage occurred in 2% of patients. Most bleeding related events were typically associated with severe thrombocytopenia.
In clinical trials, it was recommended that treatment with imatinib be discontinued at least 7 days before starting treatment with SPRYCEL.

Adverse reactions:
Adverse drug reactions, excluding laboratory abnormalities, that were reported in ≥ 5% of patients in SPRYCEL clinical trials are shown in the following Table. These reactions are presented by system organ class and by frequency. Frequencies are defined as: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to ≤ 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 2 Adverse Drug Reactions (ADR) reported ≥ 5% in clinical trials

	All Patients(n=911) Percent (%) of Patients	
	All Grades	**Grades 3/4**
Infections and infestations		
Common: infection (including bacterial, viral, fungal, non-specific)	8	2
Metabolism and nutrition disorders		
Very common: anorexia	11	<1
Nervous system disorders		
Very common: headache	24	1
Common: dizziness,	6	<1
neuropathy (including peripheral neuropathy)	5	<1
Vascular disorders		
Very common: haemorrhage,	23	7
▪ *of which*: gastrointestinal bleeding,	8	5
▪ and CNS bleeding	1	<1
Respiratory, thoracic and mediastinal disorders		
Very common: pleural effusion,	19	4
dyspnoea	19	3
Common: cough	8	<1
Gastrointestinal disorders		
Very common: diarrhoea	34	4
nausea	22	1
vomiting	13	1
Common: abdominal pain	<10	<1
abdominal distension,	6	0
mucosal inflammation (including mucositis/stomatitis)	6	<1
Skin and subcutaneous tissue disorders		
Very common: skin rash[b]	24	1
Common: pruritus	7	0
alopecia	5	0
Musculoskeletal and connective tissue disorders		
Very common: musculoskeletal pain	14	1
Common: arthralgia	7	<1
myalgia	6	<1
General disorders and administration site conditions		
Very common: superficial oedema[a]	24	<1
fatigue	23	2
pyrexia	15	2
asthenia	12	2
Common: pain	8	<1

[a] Includes eye oedema, eye swelling, eyelid oedema, orbital oedema, face oedema, periorbital oedema, swelling face, gravitational oedema, localised oedema, oedema peripheral, pitting oedema, oedema genital, scrotal oedema.

[b] Includes erythema, exfoliative rash, generalized erythema, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, systemic lupus erythematosus rash, urticaria vesiculosa, drug eruption, and rash vesicular.

- Serious adverse event/deaths/other significant events

Chronic CML

A total of 3 (1%) deaths were reported in subjects enrolled in CA180013 and CA180017 with chronic CML. All 3 deaths occurred in CA180013. Two subjects died from disease progression and 1 died from a CNS bleed. In CA180002, 1 chronic CML subject died on-study or within 30 days of the last dose of dasatinib, and was attributed to disease progression.

Overall 45 (22%) subjects had SAEs that were considered by the investigator to be at least possibly related to study drug. Thirty-nine (19%) subjects had Grade 3 to 4 SAEs. Respiratory system SAEs made up the largest percent of the drug-related SAEs (8%) and 4% were Grade 3 to 4. Five percent of subjects had drug-related SAEs of pleural effusion (2% severe) within this category. Cardiac disorders made up 7%, with 5% considered severe by the investigator. Gastrointestinal disorder SAEs were 2%, with 1% considered severe by the investigator. Thirty-eight (32%) subjects had Grade 3 to 4 SAEs.

Accelerated CML

A total of 7 (6%) deaths were reported in subjects with accelerated CML. Two subjects died from disease progression as assessed by the investigator. Three deaths were classified as due to infection, 1 was listed as 'other', and the last was reported due to unknown causes; the 1 subject listed as 'other' died from shock. The subject listed as having an unknown cause of death died 30 days beyond the last day of dosing.

Overall, 44 (37%) subjects had SAEs that were considered by the investigator to be at least possibly related to study drug. Thirty-eight (32%) subjects had Grade 3 to 4 SAEs. Gastrointestinal disorder SAEs made up the largest percentage of drug-related nonhematologic SAEs in this group (14%) and 12% were Grade 3 to 4. Diarrhea and gastrointestinal hemorrhage made up the largest number of these events (3% each) with most of them being severe (2% and 3%, respectively). Respiratory system SAEs made up the next largest group of the drug-related SAEs (8%), and 3% were Grade 3 to 4. Most of the respiratory SAEs were pleural effusions (7%), of which most were not severe (2%). Infections and infestations made up another 6% of the drug-related SAEs with all of them considered severe (Grade 3 to 4), with pneumonia taking up the largest number of these (3%).

Myeloid Blast CML

Among 35 deaths listed as 'other', there was a death caused by bacterial sepsis and fungal pneumonia, and 1 caused by sepsis, heart failure, respiratory, and renal failure as well as pancytopenia. A third subject in this group died from a cerebellar hemorrhage, and a fourth subject died from a metastatic solid tumor. The last subject classified as 'other' died from acute respiratory distress syndrome caused by tumor lysis syndrome.

Overall, 37 (38%) subjects had SAEs that were considered by the investigator to be at least possibly related to study drug. Twenty-eight (29%) subjects had Grade 3 to 4 SAEs. Respiratory system SAEs made up the largest percentage of drug-related nonhematologic SAEs in this group (15%) and 8% were Grade 3 to 4. The largest percentage of these were pleural effusions (6%), of which 3% were severe. Gastrointestinal disorder SAEs made up the next largest group of the drug-related SAEs (11%) and 9% were Grade 3 to 4. Gastrointestinal hemorrhage made up the largest number of these events (5%) with most of them being severe (3%). Cardiac disorders made up 4% of the SAEs with 3% being severe. Infections and infestations made up another 4% of the drug-related SAEs with 1 (1%) considered severe.

Lymphoid Blast CML and Ph+ ALL

A total of 35 (40%) deaths were reported in subjects with lymphoid blast CML and Ph+ ALL. The primary reason for death as listed by the investigator was disease progression, which occurred in 16 (18%) of the subjects. In addition, 11 (13%) deaths were due to infection, 3 (3%) were due to fatal bleeding, and 6 (7%) were reported as 'other'. One subject had 2 causes of death listed (disease progression and fatal bleeding). Of the 2 subjects in CA180002 classified as 'other' for cause of death, 1 subject died of a massive brain hemorrhage that occurred beyond 30 days of the last day of dosing and while being treated with another chemotherapeutic agent. The second subject had a relapse of disease with Klebsiella sepsis, respiratory failure, acute renal failure, and disseminated intravascular coagulation. Of the 4 subjects in CA180015 classified as 'other' for cause of death, 1 subject died of hypoxia and a pleural effusion, and another died of constrictive pericarditis. A third subject died of respiratory failure and the fourth had 'damage general status' as described by the investigator.

Overall 30 (34%) subjects had SAEs that were considered by the investigator to be at least possibly related to study drug. Twenty-five (28%) subjects had Grade 3 to 4

SAEs. Gastrointestinal disorder SAEs made up the largest percentage of drug-related nonhematologic SAEs in this group (7%) and all of them were considered severe (Grade 3 to 4). Gastrointestinal hemorrhage made up the largest representative events (2%). Pyrexia was a drug-related SAE in 3% of the cases, but none of them were severe. Respiratory system SAEs made up 5% across all grades, and 3% were Grade 3 to 4. Half of these were pleural effusions (2%), of which 1 was severe. Infections and infestations made up another 3%; all were severe. Pneumonia accounted for 2 of these cases.

- Laboratory findings

The majority of patients in all studies with grade 0 absolute neutrophil counts (ANC) at baseline developed hematological toxicity with increasing severity related to advanced stages of the disease: 40% of patients with chronic CML developed grade 3-4 ANCs, compared to 68% of patients with accelerated CML, 80% of patients with myeloid blast CML, and 67% with lymphoid blast CML/Ph+ALL. The vast majority (>80%) of patients in all studies with grade 1-2 absolute neutrophil counts (ANC) at baseline developed grade 3-4 ANCs.
Similar results were observed regarding thrombocytopenia with the following percentages of patients with grade 0 at baseline developing grade 3-4 toxicities: chronic CML 40%, accelerated CML 71%, myeloid blast CML 59% and lymphoid blast CML/Ph+ALL 33%. The vast majority of patients in all studies with grade 1-2 thrombocytopenia at baseline developed grade 3-4 toxicity. Roughly 50-60% of patients with myeloid blast CML and lymphoid blast CML/Ph+ALL entered the study with a baseline platelet toxicity grade 3-4.
The time to the first occurrence of severe (grade 3-4) neutropenia or thrombocytopenia usually ranged from 0-8 weeks, 25-30% of neutropenias in chronic and accelerated CML were observed after 8 weeks.
Approximately 40-50% of patients had increases of liver enzymes at some time during the study. Depending on the stage of the disease 40-75%% of subjects with no abnormalities at baseline developed some degree of hypocalcemia at least once during the study, none of the subjects developed clinical symptoms, but care should be taken regarding possible interactions with other drugs causing hypocalcemia.

- Safety in special populations

No meaningful differences, regardless of disease phase, in overall incidence of AEs, SAEs, or AEs leading to discontinuation based on age, gender or ECOG performance status were observed.
The majority of subjects with chronic, accelerated, myeloid blast, and lymphoid blast CML and Ph+ ALL were white. Based on the limited number of subjects enrolled in other race categories, no clinically meaningful comparisons can be made based on race.
Of the 59 imatinib-intolerant subjects in study CA180013 (chronic CML), 41 subjects (69%) had no recurrence of the toxicity that caused intolerance to imatinib. Eighteen (31%) subjects experienced toxicities while on treatment with dasatinib that were similar to what they had experienced while receiving prior imatinib. Eight (8) subjects experienced similar non-hematologic toxicities to those reported while on prior imatinib: 3 toxicities of the gastrointestinal system, 1 pulmonary, 2 skin, and 2 general (1 fatigue and 1 severe cramps).
Dasatinib may cause fetal harm when administered to a pregnant woman. It is not known whether dasatinib is excreted in human milk; therefore women who are taking dasatinib should not breast-feed.
The potential effects of dasatinib on sperm have not been studied.

- Safety related to drug-drug interactions and other interactions

Dasatinib is metabolized primarily by CYP3A4 isoenzyme and, based on in vitro cytochrome P-450 [CYP] inhibition studies, is an inhibitor of CYP3A4.
Therefore coadministration of dasatinib with substances that inhibit CYP3A4 activity (eg, ketoconazole, itraconazole, clarithromycin, Retrovir, atazanavir, and lopinavir) may increase dasatinib plasma concentrations. Results of an ongoing study in adult cancer subjects (CA180021) is expected to deliver further information.
Since dasatinib is a CYP3A4 substrate, the effect of rifampin, a potent CYP3A4 inducer, on the PK of dasatinib was investigated (CA180032). Marked decreases in exposure parameters were noted when dasatinib was co-administered with rifampin compared with dasatinib given alone. The mean Cmax and AUC of dasatinib were decreased by 81% and 82%, respectively.
Another study investigated the effects of antacid coadministration on the dasatinib PK (CA180020). Concomitant administration of aluminum hydroxide or magnesium hydroxide products resulted in a

55% reduction in dasatinib AUC, and a 58% reduction in Cmax. Dasatinib may be administered with OTC antacids (aluminum hydroxide or magnesium hydroxide products) if the doses are temporally separated by at least 2 hours.
Exposure to dasatinib was decreased when administered up to 10 hours following famotidine (CA180020). Area under the curve and Cmax were reduced by 61% and 63%, respectively. Thus, administration of dasatinib with drugs that reduce gastric acid secretion (eg, famotidine, omeprazole) are likely to reduce dasatinib exposure.
Since dasatinib is a potential inhibitor of CYP3A4, the effect of dasatinib on the PK of simvastatin, a CYP3A4 substrate, was investigated (CA180022). The results of this study indicate that simvastatin exposure is increased when it is administered in combination with dasatinib; Cmax and AUC were increased by 36.9% and 19.8%, respectively. Therefore, caution is warranted when dasatinib is administered with CYP3A4 substrates with a narrow therapeutic margin (eg, cyclosporine).
Dasatinib does not inhibit the following cytochrome P450 enzymes in vitro: CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, and CYP2E1.

- Discontinuation due to adverse events

In study180002 (phase I) of the 34 subjects who discontinued, 10 subjects (6 myeloid blast, 4 lymphoid blast/Ph+ ALL, respectively) reported adverse events that led to discontinuation. However, for all of these 10 subjects, the reported reason for study discontinuation was: disease progression (8 subjects), rapid progression of solid cancer (1 subject) or resistant mutation. In all cases, the adverse events that led to discontinuation were considered by the investigator as unrelated to dasatinib.
In study CA180013 (chronic CML) thirteen (7%) subjects discontinued study drug (10 imatinib-resistant and 3 imatinib-intolerant) because of AEs of moderate to severe intensity:
-Grade 2 events in 4 cases: (i) neuropathy, (ii) QTc prolongation, (iii) pulmonary edema, and (iv) atrial fibrillation
-Grade 3 events in 5 cases: (i) left ventricular diastolic dysfunction, (ii) bone pain, (iii) pyoderma gangrenosum, (iv) erythema, and (v) pneumonia
-Grade 4 in 2 cases: (i) rhabdomyolysis, and (ii) thrombocytopenia
-Grade 5 (or death) in 2 cases: (i) CNS hemorrhage, and (ii) severe renal failure.
Most discontinuations (10 subjects, 5%) were considered by the investigator(s) to be certainly, possibly, or probably related to dasatinib.
In study CA180005 (accelerated CML) five imatinib-resistant subjects experienced AEs that led to discontinuation. One subject died (sudden death due to shock), which was considered by the investigator as not related to dasatinib. Two subjects discontinued due to progressive disease, both considered not related to study treatment; 1 subject due to dyspnea and 1 subject due to pulmonary embolism, both designated as not likely related to study treatment. One additional subject discontinued 30 days after the last dose of study therapy due to gastrointestinal hemorrhage, which was considered probably related to study treatment.
In study CA180006 (myeloid blast CML) twenty (27%) subjects experienced adverse events which led to discontinuation. Most AEs that led to discontinuation were Grades 3 to 5. The most common AE leading to medication discontinuation was disease progression. Dasatinib-related AEs led to discontinuation in 4 subjects. Three of these subjects had "study drug toxicity" as a reason for discontinuation on the End of Treatment CRF. One had "disease progression" as the reason for discontinuing.
In study CA180015 (Lymphoid Blast CML and Ph+ ALL) adverse events leading to discontinuation regardless of causality occurred in 32 (36%) subjects with lymphoid blast CML or Ph+ ALL. Most AEs that led to discontinuation were Grade 3 or greater. The most common AEs leading to treatment discontinuation were worsening of disease and blast crisis. All other AEs leading to discontinuation occurred in no more than 2% of subjects.
Among all subjects with AEs leading to discontinuation, an attribution of a potential drug relationship occurred in a total of 3 (3%) subjects. One subject discontinued because of severe dyspnea, another discontinued because of a severe lung infiltrates, and the last subject discontinued with a severe rash and an exanthema.

- Post marketing experience

N/A

- Discussion on clinical safety

The most frequently reported (≥ 10%) non hematologic AEs included gastrointestinal AEs (diarrhea [32%], nausea [19%], and vomiting [13%]), fluid retention events (peripheral edema [15%] and pleural effusion [14%]), headache (23%), fatigue (18%), asthenia (14%), rash (14%), dyspnea (14%), and pyrexia (13%). The majority of adverse events were considered to be drug-related (roughly 50-90%), except for adverse events leading to drug discontinuations (roughly 0-25% considered as drug-related), where there was a notable difference.

Important identified risks are toxicity regarding the gastrointestinal system and fluid retention. Approximately 14% of subjects in the dasatinib program experienced a pleural effusion considered related to dasatinib. Fluid retention seems usually manageable.

Hemorrhage occurred in one-third of subjects treated with dasatinib, the majority of the events were manageable.

Important missing information is long-term safety data on the treatment with dasatinib.

One out of 71 deaths in study CA180006 and CA180015 was considered to be caused by study drug toxicity. The number of deaths due to study drugs toxicity seems to be underestimated taking the toxicity of dasatinib into consideration (e.g. neutropenia, thrombocytopenia).

The majority of the SAEs were related to the respiratory system (5-15%), gastrointestinal disorders (2-14%) and cardiac disorders (1- 7%). A general pattern of SAEs depending on the stage of the disease was not identified.

The majority of patients in all studies with grade 0 absolute neutrophil counts (ANC) at baseline developed hematological toxicity with increasing severity related to advanced stages of the disease.

Similar results were observed regarding thrombocytopenia of patients with grade 0 at baseline developing grade 3-4 toxicities

The time to the first occurrence of severe (grade 3-4) neutropenia or thrombocytopenia usually ranged from 0-8 weeks, 25-30% of neutropenias in chronic and accelerated CML were observed after 8 weeks.

Overall toxicity to dasatinib is rated to be manageable. Considerable toxicity has been observed regarding cytopenia (neutropenia, thrombocytopenia) and fluid retention.

Concomitant use of dasatinib and medicinal products that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, telithromycin) may increase exposure to dasatinib. Therefore, in patients receiving SPRYCEL, coadministration of a potent CYP3A4 inhibitor is not recommended.

Concomitant use of dasatinib and medicinal products that induce CYP3A4 (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or *Hypericum perforatum*, also known as St. John's Wort) may substantially reduce exposure to dasatinib, potentially increasing the risk of therapeutic failure. Therefore, in patients receiving SPRYCEL, coadministration of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section 4.5).

Concomitant use of dasatinib and a CYP3A4 substrate may increase exposure to the CYP3A4 substrate. Therefore, caution is warranted when SPRYCEL is coadministered with CYP3A4 substrates of narrow therapeutic index, such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine)

The concomitant use of dasatinib and a H_2 blocker (e.g. famotidine), proton pump inhibitor (e.g. omeprazole), or aluminium hydroxide/magnesium hydroxide may reduce the exposure to dasatinib. Thus, H_2 blockers and proton pump inhibitors are not recommended and aluminium hydroxide/magnesium hydroxide products should be administered up to 2 hours prior to, or 2 hours following the administration of dasatinib. These issues are addressed in the SmPC section 4.5.

There are currently no data available from clinical trials with SPRYCEL in patients with moderately to severely impaired liver function. Caution is recommended when administering SPRYCEL to patients with moderate to severe hepatic impairment. This is mentioned in the SPC 4.2.

Hypokalemia or hypomagnesemia should be corrected prior to SPRYCEL administration.

Patients with uncontrolled or significant cardiovascular disease were not included in the clinical studies.

This medicinal product contains 189 mg of lactose in 140 mg daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan
The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety Concerns	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified Risks		
Myelosuppression	• Routine pharmacovigilance as listed in the current RMP • Additional information from ongoing clinical trials	• Warning in section 4.4. of the SPC • Dose adjustment guidelines in section 4.2. of the SPC • Presented as ADRs (e.g., myelosuppression, pancytopenia, neutropenia, febrile neutropenia, thrombocytopenia, anemia, etc.) in section 4.8 of SPC
Fluid Retention	• Routine pharmacovigilance as listed in the current RMP • Additional information from ongoing clinical trials	• Warning in section 4.4. of the SPC • Presented as ADRs (e.g., pleural effusion, ascites, pulmonary edema, pericardial effusion, superficial edema, etc.) in section 4.8 of SPC
Bleeding-related Events	• Routine pharmacovigilance as listed in the current RMP • Additional information from ongoing clinical trials	• Warning in section 4.4. of the SPC • Presented as ADRs (e.g., hemorrhage, petechiae, epistaxis, gastrointestinal hemorrhage, CNS bleeding, etc.) in section 4.8 of SPC • Nonclinical findings in section 5.3
QT Interval Prolongation	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Warning in section 4.4. of the SPC • Presented as Laboratory test abnormalities in section 4.8 of SPC • Nonclinical findings in section 5.3 of SPC
Important Potential Risks		
Severe Hepatotoxicities	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Presented as ADRs (e.g., hepatitis, cholestasis, etc.) and Laboratory test abnormalities (e.g., elevation of transaminases and bilirubin) in section 4.8 of SPC
Photosensitivity	• Routine pharmacovigilance • Additional information from ongoing clinical trials • A in vivo phototoxicity study in mice will be initiated, and a commitment to submit study	• Listed as ADR in section 4.8 of SPC

	reports on this potential risk and update the SPC accordingly by Dec 2008 is included in the letter of undertaking (FUM Module 4 - 2)	
Important Missing Information		
Patients with Moderate to Severe Hepatic Impairment	• Routine pharmacovigilance • Additional information from ongoing clinical trials • A commitment to submit the results of the ongoing hepatic impairment study by Jan 2009 is included in the letter of undertaking (FUM, Clinical 2).	• Warning in section 4.4. of the SPC • Drug use in impaired liver function in section 4.2 of SPC • Presented as ADRs (e.g., hepatitis, cholestasis, etc.) and Laboratory test abnormalities (e.g., elevation of transaminases and bilirubin) in section 4.8 of SPC • Information related to impaired liver function in section 5.2 of SPC
Reproductive and developmental toxicology	• Routine pharmacovigilance • An oral fertility and early embryonic development (Segment 1) study and a pre- and postnatal development (Segment 3) study in rats will be initiated during 3Q2007. The results from these studies will be submitted by Dec 2008 (Segment 1) and Mar 2009 (Segment 3), as stated in the letter of undertaking (FUM Module 4 - 1)	• Potential risk information related to pregnancy in section 4.6 of SPC • Nonclinical findings in section 5.3 of SPC
Carcinogenicity	• Routine pharmacovigilance • Additional information from ongoing clinical trials • A rat carcinogenicity study will be initiated during 2Q2007. The results from these studies will be submitted by Dec 2010, as stated in the letter of undertaking (FUM Module 4 - 3).	• Information related to carcinogenesis in section 5.3 of SPC
Other Potential Concerns		
Drug interactions: dasatinb and potent CYP3A4 inhibitors or CYP3A4 substrates	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Warning in section 4.4. of the SPC • Drug interaction information in section 4.5 of the SPC
Drug interactions: dasatinib and other highly protein-bound medicinal products	• Routine pharmacovigilance • Additional information from ongoing clinical trials	• Drug interaction information in section 4.5 of the SPC

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
There are no unresolved quality issues which may affect the Benefit/Risk balance.

Non-clinical pharmacology and toxicology

With IC_{50} values in the lower nM range, dasatinib is a potent inhibitor of members of five tyrosine kinase families: SRC family kinases (SRC, LCK, YES, FYN), BCR-ABL, KIT, EPHA2 and PDGFβ.
The pharmacokinetics of dasatinib were evaluated in 229 adult healthy subjects and in 84 patients.
Dasatinib is rapidly absorbed in patients following oral administration, with peak concentrations between 0.5-3 hours. Following oral administration, the increase in the mean exposure (AUC_{τ}) is approximately proportional to the dose increment across doses ranging from 25 mg to 120 mg BID.
The gastrointestinal, haematopoietic and lymphoid systems were the major target organs in the repeat-dose toxicity studies. The major dose-limiting event was gastrointestinal toxicity and in the 9-month monkey study, animals were euthanized due to GI toxicity when exposed to clinically relevant dasatinib plasma levels. In rats, mortalities were observed in studies of 4 weeks duration or longer at plasma exposure levels (AUC) four-fold higher than observed in patients (70 mg BID). The predominant causes of death in rats were GI and lymphoid toxicity. Consistent GI findings were dose-related enteropathy, faecal abnormalities, vomiting, distension of the GI tract with gas/fluid/digesta and GI tract haemorrhage
The haematology and clinical chemistry findings suggested inflammation, blood loss, poor food consumption and electrolyte loss. The GI toxicity findings occurred at clinically relevant AUC levels. Bleeding is exacerbated by treatment since dasatinib prolongs bleeding time via an effect on platelet function erythroid toxicity was observed in the form of reduced erythrocytes, haemoglobin and haematocrit counts. Anaemia is a common finding in dasatinib-treated patients. Lymphoid toxicity was observed in the form of lymphoid depletion of the thymus and spleen and an accompanying reduction in thymus and spleen weight. In addition, reductions in plasma lymphocytes and splenic T-cells and B-cells were observed in rats. Hypocellularity of the bone marrow was observed in rats at a dose giving rise to 4 to 6-fold higher AUC values than observed in patients. All dasatinib-related changes were generally reversible in surviving animals except for an increase in kidney mineralization.
Dasatinib was clastogenic in CHO cells. The lowest nonclastogenic concentration of 2.5 μg/mL is approximately 50-fold greater than the maximum plasma concentration (C_{max}) measured in humans given the recommended clinical dose of 70 mg BID. According to ICH S1A, long-term carcinogenicity studies are not required when the life-expectancy in the indicated population is short (i.e. less than 2-3 years). Consequently, the lack of carcinogenicity studies for dasatinib is justified.
Considering the indication the lack of a fertility study is acceptable. Administration of dasatinib to rats during the period of organogenesis induced embryolethality at clinically relevant maternal plasma exposures (AUC). In addition, dasatinib induced foetal skeletal alterations in the absence of maternal toxicity in rats and rabbits at clinically relevant maternal plasma exposures.
The lack of a prenatal and postnatal development study is acceptable when considering the life-threatening indication.
Dasatinib was phototoxic in the neutral red uptake phototoxicity assay and this is stated in the SPC section 5.3. Dasatinib treatment inhibits T-cell activation and proliferation and causes reductions in plasma lymphocytes and splenic T-cells and B-cells. Immunotoxicty studies demonstrated that a threshold exists for the dasatinib-induced immunosuppressive effect but based on the non-clinical studies some immunotoxicity findings are expected in the clinic. Dasatinib inhibited platelet aggregation in human, monkey, and rat platelet-rich plasma *in vitro*. The no-effect concentration of 0.05 μg/mL is equivalent to the plasma C_{max} measured in humans given the clinical dose of 70 mg BID. *In vivo*, dasatinib in rats prolonged cuticle bleeding time, but did not cause spontaneous bleeding.

In accordance with what has been reported for other SRC tyrosine kinase inhibitors, dasatanib potently inhibits osteoclastic bone resorption when tested *in vitro* and *in vivo* at clinically relevant concentrations.

Dasatinib is unlikely to represent a risk to the environment.

Efficacy

The demonstration of efficacy in 481 subjects with chronic, accelerated, myeloid blast, and lymphoid blast chronic myeloid leukaemia (CML) and Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) resistant or intolerant to imatinib is based upon 6 studies, one Phase I and five pivotal Phase II (CA180005, CA180006, CA180013, CA180015, and CA180017).
The efficacy of Sprycel is based on haematological and cytogenetic response rates observed in all phases of CML and in Ph+ ALL. Combined efficacy outcomes for all phase II studies are shown above in the table presented under 'Analysis performed across trials'.
In the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in 84 patients and followed for up to 19 months. Responses were durable across all phases of CML and Ph+ ALL.

Safety

The most frequently reported (≥ 10%) non hematologic AEs included gastrointestinal AEs (diarrhea [32%], nausea [19%], and vomiting [13%]), fluid retention events (peripheral edema [15%] and pleural effusion [14%]), headache (23%), fatigue (18%), asthenia (14%), rash (14%), dyspnea (14%), and pyrexia (13%). The majority of adverse events were considered to be drug-related (roughly 50-90%), except for adverse events leading to drug discontinuations (roughly 0-25% considered as drug-related), where there was a notable difference.
Important identified risks are toxicity regarding the gastrointestinal system and fluid retention. Approximately 14% of subjects in the dasatinib program experienced a pleural effusion considered related to dasatinib. Fluid retention seems usually manageable.
Hemorrhage occurred in one-third of subjects treated with dasatinib, the majority of the events were manageable.
Important missing information is long-term safety data on the treatment with dasatinib.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.
Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Sprycel leaflet passed the European benchmark for usability performance over two rounds of testing.

Risk-benefit assessment

The clinical benefit of Sprycel in the treatment of adult patients with chronic myeloid leukaemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy has been demonstrated in terms of relevant clinical endpoints such as haematological and cytogenetic response rates in patients who had failed or been unable to tolerate prior imatinib therapy. Taking into account the manageable toxicity, the risk-benefit of Sprycel in the claimed indications is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information

Similarity with authorised orphan medicinal products

The Applicant claimed at the time of submission of the application, that SPRYCEL is not similar (as defined in Art. 3 of Commission Regulation (EC) No 847/2000) to the Orphan medicinal product Glivec (imatinib) which is authorised for a condition relating to the proposed therapeutic indication for Sprycel (dasatinib).

The CHMP, having considered the arguments presented by the applicant, the Rapporteurs similarity assessment, and the conclusions of the Quality working Party, concluded that there are substantial differences in the molecular structure of the two active substances.

The CHMP concluded that dasatinib and imatinib are not similar in terms of molecular structural aspects. Both molecular structures contain an N-phenyl-amide, a piperazine ring and a pyrimidin ring, but the interconnections between these moieties do not indicate that the two molecules share a common framework such as structural analogues. Despite the presence of some common structural features, it was concluded that this is not enough to comply with the definition of structural similarity in the legislation. The overall structural differences were regarded as major, not minor.

The CHMP is therefore of the opinion that Sprycel is not similar to Glivec within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Aditionally the Applicant claimed during the evaluation procedure that SPRYCEL is not similar (as defined in Art. 3 of Commission Regulation (EC) No 847/2000) to the authorised Orphan medicinal product Evoltra (clofarabine) , which is authorized for a condition relating to the proposed therapeutic indication for Sprycel (dasatinib). The CHMP, having considered the arguments presented by the applicant, the Rapporteurs assessment, and the conclusions of the Quality working Party, concluded that there are substantial differences in the molecular structure of the two active substances.

The CHMP concluded that dasatinib and clofarabine are not similar in terms of molecular structural aspects since the molecular structural of dasatinib is not similar to clofarabine on the basis of the difference in principal molecular structural features.

The CHMP is therefore of the opinion that Sprycel is not similar to Evoltra within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Sprycel in the treatment of adult patients with chronic myeloid leukaemia (CML) or Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) with resistance or intolerance to prior therapy was favourable and therefore recommended the granting of the marketing authorisation.

In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Sprycel not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Glivec or Evoltra for the same therapeutic indication.