SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Glivec and has been updated until 1 September 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder. CML was the first neoplastic process to be linked to a consistent acquired genetic abnormality, the Philadelphia (Ph) chromosome. The Ph chromosome results from a reciprocal translocation t(9;22) in a haematopoietic stem cell and results in the transfer of the Abelson (abl) oncogene to an area of chromosome 22 termed the breakpoint cluster region (bcr) and creates a fused Bcr-Abl gene. The final product of this genetic rearrangement is an abnormal 210 kDa cytoplasmic fusion protein, or p210BCR-ABL, the oncoprotein responsible for most, if not all, phenotypic abnormalities of chronic phase CML. The Bcr-Abl protein is leukaemogenic because its Abl-derived tyrosine kinase is constitutively activated. Unlike the situation of the normal Abl protein, whose tyrosine kinase activity is tightly regulated, Bcr-Abl transduces signals to various pathways in an autonomous fashion.

The incidence of CML is approximately 1 case per 100.000 persons/year. The median age of patients diagnosed with Ph+ CML is in the range of 55-60 years. CML can occur in children (2%-3% of all childhood leukaemias are CML), but if Ph+, the prognosis for children may be better than that for adults. Median overall survival from diagnosis of CML is 4 to 6 years.

Clinically, CML progresses through distinct phases. From a relatively indolent initial stage (chronic phase), the disease inevitably progresses in a median of 3 to 5 years to an acute leukaemia (blast crisis phase), which is rapidly fatal.

In 40-50% of patients, prior to the onset of the blast crisis phase, an intermediate phase occurs (accelerated phase) and generally lasts less than one year. The criteria to define the transition to accelerated phase are not entirely agreed although the most commonly used (Kantarjian et al, 1998) rely on presence of one or more of the following: cytogenetic clonal progression, blasts greater than 15% in the peripheral blood, > 30% blasts + promyelocytes in the peripheral blood, >20% basophiles in peripheral blood, platelets <100 x 10^9/L (unrelated to therapy).

The only curative treatment of chronic phase CML is bone-marrow transplantation (BMT) but few patients (10-15%) are eligible and there is a high rate of transplants related mortality (20 to 30%). The probability of long-term survival when the BMT is performed in first chronic phase is approximately 60%.

The first line standard treatment of patients who are not candidates for BMT includes interferon-alpha (IFN) alone or in combination with cytosine-arabinoside (Ara-C). IFN is usually associated with a rate of major cytogenetic responses (MCR) of 10% to 38% in comparison with only 0 to 5% with chemotherapy. For IFN, the achievement of cytogenetic response was shown to be associated with improved survival. In patients with a complete haematologic remission, the median time to complete cytogenetic remission is 9 to 18 months, but it may occur after 4 years of therapy. The rates of both haematologic and cytogenetic responses decrease significantly as the time from initial diagnosis to the institution of IFN therapy increases (Kantarjian *et al.*, 1998).

Approximately 20 to 30% of patients stop IFN treatment because of toxicity. Some patients do not respond to IFN and the vast majority ultimately develop resistance. There is no standard definition in the literature of what constitutes “IFN failure”, in spite of some attempts to rationalise the definition (Kantarjian *et al.* 2000). For patients having failed IFN there is no generally accepted standard treatment. Patients are usually managed with hydroxyurea or busulfan. Second line chemotherapy is usually associated with a good level of haematologic control (approximately 50%) of complete haematologic response (CHR) but the rate of cytogenetic responses ranges from 0 to 5%. In these patients, the probability of response to therapy and of surviving decrease with increasing time from

initial diagnosis, regardless of subsequent treatment. The outcome of patients having failed treatment with IFN has been described rarely.

Accelerated phase (AP) CML is usually considered as the first manifestation of resistance to therapy. With IFN the response rate is lower for AP than it is for chronic phase CML although durable responses and suppression of cytogenetic clonal evolution have been reported. The median survival of patients treated with chemotherapy or IFN commonly ranges from 12 to 18 months. Using single-agent or multi-agent chemotherapy, a haematologic response can be achieved in approximately 50% of patients, but is rarely complete and cytogenetic responses are very rare. The results of BMT remain disappointing due to high rate of transplant related mortality and relapse. The introduction of donor leukocyte infusion as a treatment of post-transplant relapse has significantly improved the outcome of these patients.

Blast crisis (BC) is defined as > 30% blasts in the peripheral blood or bone marrow in the presence of fever, malaise and progressive splenomegaly. It occurs approximately 3 to 5 years after the diagnosis of CML and 18 months after the onset of the AP. BC can be either of myeloid or, less commonly, of lymphoid phenotype. It is generally refractory to treatment and median survival is 3-6 months. Only in patients with lymphoblastic crisis (who are infrequent), an improvement of a few months in survival has been observed with combination chemotherapy. Outcome of patients receiving an allogeneic BMT while in overt BC is very poor. These acute leukaemias are highly resistant to currently available cytotoxic therapy, and the results are consistently disappointing: a haematologic response can be achieved in only 20% to 40% (complete: 5% to 30%) of patients. Cytogenetic responses are exceptional. Clinical trials exploring combination chemotherapy or new chemotherapeutic agents such as 5-azacitidine and mitoxantrone alone or in combination have observed a 20% response rate.

Imatinib mesilate

The active substance is the mesylate salt form of imatinib, a phenylaminopyrimidine derivative and is the 4-[(4-methyl-1-piperazinyl) methyl] – N – [4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino]-phenyl]-benzamide methanesulfonic acid salt. It is a white to slightly yellowish crystalline powder and is prepared using a fully synthetic process. During the development the product has been referred to as STI571 (formerly called CGP57148B).

Imatinib has been identified as a tyrosine kinase inhibitor that selectively inhibits the Abl tyrosine kinases, including Bcr-Abl. Proof of concept in the clinical setting was demonstrated by the high response rates seen in a Phase I study. The biochemical mechanism of action was confirmed in the clinic, since phosphorylation of Crkl (a substrate of Bcr-Abl) was decreased in patients undergoing treatment with imatinib.
To investigate CML resistance to STI571, murine and/or human BCR-ABL-positive cell lines resistant to imatinib have been generated. These have shown that the most frequent mechanism of resistance is amplification and over-expression of the BCR-ABL gene although over-expression of the Pgp glycoprotein, the product of the multidrug resistance (MDR) gene, may also contribute to the resistant phenotype. However, imatinib-resistant clones from some cell lines do not show either of these resistance phenotypes, suggesting that resistance to STI571 may evolve by multiple mechanisms. It has been shown that patients in lymphoid BC have a rapid and significant response to treatment with STI571 but relapse after a median time of 10.5 weeks, therefore, it will be important to study the causes of resistance in these primary CML cells, in order to design modifications to the treatment. It is possible that combinations of imatinib with other drugs such as IFN, daunorubicin or Ara-C may be more effective than imatinib alone, as suggested by in vitro studies of cell lines and primary CML cells.

2. Part II. Chemical, pharmaceutical and biological aspects

Composition

The product is presented as hard gelatin capsules available in two strengths, 50 mg & 100 mg. The excipients of the powder mix are crospovidone, cellulose microcrystalline , silica colloidal anhydrous and magnesium stearate. The capsule shell is composed of gelatin, titanium dioxide, iron oxide yellow

& iron oxide red. Capsules are packaged in thermoformed blisters using rigid plastic films of PVC backed with a heat-sealable lacquered aluminium lid foil.

Active substance

Imatinib mesilate INN. The synthesis of imatinib starts with the preparation of two intermediates, and after that, the synthetic process is completed in 4 main steps.

Crude imatinib methanesulfonate is recrystallised from acetone and is sieved to prepare a uniform production batch for further processing. A detailed description of the manufacturing process has been provided and evaluated, including reaction conditions, quantities of raw materials and yields. Four in-process controls for key reactions are described, and satisfactory intermediate specifications and corrective process control actions have been established.

For storage and transport, the bulk drug substance will be packaged in two polyethylene bags and kept in tightly closed containers protected from the light.

Evidence of the chemical structure has been provided in the form of an examination of the route of synthesis, elemental analysis, IR, UV/VIS, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and X-ray crystal diffraction. Imatinib mesilate does not have chiral centres and it is not optically active. The solubility of imatinib mesilate in aqueous solutions depends on pH; at pH 5.8 it is very soluble. It is soluble in polar solvents, but only slightly soluble to insoluble in low polar solvents. The free base has very low solubility in water and in aqueous solutions that are slightly alkaline.

Two different crystalline forms are known - modifications A and B. Both of them are anhydrous polymorphs. Form A has a lower melting enthalpy, which indicates an enantiotropic relationship between both forms. Form B is the stable polymorph at 25ºC and 50ºC. Conversion to modification A does occur, but only at high temperature (175ºC). Both polymorphs show similar aqueous solubility characteristics, and therefore Polymorph B is the form chosen for the manufacturing of the finished product.

Specification

The specification includes limits on the main impurities observed in batches produced by the defined route of synthesis. The impurity limits are qualified with reference to toxicology studies and do not present a problem of safety. The analytical methods used in routine controls are suitably described.

The identity is confirmed by IR spectrum using nujol as dispersion medium, which is suitable to differentiate both crystalline forms. Water is checked by Karl-Fischer method. Clarity and colour of the solution are carried out according to general methods of the Ph.Eur.

Related substances are quantified by HPLC and GC methods. Inorganic impurities are determined by sulphated ash and heavy metals. The heavy metals are checked by IPC-OES method, which is equivalent to atomic emission spectrophotometry.

A HPLC method similar to the related substances method is used in order to determine the content calculated as imatinib, the salt forming agent is determine by potentiometric titration with sodium hydroxide. All method validation studies are in agreement with the current ICH-guideline.

A specification for particle size is also included in order to obtain adequate powder flow properties and homogeneous distribution in the powder blend for encapsulation during processing of the finished product..

Stability

Preliminary investigations have established the main degradation pathways , e.g. oxidation to N-oxide under oxidative stress conditions. Degradation was not observed after storage at high temperatures (100ºC).

Formal stability data of 3 pilot batches, 3 production batches , and 7 batches representative of the material used in pre-clinical and clinical studies, are presented.

Different types of packaging material were used, - one of them is similar to the containers used in the warehouse.

The stability studies have been performed under ICH Q1A conditions and other experimental conditions have been reported. No apparent change of the drug substance quality was observed in these studies. A re-test period of 2 years at 25ºC is proposed when the substance is stored in tight packing protected from light.

Other ingredients

The ingredients in the finished product are of Ph.Eur. specification.. The magnesium stearate is of vegetable origin and in relation to the gelatin, Certification of suitability with the monograph "products with risk of transmitting agents of animal spongiform encephalopaties" of the Ph Eur has been provided. There are no concerns in relation to TSE with any of the ingredients of the product.

Product development and finished product

Imatinib free base was not considered for development as it is practically insoluble in water (0.001 g/100 ml). The mesilate, was selected among various salts as it displays good solid state properties and stability. The B form was selected for further development as it is thermodynamically stable and shows a suitable morphology with respect to flow properties. Form B is not hygroscopic in an environment with a relative humidity up to 90%.and the mesilate is very soluble in water (pH=5.8). The investigation of bioavailability has been conducted by a three treatment randomised crossover study comparing imatinib 400 mg in the form of a hard capsule, 400 mg oral solution and 100mg given as an intravenous injection. An absolute bioavailability of 98.3 % was determined in a study comparing capsules with intravenous injection solution. Moreover, relative bioavalability of the capsules to an oral solution showed that release of the drug substance from the capsules is so rapid that it is not a rate-limiting factor for absorption.

The manufacturing process is a straightforward dry powder mixing, in which, no granulation step is involved. An optimisation of the manufacturing process with respect to the number of blending and sieving steps as well as to blending times, sieves sizes and encapsulation speed has been carried out during development. The process has been successfully scaled up to commercial batch size.

Different sorts of packages were tested during primary stability studies: high density polyethylene bottles (HDPE), PVC with aluminium foil backing blisters, PVC/PE/PVDC with foil backing blisters and full aluminium blisters. Capsules were stable in all packaging materials; neither increase on degradation products nor decrease in active substance were observed. PVC blisters were chosen as packaging material for climatic zones I and II, whereas PVC/PE/PVDC are the intended one form climatic zones III and IV.

Product Specification

An identical specification has been developed for release and end-of- shelflife. Tests include identification, disintegration time, dissolution ($Q \geq 80\%$ in 30 minutes), content uniformity, disintegration products and assay by HPLC (95-105% stated amount per capsule). Control methods have been validated and the specification is considered to be relevant for a product of this type.

Tabulated results of three production-scale 50 mg capsules batches and four production-scale 100 mg batches have been provided and indicate satisfactory compliance with the specification and uniformity of the product.

Stability of the Product

Stability studies have been carried out in a number of packaging materials and configurations. As PVC is the only packaging material proposed in the application, only the batches packaged in this material have been considered for stability evaluation. Others are considered as supportive data, since the packaging material is different as proposed for marketing.

Results of 12 months for all batches in all packaging configurations under 25ºC/ 60% RH and 30ºC/ 70% RH condition and 6 months for batches under accelerated conditions were submitted.

The tests of microbiological quality is performed according to Ph Eur.

The photostability testing were performed by means of exposure of unpacked capsules to light. The characteristics studied are appearance, dissolution rate, assay of active ingredient (HPLC/UV) and determination of degradation products (HPLC/UV). Specifications for all the mentioned tests are the same as at release. The analytical methods are identical to those described and validated for control of the product at release.

Both strengths are chemically stable in all packaging types tested. No significant changes in the content of degradation products and in the assay are produced under any of the storage conditions tested.

All the results are within specifications for physical properties in all batches, and no changes were observed under photostability stress. Supporting data (results from batches packaged in HPDE bottles, PVC/PE/PVDC and Alu-B) comply with all the stated specifications.

In summary, the stability results support the shelflife and storage conditions as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance and product are defined and characterised in an acceptable way, typical for a powder filled hard gelatin capsule. The product has been developed in a rational way and there are no special characteristics which need additional routine control to be imposed, other than those required by the product release specification.

Additional presentations: 100mg and 400mg film-coated tablets

On 11 November 2003, authorisations were granted for two line extensions of Glivec, i.e. 100mg and 400mg film-coated tablets, intended to reduce the daily 'pill burden' imposed on the patient, and intended to eventually replace the capsules. Bioequivalence between the capsule and film-coated tablets was demonstrated, and therefore it was not necessary to change the dosage or clinical use of the product.

3. Part III. Toxico-pharmacological aspects

Pharmacodynamics

Pharmacodynamic studies indicate that imatinib inhibits c-Abl, and Bcr-Abl protein-tyrosine kinases in p210bcr-abl positive myeloid and p185bcr-abl positive lymphoblastic leukaemia cell lines. Imatinib also inhibited Bcr-Abl tyrosine kinase activity in primary leukaemia cells obtained from patients with Ph positive CML and acute lymphoblastic leukaemia (ALL). Imatinib had no effect on Ph chromosome negative ALL and acute myeloid leukaemia (AML) primary blast cells. The *in vivo* antitumour effect of imatinib in nude mice has been studied using the Bcr-Abl positive KU812 cell line originally derived from a CML patient in BC. These results suggest that imatinib can be efficacious in the treatment of patients with CML.

Pharmacokinetics

A pharmacokinetic assessment was conducted from repeat-dose toxicity studies in rats, dogs and monkeys and in a 3-week dose range-finding study for teratogenicity in rabbits and all animals administered imatinib were systemically exposed to the compound. All the metabolites found in humans have been identified in animal species. A slight gender difference was observed in rats and dogs but no gender difference was observed in cynomolgus monkeys. No unexpected accumulation was observed upon repeated dosing in any species tested.

The studies have demonstrated that imatinib is distributed throughout foetuses in rats and rabbits and is excreted into milk and this is also expected to occur in humans. Therefore, adequate information should be included in the SPC regarding these issues.

No *in vivo* interaction study was conducted with drugs that might be co-administered such as hydroxyurea or citarabine but *in vitro* metabolism studies indicated that CYP3A4 is the main human P450 enzyme catalysing the biotransformation of imatinib. Of a panel of potential co-medications (acetaminophen, aciclovir, allopurinol, amphotericin, Ara-C, erythromycin, fluconazole, hydroxyurea, and norfloxacin and penicillin V) erythromycin (IC_{50} 50 μM) and fluconazole (IC_{50} 118 μM) demonstrated inhibition of imatinib metabolism, both of which could have clinical relevance. Although it is possible that no clinically relevant interaction would be expected since therapeutic levels of fluconazole are approximately 8-fold lower than the observed IC_{50}s, however this possibility cannot be discarded in at-risk patients (hepatically impaired patients, for instance.). An interaction with erythromycin cannot be excluded, caused either by metabolic and/or protein binding behaviour, which may also have been underestimated by *in vitro* data.

Imatinib was shown to be a competitive inhibitor of marker substrates for CYP2C9, CYP2D6 and CYP3A4/5. Imatinib-mediated inhibition of metabolism of co-administered drugs is therefore possible if these enzymes are involved, especially exclusively, in their clearance. Likewise, co-administered drugs which can inhibit CYP3A4 might reduce the imatinib clearance and result in an increase in plasma levels. No indication of hepatic enzyme induction by imatinib has been observed in toxicology studies as no mechanistic or *in vitro* studies on this aspect of drug metabolism have been performed.

Toxicology

A single dose intravenous study in rats and several chronic toxicity studies in rats, dogs and monkeys were conducted. In a 39-week study in monkeys treatment-related effects were reported at all dose levels. The NOAEL was not established. Target organs identified in the toxicity studies in the different animal species were bone marrow, lymphoid tissues, testis/ovaries and gastrointestinal tract. It was noted that plasma levels of imatinib in patients given a dose of 800 mg per day, the highest recommended dose, markedly exceed those at the no effect level in the investigated species. Because a safety margin of less than 1 is observed, the risk to humans cannot be discarded. Taking into consideration the severity of the disease to treat, however, the benefit/risk ratio could be considered positive.

The standard battery of genotoxicity studies was conducted and results were negative except for an increase in structural chromosomal aberrations (deletions and exchange figures) in CHO cells at the highest concentration of 125 μg/ml in the presence of rat liver S9. No effects were observed at the lower concentrations. It appears that imatinib is genotoxic *in vitro* only at very high concentrations. Taking into account the negative results in *in vivo* studies and the therapeutic indication proposed, it could be considered that there is no concern in relation to genotoxicity of imatinib.

The Applicant has conducted five reproductive toxicity studies, one of them to study the fertility and early embryonic development in rats and dogs and four studies to assess the embryo-foetal and peri-natal toxicity in rats and rabbits. There was evidence of effects on spermatogenesis in both rats and dogs. An increased post-implantation loss was observed in the rat fertility study with treatment of both males and females, and in the embryotoxicity study with the treatment of females. Consequently imatinib is considered embryotoxic at high doses. Imatinib is also teratogenic in rats. It is recommended that women of childbearing potential should use effective contraceptive measures during the entire treatment period. If treatment is necessary for women who are recently pregnant, they should be informed about the potential risk to the foetus. These issues are addressed in the SPC.

No carcinogenicity study has been conducted. Taking into account the short life-expectancy of patients with the disease for which imatinib is indicated, the lack of such studies can be considered justified.

Based on the submitted data, no adverse environmental effects are predicted from imatinib.

There is no concern in relation to GLP fulfilment

4. Part IV. Clinical Aspects

The clinical development programme has mainly focused on the different stages of CML, including Ph+ ALL or AML. At the time of submission there were several ongoing or planned trials in other types of tumours such as prostate, small cell lung cancer, sarcoma, glioma and gastrointestinal stromal tumors (GIST).

Clinical Pharmacology

Pharmacodynamics

The pharmacodynamics of imatinib were investigated in one dose-finding study (03 001) carried out in adult (>18 years) or paediatric (<18 years) patients with resistance or intolerance to IFN, and Eastern Cooperative Oncology Group (ECOG) Performance Status <3, with Ph+ CML in the chronic phase, acute Ph+ leukaemia including CML in myeloid or lymphoid BC, relapsed/refractory Ph+ ALL or Ph+ AML.

The maximum tolerated dose (MTD) was defined as the dose where 2/6 patients experienced non-haematologic Grade 3/4 study-drug-related toxicity. For the pharmacodynamic activity, relative response as % reduction in WBC after 1 month of treatment was measured (as hyperleukocytosis is a prominent feature of CML, and the normalization of WBC is an important therapeutic goal). The relation of haematologic response to exposure was examined using an E_{max} model.

The study included 84 adult patients with chronic phase CML intolerant to IFN and 59 adult patients with either CML in BC (n=48) or ALL/AML (n=11). The study also included a limited paediatric population (n=6).

The relationship between pharmacodynamics and PK parameters at steady state indicated that, for chronic phase CML, the efficacy of imatinib was related to exposure (expressed as daily dose, AUC, C_{min} or C_{max}, or time above the 1µM plasma level leading to apoptosis *in vitro*), the best fit was obtained with dose, suggesting that outcome might be highly dependent on administered dose for adult CML patients in chronic phase. Simulations of the E_{max} model parameters predict that with a dose of 400 mg daily, 76% of patients are expected to achieve a reduction of WBC count to $<10 \times 10^9$/L. However, for acute patients, it is not possible to observe a relation between dose and WBC counts.

In IFN-intolerant patients with chronic phase CML, CHRs were seen already at 140 mg, and was achieved in 48 of 49 fully assessable patients treated at doses >300 mg. The data show dose-response relationship with a rate of CHR of 39% (11/28) and 98% (48/49) in patients treated at doses below or >300 mg, respectively. In chronic phase patients, a MCR was achieved in 41% of assessable patients and was complete in 18%.

The 59 patients with BC or ALL/AML were treated at doses ranging from 300 to 1000 mg/day. Patients with lymphoid BC and ALL were grouped together as "lymphoid phenotype" acute leukaemias, whereas the patients with AML and the myeloid BC were grouped as acute leukaemias with myeloid phenotype. The overall rate of haematologic response was 70% and 54% in the patients with a lymphoid and a myeloid phenotype, respectively. However, the confirmation of response was not required. Haematologic response was complete in 13% of patients with CML myeloid BC and, in 20% of patients with lymphoid Ph+ acute leukaemias, without an apparent dose-response relationship. Duration of response was shorter in lymphoid phenotypes. A MCR was achieved in 14% of patients (4 out of 28) with a myeloid BC and 30% (3 out of 10) in lymphoid BC.

Safety results showed that 85.7% of patients suffered adverse drug reactions and in 28.6% of patients these were grade 3/4. The most frequent suspected adverse drug reactions were nausea, muscle cramps, oedema, peri-orbital oedema and leg cramps and haematological toxicity such as anaemia, thrombocytopenia and granulocytopenia.

Based on non-haematologic toxicity, an MTD for imatinib as defined in the protocol was not established in chronic phase CML patients. However, even though these events were not dose-limiting, there was a consistent trend for a higher frequency of adverse drug reactions as dose increased. Grade 3/4 granulocytopenia and thrombocytopenia were clearly dose-related with an incidence of 54% and 59%, respectively, at doses >750 mg daily. No clear dose relationship was apparent in patients with BC or other Ph+ acute leukaemias.

Pharmacokinetics

A total of four pharmacokinetics studies were submitted (studies 0107, 0108, 0118 and 0119). Studies 0107 and 0108 were performed to characterise the ADME processes and the absolute and relative

bioavailability of oral imatinib, respectively and both of them were performed in healthy volunteers. Studies 0118 and 0119 were planned as interaction studies. One of them was performed in healthy volunteers and the other one in patients diagnosed with CML. The pharmacokinetic profile of imatinib after single and multiple doses, and the relationship between dose and drug exposure and drug effect were also investigated in the pharmacodynamic study 03 001. The effect of food on bioavailability was examined in 10 patients included in the efficacy and safety trials 0109 and 0110 (phase II). Finally, a population pharmacokinetics approach was applied to data from 491 patients enrolled in the three phase II studies (0102, 0109, and 0110).

ADME

Following oral administration of 200 mg, [^{14}C]imatinib was rapidly absorbed and C_{max} was 1-2 hours after dosing (t_{max}). The extent of absorption was estimated to be approximately 70% of dose.

Regarding metabolism, the major radioactive compound in plasma was STI571, followed by the N-desmethyl metabolite of imatinib CPG 74588, which is the major metabolite *in vitro*, and *in vivo* and has similar potency to imatinib and its AUC was 16% of that for imatinib.

Two thirds (66%) of ^{14}C-$AUC_{(0-48h)}$ were covered by unchanged drug (58%) and the main metabolite CPG 74588 (8%). The remaining one third was accounted for minor unidentified metabolites.

The ^{14}C radioactivity was excreted slowly, mainly in faeces (68%) and to a minor extent in urine (≈10-15%). Excreted radioactivity consisted mainly of unchanged imatinib. The bulk of the dose was recovered within 7 days. Study 0108 was designed as a single dose, open label, 3 period, 3 treatment, randomised, crossover study to investigate the absolute bioavailability of a single oral dose of STI571 400 mg hard gelatine capsule and STI571 400 mg oral solution relative to STI571 up to 100 mg given IV to a total of 17 healthy volunteers. The bioavailability was >97%. The volume of distribution was ≈435 L. At clinically relevant concentrations of imatinib, binding to plasma proteins was approximately 95% on the basis of *in-vitro* experiments, mostly to albumin and α-1-acid glycoprotein, with little binding to lipoproteins. Total plasma clearance was about 14 L/h. With the capsule formulation, the terminal $t_{1/2}$ was approximately 18 hrs, suggesting that once a day dosing, as proposed, is appropriate.

Multiple dose pharmacokinetics

A total of 70 patients diagnosed with CML received single and multiple and escalating doses in the open label study 03 001. Imatinib was rapidly absorbed after oral administration, with C_{max} being reached at about 2-4 hours post dose.

Pharmacokinetics were examined on day 1 (first dose) and day 28 (multiple dose, steady state). At steady state, plasma $AUC_{(0-24)}$ rose 1.5 to 3 fold after multiple dosing on a once daily schedule. Mean $AUC_{(0-24)}$ rose linearly with dose from 25 to 1000 mg for both single and multiple doses. The metabolite CPG 74588 showed the same dose-dependency as STI571, but its $t_{1/2}$ was longer (27-58 hours).

The influence of dosing by body weight or body surface area on plasma AUC showed no reduction in inter-patient variability in AUC, indicating no advantage in normalising the dose of imatinib to match differences in body size. The C_{min} at >400 mg exceeded the minimum concentration leading to cell death *in vitro,* confirming that once daily dosing is adequate for achieving therapeutic levels.

Drug interactions

As *in vitro* studies had shown that imatinib is mainly transformed by CYP3A4 and, in addition, it competitively inhibits CYP2C9, CYP2D6 and CYP3A4/5, two interaction studies were carried out, one with a CYP3A4 inhibitor (ketoconazole) and the other with a substrate (simvastatin).

Fourteen healthy male and female subjects were included in study 0119, a single dose, open label, and randomised crossover design study whose main objective was to assess the effect of the co-administration of ketoconazole on the pharmacokinetics of imatinib.

Following ketoconazole co-administration, the mean imatinib $C_{max,}$ AUC $_{(0-24)}$ and AUC $_{(0-\infty),}$ increased significantly by 26%, 40% and 40%, respectively. There was a statistically significant decrease in CL/F with a mean reduction of 28.6%. Regarding the N-desmethyl metabolite of imatinib CPG 74588, the mean C_{max} and AUC $_{(0-24)}$ decreased significantly by 22.6% and 13% after ketoconazole treatment. The AUC $_{(0-\infty)}$ only decreased by 5% and this decrease was not statistically significant.

Study 0118 is an ongoing open-label, non-randomised one-sequence crossover design study, to investigate the effects of imatinib on the pharmacokinetics of simvastatin (substrate of CYP3A4) in 20 patients with CML. Preliminary results (n=9) showed that imatinib increase the mean Cmax value of simvastatin 2 fold and the $AUC_{(0-\infty)}$ value 3.5 fold compared with simvastatin alone. The mean half life of simvastatine was prolonged from 1.4 h to 3.2 h when co-administered with STI571.

The effect of food on bioavailability was examined at steady state in a cross-over trial in 10 patients (enrolled in study 0109 or study 0110) given 400 mg imatinib under fasted conditions or with a standardised high fat meal. The mean PK parameters indicate that AUC and C_{max} were little affected and the prolongation of t_{max} was small.

Pharmacokinetics in special populations

Specific studies investigating the use of imatinib in special populations have not been carried out.

A population PK approach was applied to data from 491 patients enrolled in the three phase II studies (0102, 0109, and 0110), to search for differences among population sub-groups. Small and clinically irrelevant effects were observed with the co-variates age and body weight and no effects of gender and disease stage were found using a one-compartment model with first order absorption and linear pharmacokinetics. No patient was < 18 years and altered PK in children cannot be excluded.

On the basis of the findings of the ADME study (0107), exposure to imatinib may be expected to increase if liver function is impaired. However, the population pharmacokinetics analysis did not obtain any conclusion about this and no specific studies have been performed in patients with impaired liver function.

Since the kidney is not a major excertion route for imatinib and its metabolites, studies in patients with impaired renal function are not deemed necessary.

Clinical Efficacy

The main clinical efficacy data with imatinib in CML have been obtained from three open-label, non-controlled pivotal phase II studies which recruited a total of 1027 patients in advanced stages of CML or in chronic phase after failure of IFN therapy (0102, 0109, 0110) and from a phase I study (03 001) as reported in Table 1. Among the 1027 CML patients enrolled in the phase II studies, a total of 638 patients were treated with 400 mg and 389 were treated with600 mg. All enrolled patients actually started treatment with imatinib.

Table 1. Clinical Studies for determining efficacy and safety

Study No.	PATIENT POPULATION	Objective	n (total)	Imatinib therapy (daily dose)
03 **001**	1. **CML chronic phase**: IFN-refract/intol	Mult dose tol., dose-finding, PK/PD	84 (2*) 38	25 – 1000 mg (adults) 150 – 425 mg (6 children)
(ph I)	2. **CML myeloid blast crisis**		10	
	3. CML lymphoid blast crisis		1	
	4. Ph+ AML		10 (4*)	
	5. Ph+ ALL		**(149)**	
0102	**CML myeloid blast crisis**:	safety, efficacy, PK		400 mg
(ph II)	a. Previously treated		95	(first 37 patients)
	b. Untreated		165	600 mg
			(260)	(later patients)
0109	1. **CML accelerated phase**	safety, efficacy, PK	235	400 mg
(ph II)	2. CML lymphoid blast crisis		8	(first 87 patients)
	3. Ph+ ALL		48	600 mg
	4. Ph+ AML		2	(later patients)
			(293)	
0110	**CML chronic phase**:	safety, efficacy, PK		400 mg
(ph II)	a. Haematol. Resistant & relapse		152	
	b. Cytogen resistant & relapse		186	
	c. IFN intolerant		194	
			(532)	

* age <18 years

Clinical Efficacy

Endpoints and Methods

Definitions of the phases of CML and efficacy criteria are reported in Table 2. The primary efficacy endpoint in study 0110 was the proportion of patients achieving complete and partial (≤35% Ph+ cells cytogenetic response MCR and was based on cytogenetic analysis. Bone marrow cytogenetic analysis was required at baseline and every three months thereafter to evaluate Ph positivity. Due to the short follow-up, unconfirmed cytogenetic response rate was considered the main outcome although confirmation of response was additionally calculated for study 0110. The rate of unconfirmed MCR was a secondary endpoint in studies 0102, 0109. Haematological response (HR) rate with confirmation after ≥ 4 weeks was the primary endpoint in studies 0102, 0109 and secondary in 0110.

Other secondary efficacy endpoints were time to haematological response and duration of haematologic response defined as time between first documented response, with ≥ 4 week confirmation, and loss of response (any haematologic response criterion no longer fulfilled), progression to AP (study 0110) or BC (studies 0109, 0110), discontinuation due to unsatisfactory therapeutic effect or death, whichever first. Time to MCR was defined as time until first documented MCR and duration of MCR defined as time between first documented major response and loss of cytogenetic response, discontinuation due to unsatisfactory therapeutic effect or death, whichever first. Time to progression was defined as time between start of treatment and loss of haematological response, progression to AP (study 0110) or BC (studies 0109, 0110), discontinuation due to unsatisfactory therapeutic effect or death, whichever first. For study 0110 the definitions above refer to confirmed CHR. Overall survival was defined as time between start of treatment and death).

Time to and duration of response were estimated using the Kaplan-Meier method. Observations were censored at time of discontinuation for patients discontinuing to undergo BMT, at the time of their last bone marrow evaluation date for cytogenetics, as long as there was no evidence of loss of cytogenetic response for patients still on study at the date of cut-off, and at the date of the last bone marrow evaluation if the discontinuation was for reasons other than AE, lab abnormality, unsatisfactory therapeutic effect or death and were followed up for survival.

For studies 0102 and 0109 (but not study 0110) any discontinuation due to AE or lab abnormality was also considered an event in any of the time to event analyses for response duration. Patients who discontinued were declared non-responders at all points after their withdrawal.

The association between response and survival was explored using the landmark method, considering all patients alive and still on study with an assessment performed at 3 months.

Exploratory multivariate analysis of the association between baseline variables and the primary endpoints of each of the studies were performed using logistic regression (5% significance level).

All studies used Fleming's single-stage procedure, using an alpha-level of 2.5% (one-sided) and a power of 90% (H_0: $p \leq p_0$ and H_1: $p \geq p_1$) with p_0 ("uninteresting" response rate) specified to be 15, 30, 10 and 15%, p_1 (response rate which should not be missed) specified to be 30, 50, 20 and 30% and p (the minimum observed response rate such that the lower limit of CI for response rate > p_0) calculated (taking into account actual sample size of 165, 235, 152 and 186) to be 21.2, 36.2, 15.8 and 21.0 for studies 102,109, 110 (haematologically resistant/relapsed group), 110 (cytogenetically resistant/relapsed group), respectively. The main study objectives were considered as met if the lower limit of the exact binomial two-sided 95% CI of response rate exceeded the "uninteresting" response probability. The main analyses on efficacy endpoints were carried out on the intent to treat population (all enrolled patients).

Within each CML phase, different sub-populations were included: patients with chronic phase were grouped according to failure of IFN treatment (haematologic or cytogenetic failure) *versus* IFN-intolerance whilst patients with BC phase were grouped according to previously treated *versus* untreated status.

Table 2. Definitions of the Phases of CML and efficacy criteria (haematologic and cytogenetic response)

Chronic phase (all 5 criteria must be fulfilled): < 15% blasts in PB and BM < 30% blasts+promyelocytes* in PB and BM < 20% basophils in PB ≥ 100 x 10^9/L platelets No extramedullary involvement other than spleen or liver	**Accelerated phase (at least one):** ≥ 15% - < 30% blasts in PB or BM ≥ 30% blasts+promyelocytes* in PB or BM (but < 30% blasts in PB and BM) ≥ 20% basophils in PB < 100 x 10^9/L platelets#	**Blast crisis** (these two evaluations take preference over chronic and accelerated phase results) ≥ 30% blasts in PB or BM, or Extramedullary involvement other than spleen or liver
Cytogenetic response: 0% = complete, > 0 – 35% = partial, > 35 – 65% = minor, > 65 – 95% = minimal, > 95 = none, <20 metaphases were examined and/or response could not be assigned; complete+partial = major **Loss of major cytogenetic response** = ≥ 30% absolute increase in Ph+ cells compared to lowest value during study or an increase to ≥ 65% Ph+ cells **Loss of complete cytogenetic response** = increase to >0 % Ph+ cells after complete response		
Complete haematologic response (CHR): WBC < 10 x 10^9/L Platelets < 450 x 10^9/L Myelocytes + metamyelocytes** < 5% in PB No blasts and promyelocytes** in PB Basophils < 20% No extramedullary involvement **Loss of CHR:** WBC > 20 x 10^9/L or loss of any of the other response criteria or progression to accelerated phase or blast crisis or discontinuation due to progressive disease or death	**Haematologic response (HR)** **Complete haematologic remission (CHR):** < 5% blasts in BM No blasts in PB ANC ≥ 1.5 x 10^9/L and Platelets ≥ 100 x 10^9/L No extramedullary involvement **No evidence of leukaemia (NEL):** As for CHR, but without complete recovery of peripheral blood, i.e. 1.0 ≤ ANC < 1.5 x 109/L and 20 ≤ Platelets < 100 x 109/L **Return to chronic phase (RTC):** < 15% blasts in PB and BM < 30% blasts+promyelocytes* in PB and BM < 20% basophils in PB No extramedullary involvement other than spleen or liver	

Abbreviations: PB, peripheral blood; BM, bone marrow

* As promyelocytes in PB were not recorded separately in the CRF, but rather the sum of early forms (which also included metamyelocytes and myelocytes), the value of early forms was used for these calculations. If this value was not available, the sum was taken to be that given for blasts only.

** The criteria for CHR were considered fulfilled, if the early forms were < 5%.

\# This criterion was not used for progression to accelerated phase in study 0110.

Clinical Efficacy Results

Chronic phase CML resistant or intolerant to IFN (Study 0110)

Patients in chronic phase CML were eligible for this study if they met one of the following criteria for IFN failure: haematologic failure (failure to achieve a CHR after ≥6 months of IFN, or relapse with a rising WBC to ≥20 x10^9/L), cytogenetic failure (failure to achieve a MCR after ≥12 months of IFN, or relapse with a ≥30% increase in the % of Ph+ marrow metaphases to ≥65%), or intolerance to IFN defined as a ≥grade 3 non-haematological IFN-related toxicity persisting for ≥1 month. The primary endpoint of the study was the rate of MCR (see response criteria in the footnote of Table 2). The target response rate of interest was 30% and the rejection rate 15% in patients with cytogenetic failure, and 20% and 10% in patients with haematologic failure, respectively (Fleming's single stage procedure).

In this study, 532 patients were enrolled with either haematologic failure (29%), cytogenetic failure (35%), or intolerance to IFN (36%). These patients had received prior IFN (given alone or in combination with other drugs) at a dose ≥25 MIU/week for a median of 14 months (25^{th}-75^{th}

percentile: 7-27 months). The patient baseline characteristics were typical of pre-treated chronic phase CML (60% of patients had a baseline WBC count <20 x10^9/L, which was <10 x10^9/L in 37%). On the basis of data recorded in the CRF, the diagnosis of chronic phase was confirmed in 454 patients (85%). The remaining patients had features of BC (2%), AP (3%), or had insufficient data to be assigned to a particular disease phase (9%). 40% of the patients were ≥60 years (10% older than 70 years). Patients were late in the course of the disease with a median time from diagnosis of 32 months.

Main study results are reported in Table 3. Unconfirmed MCR rate was 49.4% (CI: 45.1-53.8). Confirmed MCR rate was 38.0% ($CI_{95\%}$ 33.8-42.2). The median time to MCR (overall) was 2.89 months. Follow-up of these patients was short and at cut-off, 10 patients had relapsed at times ranging from 2.8 to 5.8 months. Median duration of MCR had not been achieved for any of the subgroups.

CHR rate was 88.0% ($CI_{95\%}$ 84.9-90.6). Results were similar for the three subgroups based on IFN treatment failure type (Table 4). The duration of CHR for all groups was also similar with over 80% CHR at 6 months.

The estimated 6 and 9-month disease progression-free survival probability was 83.7% and 78.7%, respectively. At cut-off date, 102/532 (19.2%) patients showed evidence of progression with 22 (4.1%) due to unsatisfactory effect, 21 (3.9%) progressed to BC, 18 (3.4%) progressed to AP and 63 (11.8) lost their response (in the absence of progression to AP or BC phase).

At the time of analysis, 98.3 % patients were alive between 3.9-11.4 months, with treatment duration ranging from 0.5-10.5 months. The estimated 9-month survival probability was 98.1% ($CI_{95\%}$ 96.9%-99.3%).

Factors associated with improved cytogenetic response in the multivariate analysis were platelets <450 x10^9/L, WBC<20 x10^9/L, hemoglobin ≥100 g/L, time from diagnosis of CML <2 years and blasts <3%.

Table 3. Cytogenetic response rate (Study 0110)

	Cytogenetic response			
Response	**Unconfirmed response**		**Confirmed response**	
	n (%)	**95 % CI**	**n (%)**	**95 % CI**
All patients n=532				
Major (CR+PR)	263 (49.4%)	45.1 - 53.8	202 (38.0%)	33.8 - 42.2
Complete	160 (30.1%)	26.2 - 34.2	78 (14.7%)	11.8 - 18.0
Partial	103 (19.4%)	16.1 - 23.0	124 (23.3%)	19.8 - 27.1
Minor	30 (5.6%)		32 (6.0%)	
Minimal	63 (11.8%)		38 (7.1%)	
None	121 (22.7%)		111 (20.9%)	
Not done	50 (9.4%)		135 (25.4%)	
Progression	3 (0.6%)		12 (2.3%)	
Ph- at baseline	2 (0.4%)		2 (0.4%)	
Haematologic IFN Failure Subgroup n=152				
Major (CR+PR)	55 (36.2%)	28.6 - 44.4	33 (21.7%)	15.4 - 29.1
Complete	31 (20.4%)	14.3 - 27.7	8 (5.3%)	2.3 - 10.1
Partial	24 (15.8%)	10.4 - 22.6	25 (16.4%)	10.9 - 23.3
Minor	8 (5.3%)		8 (5.3%)	
Minimal	23 (15.1%)		10 (6.6%)	
None	41 (27.0%)		34 (22.4%)	
Not done	21 (13.8%)		61 (40.1%)	
Progression	2 (1.3%)		4 (2.6%)	
Ph- at baseline	2 (1.3%)		2 (1.3%)	
Cytogenetic IFN Failure Subgroup n=186				
Major (CR+PR)	95 (51.1%)	43.7 – 58.5	76 (40.9%)	33.7 - 48.3
Complete	56 (30.1%)	23.6 – 37.2	29 (15.6%)	10.7 - 21.6
Partial	39 (21.0%)	15.4 – 27.5	47 (25.3%)	19.2 - 32.1
Minor	15 (8.1%)		14 (7.5%)	
Minimal	21 (11.3%)		15 (8.1%)	
None	38 (20.4%)		39 (21.0%)	
Not done	16 (8.6%)		40 (21.5%)	
Progression	1 (0.5%)		2 (1.1%)	
Ph- at baseline	0		0	
IFN Intolerant Subgroup n=194				
Major (CR+PR)	113 (58.2%)	51.0 - 65.3	93 (47.9%)	40.7 - 55.2
Complete	73 (37.6%)	30.8 - 44.9	41 (21.1%)	15.6 - 27.6
Partial	40 (20.6%)	15.2 - 27.0	52 (26.8%)	20.7 - 33.6
Minor	7 (3.6%)		10 (5.2%)	
Minimal	19 (9.8%)		13 (6.7%)	
None	42 (21.6%)		38 (19.6%)	
Not done	13 (6.7%)		34 (17.5%)	
Progression	0		6 (3.1%)	
Ph- at baseline	0		0	

Table 4. Study 0110: Haematologic response rate (Study 0110)

	N (%)	95 % CI
All patients (N=532)		
Complete haematologic response	468 (88.0%)	84.9 - 90.6
No response	54 (10.2%)	
Not assessable	10 (1.9%)	
Haematologic IFN-Failures (N=152)		
Complete haematologic response	126 (82.9%)	76.0 - 88.5
No response	22 (14.5%)	
Not assessable	4 (2.6%)	
Cytogenetic IFN-Failures (N=186)		
Complete haematologic response	173 (93.0%)	88.3 - 96.2
No response	12 (6.5%)	
Not assessable	1 (0.5%)	
INF Intolerant (N=194)		
Complete haematologic response	169 (87.1%)	81.6 - 91.5
No response	20 (10.3%)	
Not assessable	5 (2.6%)	

Literature review of efficacy results in chronic phase CML

In view of the current lack of randomised studies in chronic phase CML, historical data from a literature review relative to the management and outcome of patients in chronic phase CML failing IFN therapy have been submitted (Table 5). In patients failing first-line IFN therapy with a median time from initial diagnosis of 10 to 14 months, which is lower that the 32 months in study 0110 (suggesting less advanced disease), overall survival was 53 to 64 months. Due to the fact that no mature survival data were available in study 0110, an indirect comparison of survival imatinib with IFN was not possible.

Table 5. Outcome of chronic phase CML patients failing IFN (literature review)

Study	N	Time from diagnosis (months)	CHR	MCR	Survival (months)
Newly diagnosed CML (hydroxyurea or busulfan)					
Published randomized studies*	952	NA	20-54%	0-5%	NA
Chronic phase, IFN-failure, treated with second-line hydroxyurea or busulfan					
Hehlmann 1994	65	4.9	NA	NA	52.5
Guilhot 1993, Guilhot 1996, Guilhot 1997 (CML 88)	134	12.6	NA	NA	56.1
Guilhot 1997, Guilhot 1999 (CML 91)	541	10.4	NA	NA	63.7
ICSG 1994 and 1998 (Rof/CML)	129	14.2	NA	NA	59.6
Rosti 1999 (CML 94)	240	10.2	NA	NA	55.8
Late chronic phase, treated with various second-line therapies					
Rodriguez 1998	257	30.4	NA	NA	43
Sacchi 1997	137	30.5	57%	8%	49

* Hehlmann 1994, Onishi 1995, ICSG 1994, Benelux 1998, Allan 1995,

Abbreviations: NA: not available/applicable, CHR complete haematologic response, MCR major cytogenetic response

Accelerated Phase CML (Study 0109)

Entry criteria for this study were designed to include patients aged >18 years with histologically confirmed Ph+ leukaemia of either AP CML, or relapsed/refractory ALL or AML, or CML in LBC (recruitment of this disease group was stopped), and specified values of clinical laboratory parameters (transaminases, creatinine and bilirubin), no leukaemic involvement of the CNS and ECOG performance status score of <3.

A total of 293 patients entered the study: 235 patients with AP CML 77 started at 400 mg and the subsequent 158 patients at 600 mg. The patient population recruited exceeded the planned target (minimum 68 patients with AP CML, increased to 100 to take dropout into account). Other patients recruited were 48 with relapsed/refractory ALL, 2 with relapsed/refractory AML, 8 with relapsed/refractory CML in LBC. 48 ALL, 2 AML, 8 CML in LBC patients.

Local AP diagnosis was confirmed in 181 patients (77%). The remaining patients had features of BC (12%), chronic phase (7%), or could not be assigned to a particular disease phase (4%). Of note, 24% of the patients had >20% marrow blasts, a feature now considered as evidence of BC according to a new definition recently proposed by the WHO (Harris *et al.*, 1999).

The median time from the diagnosis of AP was 1.1 months and >6 months in 26% patients. Notably, 40% of patients were ≥60 years (with 12% being older than 70).

Imatinib was supplied as 25 mg, 50 mg and 100 mg capsules, taken orally, once a day with 250 ml of water after breakfast for 400 mg/d and 600 mg/d doses, or twice a day after breakfast and the evening meal for 800 mg/d (2x400 mg/d) dose. In terms of treatment duration, the study was open-ended with patients able to remain on treatment for as long as they were alive and able to derive benefit. Dose escalation was permitted to a maximum 800 mg/day (400 mg bid) and dose reduction or interruption was foreseen in case of toxicity.

Main clinical efficacy results for are summarised in Tables 6 and 7. In the whole AP CML population (N=235) the number of observed HR was 148 (63%, CI: 56.5% - 69.2%). The median time to HR was 0.95 months in the overall population and in the two dose subgroups. At data cut-off (median follow-up time 7.4 months, range 2-12 months), 115/148 (78%) of responders maintained their response. The median duration of response had not been reached. The number of observed unconfirmed MCR was 50 (21.3%, CI: 16.2% - 27.1%) with median time to MCR of 2.8 months (CI: 2.8-2.9) and median duration (n=50, 42 observations censored) of 7.39 months (CI: 5.7-7.4).

Median overall survival was 13.5 months (CI: 13.5-NA). The estimated 6, 9 and 12-month overall survival probability (N=235; 184 observations censored) was 85.8% (CI: 81.3-90.3%), 79.9% (74.5-85.3%), 73.0% (65.3-80.7%), respectively. The estimated 9-month overall survival probability in the 400 mg and 600 mg subgroups was 74% (95% CI 64-84%) and 83% (95% CI 76-89%), respectively.

In multivariate analysis, variables significantly associated with an improved haematologic response rate in the multivariate analysis were hemoglobin ≥100 g/L and female gender.

Table 6. AP CML Haematologic response (Study 0109)

	AP CML		
Initial dose (mg/day):	**400 mg N=77**	**600 mg N=158**	**All doses N=235**
Haematologic response [n (%)]			
Overall	48 (62.3)	100 (63.3)	148 (63.0)
95% CI (%)	50.6 - 73.1	55.3 - 70.8	56.5 - 69.2
Complete	21 (27.3)	44 (27.8)	65 (27.7)
No evidence of leukaemia	7 (9.1)	20 (12.7)	27 (11.5)
Return to chronic phase	20 (26.0)	36 (22.8)	56 (23.8)
Absence of response			
No response	15 (19.5)	23 (14.6)	38 (16.2)
Progression without response	7 (9.1)	17 (10.8)	24 (10.2)
Death without response	2 (2.6)	1 (0.6)	3 (1.3)
Not assessable	5 (6.5)	17 (10.8)	22 (9.4)

Table 7. AP CML Cytogenetic response rates (Study 0109)

Initial dose group:	**400 mg N=77**	**600 mg N=158**	**All doses N=235**
MCR n (%)	12 (15.6)	38 (24.1)	50 (21.3)
95% CI	8.3-25.6	17.6-31.5	16.2-27.1
Complete	7 (9.1)	27 (17.1)	34 (14.5)
Partial	5 (6.5)	11 (7.0)	16 (6.8)
Minor	5 (6.5)	8 (5.1)	13 (5.5)
Minimal	9 (11.7)	21 (13.3)	30 (12.8)
Absence of response			
No response	32 (41.6)	59 (37.3)	91 (38.7)
Progression without response	10 (13.0)	13 (8.2)	23 (9.8)
Death without response	2 (2.6)	1 (0.6)	3 (1.3)
Not assessable			
Ph negative at baseline	1 (1.3)	0	1 (0.4)
Not done	6 (7.8)	18 (11.4)	24 (10.2)

Myeloid Blast Crisis CML (Study 0102)

In this study, patients with previously untreated or treated myeloid BC were enrolled. The primary endpoint was the rate of haematological response.

A total of 260 patients were enrolled, of whom 165 (63%) were previously untreated and 95 (37%) had received prior therapy for either AP or BC. Baseline patient characteristics were typical for a population of patients with BC. However, in contrast with most published studies, 38% of patients were ≥60 years (with 12% being older than 70 years). Local diagnosis of BC was made for 229 patients (88%). The remaining patients had local diagnosis of AP (6%), chronic phase (1.5%), or could not be assigned to a particular disease phase (3%). Central histopathology review was available for 124 patients and resulted only in one discordant diagnosis.

The first 37 patients were treated at a dose of 400 mg and the subsequent 223 patients at 600 mg. At the cut-off date, 93 (35.8%) of patients were still on protocol treatment. The main reason for treatment discontinuation was unsatisfactory therapeutic effect in 113 patients (43%).

Main study results are reported in Tables 8 and 9. The number of HR were 68 (26.2%, CI: 20.9-31.9). Response was higher in the 600 mg/d group than in the 400 mg/d group (28.7% vs 10.8%). Median

time to confirmed HR was 1 month for all patients and for the untreated or treated subgroups. Median duration of response was 6.6 months (49/68 censored observations, 4.6 months in pre-treated patients). The number of observed unconfirmed MCR was 35 (13.5%, CI: 9.6-18.2) with 13 (5%) complete responses. Median time to unconfirmed MCR was 2.6 months and median duration was 2.5 months (17/35 censored observations). Overall survival was 6.3 months (142/260 observations censored).

In this study, in the multivariate analysis, the variable with the strongest association with an improved haematological response rate was age ≥60 years, followed by platelets ≥100x10^9/L, peripheral blood blasts <50%, hemoglobin ≥100 g/L and initial dose of 600 mg.

Table 8. Study 0102: Confirmed haematologic response

	Subgroup		All patients N=260
	Previously Untreated N=165	Previously Treated N=95	
	No. (%)	No. (%)	No. (%)
Haematologic response [n (%)]	50 (30.3)	18 (18.9)	68 (26.2)
95% CI	23.4-37.9	11.6-28.3	20.9-31.9
Complete haematologic remission	7 (4.2)	3 (3.2)	10 (3.8)
No evidence of leukaemia	7 (4.2)	1 (1.1)	8 (3.1)
Return to chronic phase	36 (21.8)	14 (14.7)	50 (19.2)
Absence of response			
No response	50 (30.3)	34 (35.8)	84 (32.2)
Progression without response	37 (22.4)	29 (30.5)	66 (25.4)
Death without response	9 (5.5)	3 (3.2)	12 (4.6)
Not assessable	19 (11.5)	11 (11.6)	30 (11.5)

Table 9. Study 0102: Cytogenetic response

	Subgroup		All patients N=260
	Previously Untreated N=165	Previously Treated N=95	
	No. (%)	No. (%)	No. (%)
MCR	20 (12.1)	15 (15.8)	35 (13.5)
95% CI	7.6-18.1	9.1-24.7	9.6-18.2
Complete	8 (4.8)	5 (5.3)	13 (5)
Partial	12 (7.3)	10 (10.5)	22 (8.5)
Minor	4 (2.4)	2 (2.1)	6 (2.3)
Minimal	18 (10.9)	9 (9.5)	27 (10.4)
Absence of response			
No response	70 (42.4)	29 (30.5)	99 (38.1)
Progression without response	30 (18.2)	28 (29.5)	58 (22.3)
Death without response	6 (3.6)	5 (5.3)	11 (4.2)
Not assessable			
Ph negative at baseline	2 (1.2)	3 (3.2)	5 (1.9)
Not done	15 (9.1)	4 (4.2)	19 (7.3)

Abbreviations: MCR: Major cytogenetic response (complete + partial)

Other Ph positive leukaemias

A few patients with other Ph+ leukaemias (CML in lymphoid BC, Ph+ ALL or AML) have been enrolled in study 03 001 and study 0109. In study 03 001, 14 out of the 20 patients with ALL or lymphoid BC achieved a haematologic response. However, these responses were extremely short-lived and 12 patients relapsed at a median of 58 days. The median survival of the 58 patients with various Ph+ acute leukaemias or lymphoid BC enrolled in study 0109 was 5 months.

Association between haematological/ cytogenetic response and survival

An association between haematologic response at 3 months and prolonged survival was observed in studies 0102 and 0109 (log-rank p=0.0001). Achievement of a MCR by 3 months was associated with prolonged survival in study 0109 (log-rank p = 0.046). This analysis (landmark method) was based on 101 patients (62 responder and 39 non-responder) in study 0102 and 142 AP CML patients (122 responder and 21 non-responder) in study 0109.

Discussion on Clinical Efficacy

In the main clinical studies, cytogenetic response has been measured by conventional techniques, such as bone marrow cultures and assessing metaphases for Ph+ chromosome, which is a relatively insensitive method. The use of molecular methods with a higher sensitivity such as FISH or PCR would have been desirable.

Chronic Phase CML

Study (0110) is the main study that was presented to support efficacy and safety of imatinib in chronic phase CML. The primary endpoint was unconfirmed MCR.
The results submitted show efficacy of imatinib as measured by the pre-specified primary and secondary endpoints. Unconfirmed MCR rate was 49.4% (n=532). Results were more favourable for patients initially IFN intolerant or patients that had cytogenetic IFN failure. Unconfirmed MCR rate was 51.1% (complete: 30.1%) in the cytogenetic failure group (n=186) and 58.2 (complete: 37.6%) in the IFN intolerant subgroup (n=194) whereas it was 36.2% (complete: 20.4%) in the haematologic failure subgroup (n=152).

Complete haematological response was observed in 88% of all patients with 82.9% achieved within the haematologic IFN failure subgroup and 93% within the cytogenetic IFN-failure subgroup. The estimated 9-month overall survival and progression-free survival were 98.1% and 78.7%. The results observed for secondary endpoints were consistent with the results obtained for the primary endpoint. The first significant responses were seen at 2 weeks of therapy. Maximum effects were reached after 1-3 months. This is in accordance with the results obtained in the phase I study 03 001.

Compared to the 4 randomised with IFN (ICGS studies: Rof/CML, CML94, and FCGS studies: CML88 and CML91) the patients enrolled in study 0110 were at a later stage. Time since diagnosis is a known important prognostic factor for patient outcome in late chronic phase and the patient selection in study 0110 might be considered to have a worse prognosis than in the published series. It is also important to note that according to recent publications, patients not achieving CHR at 3 months, have very poor chance to achieve a cytogenetic response at 6 months, and among the 6 month cytogenetic non responders, it is assumed that only 5% of them may achieve a cytogenetic response at 12 months.

Patients in chronic phase CML failing IFN therapy are usually managed with second line hydroxyurea or busulfan, with a rate of haematologic and cytogenetic response probably in the range of 20-54% and less than 5%, respectively. No published data are available on the response to this second line. However, it is assumed that it cannot be superior to the response to the same therapy used as first line (rate of haematologic and cytogenetic response less than 50% and 5% respectively).

According to the literature, overall survival improvement is the primary objective and achievement of cytogenetic response is usually a secondary objective. The experience with IFN in the treatment of CML showed a strong association between haematologic response, cytogenetic response, and survival. Thus, cytogenetic response has become a main endpoint of therapeutic evaluation. However, the

mechanisms of action of imatinib and IFN are different and the association between survival improvement and achievement of cytogenetic response needs to be confirmed for imatinib.

Accelerated Phase CML

Study 0109 in patients with AP CML is the main study submitted to support this indication (n=235).

The proposed dose of imatinib for adult patients with AP CML is 600 mg given daily. In addition, a dose increase from 600 mg to 800 mg may be considered in cases of in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory haematological response after at least 3 months of treatment; loss of a previously achieved haematological response.

The selection criteria of the study were rigorously defined according to well documented criteria. The primary endpoint was haematologic response rate: overall, haematologic response rate was 63% (complete: 28%), with very similar results for the two doses. The objectives of the study were met (target response was 50%). The median time to overall haematologic response was 1 month, range 0.9 to 9.3 months. The estimated proportion of haematologic responses lasting at least 6 months was 84% (95% CI 78-90%). The estimated 9-month progression-free survival rates (haematologic) were 60% for 400 mg and 82% for 600 mg.

Results on secondary endpoints were consistent with those obtained on the primary endpoint. A MCR was achieved in 21.3% of patients, with a trend towards higher response rates in the 600 mg group than in the 400 mg group (24.1% and 15.6% respectively). Complete cytogenetic responses were achieved in 14% of patients (17.1% and 9.1% respectively). Median duration of cytogenetic response was 7.39 months. The estimated overall 9-month overall survival rate was 80% (95% CI 75-85%).

The included population is appropriate relevant to the definition of AP CML used. However, it is important to stress that other definitions (e.g., using other definitions based on blast excess or other criteria) would not necessarily lead to the same response to treatment.

Unfortunately the design of this study is not a controlled one. So, it is not possible to compare directly the efficacy and safety of imatinib of imatinib with the current standard therapy in these patients.

Blast Crisis CML

Study 0102 (n=260) was the main study submitted to support the efficacy of imatinib in BC CML: at entry, 165 patients were untreated and 95 had been previously treated for AP CML. The primary endpoint was haematologic response.

Baseline patient characteristics were typical for a population of patients with BC phase CML. However, in contrast with most published studies, 38% of patients were 860 years (with 12% being older than 70 years).

MCR were observed in 13.5% of patients (untreated: 12.1%, treated: 15.8%), with a median time to response of 2.6 months. Median survival was 4.5 or 7 months depending on whether patients were pre-treated or not. The current estimated 6-month survival rates are 60.3% (untreated patients) and 43.1% (treated patients).

Response was higher in previously untreated patients than in treated patients (30.3% vs 18.9%) and in the 600 mg/d group than in the 400 mg/d group. The median time to confirmed response was approximately one month, the first favourable responses were seen in the first assessment on week 2 of therapy. The first losses of response are seen within two months and continue progressively. The median duration of response was 6.6 months.

The response rate obtained with imatinib in the in CML myeloid BC was high with a rapid reduction in leukocytosis and blasts in approximately 50% of patients. This response rate is lower than that obtained in other stages of CML. For the majority of responders, duration of response was limited. Only a subgroup of patients (approximately 25%) obtained a longer response.

Concerning overall survival, although only short term data available, results obtained with imatinib are interesting with a median survival of 13 months in the 400 mg treated population and a median survival that might be superior in the 600 mg treated population.

Except for the high rate of cytogenetic responses, the haematologic response rate and the median survival of patients treated with imatinib are comparable to some of the results obtained with combination chemotherapy regimens (in the more positive published studies). However, published series concern the pooled myeloid and lymphoid BC population and the latter are known be probably more sensitive to chemotherapy. With this respect, the population recruited in this study submitted is probably one with worse prognosis than that of available published series.

Clinical Safety

The key safety population consists of patients from the phase I study, 03 001 and the 3 phase II studies, 0102, 0109, 0110.

Methods

The population included in the clinical safety analysis consists of all patients who started treatment. AEs and laboratory abnormalities were graded for severity using the NCI/NIH common toxicity criteria (CTC). Adverse events (AEs) are summarized by preferred term and body class; because AEs were coded using SMTT in study 03 001 and MedDRA in the phase II trials, these data cannot be pooled. Summary tables are provided for AEs by highest CTC grade for each event as well as for AEs considered related to study drug.

An AE was defined as any adverse medical change from the patient's baseline (or pre-treatment) condition which occurred during the course of the study, after study enrollment, whether considered treatment-related or not. For any abnormal laboratory or vital sign finding, investigators were asked to record it as an AE only if it constituted the main indicator of a severe AE or SAE or led by itself to premature discontinuation.

Clinically important AE were defined as suspected drug-related adverse events which led to discontinuation, or death within 28 days of treatment not described as disease progression

Special analyses of safety were performed on the following SAEs: rash (a frequently reported event, leading to hospitalization and study drug discontinuation in a minority of cases), liver toxicity (one of the main findings in animal toxicology studies), fluid retention, oedema, renal failure (consistently among the most commonly reported AEs, occasionally associated with renal failure), GI tract hemorrhage (imatinib was shown to be a local irritant in toxicology studies), subdural haematoma and cerebral hemorrhage (a relatively frequently reported AE).

Exposure

The median drug exposure was shorter in study 0102 (99 days) in comparison to study 0109 (240 days) and study 0110 (254 days), reflecting a higher discontinuation rate for death or progressive disease with increasing disease severity. The longest exposure to imatinib was 320 days (study 0110). The number of patients with drug exposure ≥12 months was 6 and 3 in studies 0109 and 0102, respectively. At the cut-off date, the proportion of patients still on treatment was 93%, 65% and 36% in studies 0110, 0109, and 0102, respectively (Table 10). The main reason for treatment discontinuation was progressive disease.

Table 10. Treatment exposure in phase II studies (October 2000)

	Study 0102 (n=260)	Study 0109 (n=235)	Study 0110 (n=532)
First patient enrolled	26-Jul-1999	09-Aug-1999	03-Dec-1999
Last patient enrolled	30-Jun-2000	09-Mar-2000	24-May-2000
Cut-off date for analysis	02-Oct-2000	09-Oct-2000	30-Oct-2000
Patients still on treatment [n(%)]	93 (36%)	154 (65%)	497 (93%)
Months on treatment: median (range)	5.6 (2.7-13.8)	8.6 (6.7-13.1)	8.4 (4.7-10.5)
Discontinued treatment [n(%)]	167 (64%)	81 (34%)	35 (7%)
Months on treatment: median (range)	2.3 (0.1-7.8)	3.6 (0.2-12.0)	5.8 (0.5-9.8)
Drug exposure (months)			
Median (range)	3.3 (0.1-13.8)	7.9 (0.2-13.1)	8.3 (0.5-10.5)
Treatment≥12 months [n(%)]	3 (1%)	6 (3%)	0

Adverse events, Serious Adverse Events

The overall incidence of AEs was close to 100% in all disease groups, the digestive system being the most frequently affected body system in all disease groups.

According to the severity of CML , the rate of deaths is increasing from study 0110 to study 0102. In the same way, the rate of serious adverse events and discontinuation due to adverse events is increasing with the progression of disease.

Guidelines for dose reduction or interruption were provided for any grade 2 non-haematological toxicity resistant to symptomatic treatment or any grade 3-4 toxicity. Less than 50% of patients required dose reduction at any time. Treatment interruptions were required in 25-45% of patients. Despite these dose changes, the overall median dose-intensity over the whole study period remained close to the initially planned dose in each study.

Although almost all the patients experienced adverse events which were assessed as related to treatment by the investigator, these events were generally mild to moderate in severity and grade 3-4 non-haematological events were reported in <5% of patients. AEs were easy to manage and treatment was discontinued because of drug-related AEs in only a minority of patients (1% in study 0110 , 2% in study 0109, and 5% in study 0102).

Non-haematological Toxicity

The most frequent drug-related adverse events were gastrointestinal toxicity, fluid retention and musculo-skeletal toxicity (Table 11).

Gastrointestinal toxicity including nausea, vomiting and diarrhoea was more frequent in advanced CML studies. Nausea with or without vomiting were the most frequent events reported in 51% to 61% of the treated patients, but was severe in 1% to 3.4% of patients and reported as serious in <3% of patients. Drug discontinuation was required in only 3 patients. These symptoms relate to a direct irritant effect of imatinib, as suggested by the toxicological data.

Oedema was one of the most frequently reported related AE, but was severe in only 1.1% to 3.1% of patients and reported as serious in <2% of patients. Face, peri-orbital region and limb were involved. Oedema usually appeared within the first 2 months of treatment. The overall frequency of grade 1-2 oedema was higher at 600 mg (56-69%) than at 400 mg (19-44%) in studies 0102 and 0109. Dose reduction or interruption was useful in 1.9% to 4.1% of patients, but treatment was discontinued due to death in only one patient in study 0102 in a context of congestive heart failure, renal failure and pleural effusion. Another patient discontinued imatinib due to grade 2 generalised oedema.

Table 11. CML Patients with study-drug-related AEs in the Phase II trials

Preferred term	Study 0102 n=260		Study 0109 n=235		Study 0110 n=532	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Nausea	61.2	1.9	62.1	3.4	51.3	1.1
Vomiting NOS	41.2	1.2	47.7	1.3	22.2	0.4
Periorbital oedema	26.5	0.4	37.4	0.4	27.6	0.8
Muscle cramps	23.5	0.4	29.4	0.4	38.7	0.8
Oedema lower limb	22.7	1.9	23.0	0	12.4	0.4
Diarrhoea NOS	21.9	0.8	33.6	0.4	20.3	0.4
Dermatitis NOS	13.5	1.9	18.7	1.3	17.1	2.1
Headache	9.2	0.8	11.5	0.9	10.7	0
Face oedema	7.3	0	12.8	0.4	8.5	0.2
Arthralgia	6.9	0.8	12.3	3.0	12.6	0.4
Pain in limb	6.2	0	10.6	0.9	8.6	0
Dyspepsia	5.8	0	14.9	0	13.5	0
Myalgia	4.6	0	11.1	1.3	13.9	0.2
Abdominal pain	4.2	0.6	10.2	0.4	11.5	1.5
Weight increase	3.0	0	5.1	0.7	16.7	1.6

Note: only AE reported in ≥10% of patients in any of the three trials are listed

Fluid retention was reported in 6.9% to 13% of treated patients and was more frequent in study 0110. This event was severe in 1.4% to 2.3% of patients and reported as serious in 0.6% to 3.1% of patients. No treatment discontinuation was reported due to fluid retention. Dose reduction or interruption was necessary in 0.2% to 1% of patients.

Among all the serious or severe cases of fluid retention or oedema, half of patients presented a medical history of hypertension or cardiac failure or renal impairment or coronary artery disease or pulmonary disease.

Muscle cramps, myalgia, arthralgia were common (from 4.6% to 38.7% of treated patients), but were less frequent in advanced CML studies. Grade 3-4 musculo-skeletal events were recorded in 2.4% to 0% of patients. Serious musculo-skeletal adverse events were reported in few patients (0 to 1.2% of patients). Only one patient discontinued imatinib due to joint pain during study 0110. Dose reduction or interruption was necessary in 0 to 1.4% of patients. However two patients experienced severe and disabling myalgia or arthralgia, requiring analgesia with morphine.

Drug-related skin rashes were collected in 21% to 26% of patients, but were severe or serious in approximately 3% of patients (Table 12). Half of serious or severe cases were related to study drug. One case of urticaria/angioedema andtwo cases of Sweet syndrome (1 appearance and 1 worsening) were notified. One case of multiforme erythema was not related to study drug. Other cases were described as generalised, erythmatous or maculopapular, sometimes hemorrhagic or pruritic rashes, and occasionally had an exfoliative component. 0.7% of patients experienced positive re-challenge when imatinib was reintroduced. Rashes were associated with elevation of liver enzymes levels in 0.6% of cases. They were managed with anti-histaminics or topical corticosteroids. They had required dose reduction or interruption in 4 to 5% of patients and treatment discontinuation in 0.4 to 1% of patients.

Liver toxicity : 2-5% of patients experienced drug-related liver toxicity, 1-3% of them were severe. 1-3.5% of patients presented serious adverse events. Treatment was discontinued in less than 0.5% of patients. Dose reduction or interruption was necessary in 2-6% of cases.

Renal toxicity : 0.4-1% of patients experienced drug-related renal toxicity, less of 0.5% of them were severe. 0.4-3% of patients presented serious adverse events. Treatment was discontinued in less than 1% of patients. Dose reduction or interruption was not necessary.

During the phase II programme, 2.2% of treated patients experienced gastrointestinal haemorrhage. Half of cases occurred in a context of disease progression. A quarter of cases were drug-related. Severe thrombocytopenia were present in more than half of cases. Two cases of Mallory Weiss syndrome were reported. Less than 1% of patients discontinued treatment as a result of these events.

Two cases of neutropenic colitis and *clostridium difficile* pancolitis were recorded during study 0109.

In phase II studies 2.8% of patients treated experienced serious cases of CNS haemorrhage. The majority occurred in a context of rapidly progressive disease, with concomitant thrombocytopenia. One case was considered to be potentially related to a drug interaction between imatinib and warfarine, leading to a permanent discontinuation of imatinib.

Table 12: Clinically important adverse events in phase II trials

Event (% of patients)	Drug-related AE		SAE° %	Treatment discontinuation° %	Dose reduction or interruption° %
	Any grade %	Grades 3-4 %			
Oedema	47-59	1-3	0.4-2	0-0.4	2-4
Fluid retention	7-13	1-2	0.6-3	0	0.2-1
Skin rash	21-26	2-3	1-2	0.4-1	4-5
Hemorrhage	2-10	0-2	1-18*	1-2	1-5
Cerebral hemorrhage	<0.5	0	1-4	<0.5	0
GI tract hemorrhage	0-2	0-1.5	0-2	0-1	0-2
Renal toxicity	0.4-1	<0.5	0.4-3	0-1	0
Liver toxicity	2-5	1-3	1-3.5	<0.5	2-6

Numbers indicate the range of % between the three trials **0110, 0109** and **0102** (CML patients only).
* the frequency of hemorrhages reported as SAE was 1%, 6% and 18% in study 0110, 0109 and 0102, respectively
° irrespective of drug causality assessment

Fatal Adverse Events

In most cases, deaths were related to disease progression. Only two deaths were related to imatinib toxicity (in one case this occurred with paracetamol used as concomitant medication). The relationship with study drug was suspected in a third case.

Clinical Laboratory Evaluations

Haematology

Blood cytopenia was a very common finding in all studies (Tables 13 and 14). The occurrence of drug related severe haematotoxicity correlated with the CML seriousness. The time to nadir of neutropenia and thrombopenia was shorter in advanced CML and the duration of grade 3-4 neutropenia and thrombopenia was longer in advanced CML. The median duration of the neutropenic and thrombopenic episodes ranged from 2 to 3 weeks, and 3 to 4 weeks, respectively. In studies 0102 and 0109, there were no apparent differences in the frequency and kinetics of these events between the 2 doses of 400 and 600 mg.

Table 13: Newly occurring or worsening grade 3-4 haematologic abnormalities in phase II studies

% of patients	Grade	Study 0102 N=260	Study 0109 N=235	Study 0110 N=532
Neutropenia	**3**	16%	24%	25%
	4	46%	34%	8%
Thrombopenia	**3**	27%	30%	16%
	4	31%	12%	<1%
Anemia	**3**	40%	31%	4%
	4	10%	5%	<1%

Table 14: Time to nadir and duration of grade 3-4 neutropenia and thrombocytopenia

		Study 0102 N=260	Study 0109 N=235	Study 0110 N=532
Neutropenia	No.	162	140	174
Time to grade 3-4 (days)	Median	36	43	57
	Range		2-289	8-214
Neutropenia	N. *		276	316
Duration of grade 3-4 (days)	Median	Unk.	21	14
	Range		1-317	1-222
Thrombocytopenia	No.	152	120	88
Time to grade 3-4 (days)	Median	30	25	50
	Range		2-347	8-260
Thrombocytopenia	N.*		217	126
Duration of grade 3-4 (days)	Median	Unk.	28	20
	Range		1-300	1-114

N.*: number of episodes of grade 3-4 haematotoxicity
Unk. unknown

Biochemistry

Grade 3 elevations of creatinine were uncommon and were reported in 3 patients each in study 0102 and 0109. All 6 patients presented advanced disease or had pre-existing renal problems. No grade 4 creatinine elevation were reported in any study.

Elevation of transaminases occurred with a similar frequency across studies. There was a decreasing frequency of grade 3 bilirubinemia from study 0102 to study 0110, which suggest a relationship to the underlying disease. The median duration of hyperbilirubinemia and elevated transaminases was approximately 1 week.

The rate of discontinuation or dose modification or interruption due to serious or severe hepatotoxicity is between 2.6% and 0.3%. Confounding factors (pre-existing elevation of hepatic enzymes) and promoting factors (sepsis, cardiac failure, shock…) were frequent in study 0102. The seriousness of hepatotoxicity was significant in study 0102.

Table 15: Newly occurring or worsening grade 3-4 biochemistry abnormalities in phase II studies

% of patients	Grade	Study 0102 N=260	Study 0109 N=235	Study 0110 N=532
Creatinine	3	1.2	1.3	0
Bilirubin	3	3.5	1.7	0.4
Alkaline phosphatase	3	4.6	5.1	0.2
	4	0	0.4	0
AST	3	1.9	2.1	1.1
ALT	3	2.3	3.0	1.7
	4	0.4	0	0

Discussion on Clinical Safety

The most frequent drug-related clinical adverse effects were gastrointestinal toxicity (nausea, vomiting, diarrhoea, gastrointestinal hemorrhage), fluid retention or oedema (peri-orbital, limbs, and face), musculo-skeletal toxicity (cramps, myalgia, arthralgia), and skin toxicity (maculopapular rash). Oedema was the only clinical side effect dose-related, and aetiology remains almost unknown. The MAH should commit to propose further evaluation of this adverse event management.

Gastrointestinal toxicity occurred more often in advanced CML patients, while fluid retention and musculo-skeletal toxicity occurred rather in early CML patients. All these adverse events were severe only in few cases and did not lead to a high rate of protocol treatment discontinuation.

Serious rash was a common side effect of imatinib, leading to interruption or discontinuation of treatment. No case of bullous rash has been reported and the applicant has committed to monitor this issue closely.

The occurrence of CNS hemorrhage was related to disease progression except in one case of interaction between imatinib and warfarine. The common way of metabolism of imatinib and warfarine may increase the concentrations of warfarine and in case the use of warfarine in thrombosis prophylaxis becomes necessary, special caution has to be taken.

Gastrointestinal hemorrhage is an expected adverse effect of imatinib due to its direct irritant effect. This potentially serious side effect is addressed adequately the SPC and a warning on the possibility of gastrointestinal hemorrhage has been added. Colitis should be monitored.

Haematologic toxicity (all three lineages) and alteration of liver parameters were observed. The frequency of this toxicity increased with the seriousness of CML. Haematologic toxicity was not dose related. Additional data on time to onset and particularly duration of grade 3-4 haematotoxicity during study 0102 should be provided, as well as the relationship between severe neutropenia and occurrence of infections.

Regarding the case of fatal hepatic failure, the probability of an increase in paracetamol concentrations is high in view of imatinib pharmacokinetics. Therefore the SPC recommends restricting or avoiding paracetamol use. This analgesic is frequently used in this population either as a prescription or over-the-counter medicinal product. At present, no study to investigate the effects of paracetamol on the pharmacokinetics of imatinib was provided. The hepatotoxicity of imatinib, already observed in pre-clinical study, was also observed during the phase II studies and lead to dose modification or interruption or discontinuation of treatment. Appropriate dose modification/interruption of imatinib are detailed in the sections 4.2 and 4.4 of the SmPC.

The safety profile of imatinib in AP patients was similar to the chronic phase study but adverse reactions were more frequent and severe in this study. The toxicity was more intense for the 600 mg dose than for 400 mg.

In conclusion, 15-64.6% of patients experienced serious adverse effects and 2.4-21.9% of patients discontinued imatinib due to adverse effect. The safety profile of imatinib is dependant on stage of CML disease. In advanced CML patients, the exposure to study drug is shorter, whereas there is higher rate of SAE, deaths and discontinuation of treatment.

Discussion on clinical aspects

Clinical Pharmacology

Imatinib has shown effects in the specified pharmacodynamic (reduction in leukocyte count) and efficacy endpoints (haematologic and cytogenetic responses). A dose-response was observed, with an increase in response rate at doses higher than 300 mg. The results obtained for chronic phase were positive and consistent across the different endpoints while for acute phase patients this was less so.

A 400 mg dose for imatinib monotherapy was initially chosen for the clinical program. As more safety data became available, the protocols in accelerated and BC phases were amended to make 600 mg the starting dose. Protocols allowed dose escalation in patients who failed to respond at a lower dose or who subsequently relapsed, *i.e.*, from 600 mg to 800 mg, and from 400 to 800 mg in study 0110 (chronic phase) despite an increased frequency of AEs at higher doses (results not submitted).

The pharmacodynamic effects of imatinib regarding resistance to treatment and therefore, the consequences in the treatment of CML have not been described. Pre-clinical *in vitro* data suggested that an important mechanism of drug resistance is the amplification of the *Bcr-Abl* gene, leading to increased amounts of the target protein. It was hypothesised that high doses could be more effective in inhibiting the target kinase in these patients with overall poor prognosis.

In conclusion, the pharmacodynamic investigations of a proposed starting dose, doses increases and the maximum dose although limited, provides enough evidence to support the proposed posology for continuing the investigation with imatinib in the phase II studies, although optimal dose regimen has not been completely established.

The oral bioavailability of imatinib in capsules is high (97%), with a rapid absorption (t_{max}: 2-4 h). Half-life of elimination $t_{1/2}$ is 18 hours, which is supportive of the proposed posology of one daily administration. The volume of distribution was approximately 435 L, reflecting extensive distribution.

At multiple doses, imatinib has shown a dose-proportionality for the dose range of 25-1000 mg in patients diagnosed with CML.

Imatinib is mainly transformed by the cytochrome CYP3A4 and also it competitively inhibits CYP2C9, CYP2D6 and CYP3A4/5.

In the two interaction studies submitted, it has been shown that the co-administration of imatinib and the metabolic inhibitor ketoconazole increased significantly the exposure to imatinib. In addition, an inhibition of the metabolism of simvastatin by CYP3A4 by imatinib was observed. Therefore, imatinib may increase the exposure to co-medications that are substrates of these cytochromes, but this has not been sufficiently investigated yet.

The main metabolite of imatinib is CGP 74588. Its AUC was 16% of that for imatinib with a similar pharmacodynamic potency to it. In addition, on third of the dose was accounted by minor unidentified metabolites.

For cytochrome CYP2D6, no studies specifically investigating this question have been performed yet.

Preliminary clinical consequences regarding toxicity are also associated with these findings. The concomitant administration of simvastatin and imatinib should not be recommended because of an increased risk of myopathy associated with high plasma concentration of statins.

Concomitant use of imatinib with substances that inhibit or induce the CYP3A4 or with CYP3A4 substrates is not recommended until reassuring data are available.

A statement indicating that no specific studies have been performed with imatinib and CYP2D6 substrates has been included in the SPC. It would be of interest to know the real clinical implications of this interaction showed only by in vitro tests.

A statement recommending the intake of imatinib with food in order to reduce gastrointestinal toxicity is included in the SPC. With the available pharmacokinetic data regarding food interaction with imatinib, this recommendation is acceptable, since the presence of food did not modify substantially the pharmacokinetic parameters.

Exposure to imatinib increases in patients with hepatic impairment although the potential clinical relevance of this issue is unknown in the absence of specific trials.

The investigation of interactions for imatinib cannot be considered extensive enough to characterise it appropriately. There are no specific studies in special populations. Taking into account the hepatic elimination of imatinib, its pharmacokinetics should be investigated in patients with hepatic impairment. Although the dossier contains a description of the pharmacokinetics profile of imatinib, there are some aspects that require further investigation such as the interactions with the drugs currently used in CML patients and, the pharmacokinetics in special populations such as renal and hepatic impairment, particularly the possibly reduced clearance in hepatic impaired patients.

Clinical Efficacy

The phase I study showed a dose-response relation with a haematologic response rate of 39% in patients who started imatinib with <300 mg per day compared to 98% of patients who received ≥300 mg (chronic phase CML). The MCR rates were 18% and 41% respectively.

The main evidence of efficacy of imatinib in CML comes from three uncontrolled, open-label studies (0110, 0109 and 0102), for the three submitted indications (chronic phase CML, AP CML and BC CML) in 1057 CML patients.

In these phase II studies, haematological or cytogenetic response by starting dose suggests that the response was somewhat greater with the higher dose than with the lower dose. This was confirmed by an exploratory analysis adjusted for patient and tumour characteristics.

Long term efficacy and safety data are limited or absent. In the main phase II studies 0109 and 0102 the number of patients with drug exposure ≥12 months was 6 (2.6%) and 3 (1%) in studies 0109 and 0102, respectively. In the main phase II study 0110, the longest exposure to imatinib was 320 days. At present, in the absence of mature data on overall survival and progression free survival, assumptions on the relevance of the pre-defined primary endpoints are required. The assumptions appear justified as the achievement of a haematological response implies a degree of disease control and that the validity of cytogenetic and haematological response has been shown for IFN. Nevertheless, the validity of such assumption on the chosen surrogate endpoint will need to be proven.

The definitions and evaluation criteria for CHR and MCR are acceptable. The definition for CHR is comparable to those used in the Italian and the French co-operative group studies with the exception of the criteria for the platelet count; the definition of MCR is comparable to the French and Italian studies.

Chronic Phase CML

The overall MCR rate in this study (including IFN intolerant patients) was 49.4%. The pre-defined objectives of the study were met with a MCR rate of 36.2% (complete: 20.4%) in the haematologic IFN failure sub group and 51.1% (30.1%) in the cytogenetic IFN failure subgroup. Overall, 88% patients had a complete haematological response with 82.9% achieved within the haematologic IFN failure subgroup and 93% within the cytogenetic IFN failure subgroup. The estimated 9-month survival and time to progression rates were 98.1% and 78.7%.

Despite the known drawbacks of this approach, compared to historical controls from published series, cytogenetic and haematologic responses are considered as outstanding, with close to 50% response rate after 3 months of treatment and especially taking into account that the included patients have bad prognosis because the interval since diagnosis is long.

Accelerated Phase CML

The overall haematologic response rate (primary endpoint) was of 63% (28% complete), with very similar results for the two doses. A confirmed MCR was achieved in 21.3%, with a trend towards higher response rates in the 600 mg group than in the 400 mg group (24.1% and 15.6% respectively). Complete cytogenetic responses were achieved in 14% of patients (17.1% and 9.1% respectively).

Results of time to progression and survival are very limited and should be updated. A landmark analysis of this study suggested that the achievement of such responses is probably clinically relevant. These results will need to be confirmed as more mature survival data become available.

In conclusion for patients in AP, haematological results were interesting, and cytogenetic results are outstanding in spite of the lack of a demonstrated association between achievement of cytogenetic response and survival.

Blast Crisis Phase CML

Haematological response rate was 51%, confirmed in half of these. Response was higher in previously untreated patients than in treated patients (30.3% *versus* 18.9%) and in the 600 mg/d group than in the 400 mg/d group (28.7% *versus* 10.8%). MCR were recorded in 13.5% of patients (previously untreated: 12.1%, previously treated: 15.8%) and, complete CR were respectively 4.8 and 5.3%.

Taking in due account the severe prognosis in this very advanced phase, results show a clinical benefit in the elderly patients subgroup, where an improved response rate in patients with age >60 years (CHR=39.2% *versus* 19.1% for patients <60 years). This is a very interesting finding, particularly taking into account the high toxicity of cytotoxic regimens commonly observed in elderly patients.

In addition the dramatic improvement observed in a few patients is outstanding: CHR and, more importantly, unconfirmed MCR results are outstanding as compared to what reported in the literature.

The responses obtained in BC phase CML are much poorer than those obtained in the previous stages of CML. The magnitude of effect of imatinib seems comparable to that obtained in historical data where no effective treatment is available.

Clinical Safety

Imatinib was generally well tolerated in patients with CML. The majority of patients experienced adverse events at some point in time, but most were of mild to moderate grade, and in clinical trials drug discontinuation because of drug-related adverse events was observed in only 1% of patients in chronic phase, 2% of patients in AP and 5% of BC patients.

The most commonly reported related adverse events were nausea, sometimes accompanied by vomiting, dyspepsia and/or upper abdominal pain. Other commonly reported toxicity was oedema at various sites (most frequently in the peri-orbital region), and a variety of musculo-skeletal symptoms including muscle cramps, myalgia and arthralgia. Neutropenia, thrombocytopenia and anaemia, have been a consistent finding in all studies

Miscellaneous adverse events such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as “fluid retention”. These events can usually be managed by interrupting imatinib and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life-threatening and one patient with BC died with a complex clinical history of pleural effusion, congestive heart failure and renal failure.

Excluding myelosuppression, which was an expected effect, some SAEs warrant special mentioning. Rash was occasionally quite severe and led to discontinuation in a minority of patients. Liver toxicity - manifesting as raised transaminases, though sometimes accompanied by raised bilirubin and/or alkaline phosphatase Fluid retention, oedema and/or renal toxicity - leading in severe cases to generalized fluid retention, weight gain and pleural or pericardial effusions and ascites, and more rarely to congestive heart failure or pre-renal failure. GI tract hemorrhage - though usually observed in

the setting of profound thrombocytopenia, this AE may be related to local irritation of the upper GI tract. CNS hemorrhage - episodes of cerebral bleeding were generally associated with profound thrombocytopenia and their frequency seems to be no higher than expected in this patient population.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality

The active substance is well-defined, and the product is formulated, manufactured and controlled in a way that is characteristic of a powder-filled hard gelatin capsule. The specifications guarantee a consistent product with uniform bioavailability from batch to batch and the safety of the impurities has been demonstrated with reference to toxicology studies.

Therefore in general, there are no outstanding major quality issues which may have a negative impact on the benefit/risk balance. The applicant has committed to confirm the stability of the product by providing the results of two additional production-scale batches of product packaged in PVC and Triplex which have been placed on stability trials as extra confirmation.

Preclinical pharmacology and toxicology

In vitro and *in vivo* pharmacodynamic studies demonstrate that imatinib inhibited Bcr-Abl protein-tyrosine kinase activity in leukaemic cell lines as well as in primary leukaemia cells from patients with Ph positive CML and ALL. Imatinib showed antitumor activity in nude mice injected with the Bcr-Abl positive KU812 cell line derived from a CML patient in BC supporting the hypothesis that imatinib could be efficacious in the treatment of patients with CML. The applicant has agreed to justify the lack of pharmacodynamic studies comparing the activity of imatinib with that of standard therapies.

From the few interaction studies performed by the applicant only erythromycin and fluconazole showed an inhibition of imatinib metabolism which could be clinically relevant. Imatinib was shown to be metabolised by CYP2C9, CYP2D6 and CYP3A4/5 enzymes.

Imatinib was systemically exposed to several animal species to evaluate pharmacokinetics. Gender differences were slight and only observed in some species, and accumulation after repeated dosing was not observed in any species tested. Imatinib is distributed in foetal tissue and is excreted into milk; this is also expected to occur in humans.

From toxicity studies, imatinib was found to be genotoxic only under the most extreme *in vitro* conditions. Imatinib was also shown to be embryotoxic (increased post-implantation loss) and is teratogenic in rats. The risks of imatinib treatment in women of childbearing potential is addressed in the SPC: contraceptive measures should be used during treatment and women already pregnant before treatment start should be warned of the risks. No carcinogenicity studies have been performed. Overall, the target organs for imatinib toxicity were identified as including bone marrow, lymphoid tissues, reproductive organs and gastrointestinal tract. This may occur at therapeutic doses, but given the severity of the disease, the benefit/risk ratio can be considered positive.

Clinical aspects

In chronic and accelerated phases, the efficacy results regarding response rate were outstanding compared to historical series. In fact, the results in terms of MCR rate in chronic phase CML resistant or intolerant to IFN are outstanding (close to 50%) after a short time of treatment (3 months). At present, apart from BMT, no other treatments are known to achieve this size of effect on this endpoint.

In BC, one phase II uncontrolled study with a total of 260 patients with CML myeloid BC (95 pre-treated and 165 untreated) was submitted. The response rate was high, with a rapid reduction in leukocytosis and blasts in approximately 50% of patients. However, the duration of this response is extremely limited. Median survival was 4.5 or 7 months depending on whether they were pre-treated or not.

In the absence of mature data on overall survival and progression free survival, assumptions on the relevance of the primary clinical efficacy endpoints studies are required. Specific analysis updates on relevant endpoints will be submitted as specific obligations.

Regarding safety, imatinib appears acceptably tolerated in the studies where it was studied. Incidence and severity of adverse events increased with dose escalating and disease progression, including severe medullar aplasia, especially neutropenia and thrombocytopenia. Complications of fluid overload or redistribution occurred in some patients, suggesting a potentially serious drug effect.

The long-term benefits of imatinib are not yet known. Specific protocols for longer-term follow up will be submitted as specific obligations.

In addition, further data must be gathered on an ongoing basis and the benefit/risk re-evaluated, as new data are available to clarify the population that could benefit from imatinib.

Benefit/risk assessment

In an oral explanation, the applicant has provided additional argumentation to support the assumptions related to the clinical relevance of the main endpoints and to the relative treatment effect of imatinib compared to published series.

An update (cut-off date 31 January 2001) of the primary and secondary endpoints of the three pivotal studies was presented confirming the results previously submitted. With up to four months of additional follow-up, the efficacy update showed a higher rate of haematological response, major and complete cytogenetic response in all trials and a similar duration of response, time-to-progression and overall survival.

An update of analyses exploring the association between response and survival confirmed that the achievement of a haematologic response at 3 months is associated with a prolonged survival in studies 0102 and 0109. Achievement of a MCR at 3 months was associated with an improved survival in study 0109. In study 0110, the achievement of a MCR at 3 months was associated with an improved time to progression.

According to currently available data imatinib appears promising compared to alternative second line chemotherapy in terms of both haematologic and cytogenetic response. The rate of CHR to second line therapy usually ranges from 20 to 54% with HU or BU, and was 72% in two single-centre studies of the investigational agent HHT. In contrast, in study 0110 (n=532), the rate of CHR was 89%. The rates of MCR that can be expected with HU and BU are in the range of 1 to 5%, up to 15% in the HHT trials. Notably, when IFN is started late in the chronic phase, the rate of MCR decreases rapidly to only 8%. In comparison, the rate of major and complete cytogenetic responses were 55% and 36% in study 0110.

Blast crisis is the terminal event in the clinical course of CML, defined usually as the presence of ≥30% marrow blasts. There is no standard therapy available for these patients. Treatment usually includes combination chemotherapy regimen commonly used to treat ALL or AML, as appropriate. Published series have reported a haematological response in the range of 20% to 40%, but response is complete in only 5% to 30% of patients, and generally short-lived. The prognosis of patients with CML in myeloid BC has is poor and median survival is in the range of 3 to 6 months.

The data presented showed that imatinib was active in patients with myeloid BC, inducing a rate of haematological response which was in the range of what reported for chemotherapy but with a higher rate of cytogenetic response and a median survival which compared favourably with what is usually reported with chemotherapy.

Although the clinical relevance of complete cytogenetic response for imatinib mesilate has not been validated, this endpoint is directly linked with the well established pathology of the disease and association with clinical benefit can be in principle assumed pending further validation as follow up measures and specific obligations (see Specific obligations and follow-up measures of the Marketing Authorisation Holder).

Given the outstanding activity observed, the CPMP considered that an approval under exceptional circumstances could be considered, provided that the applicant commits to fulfil the agreed follow-up measures and to complete the identified programme of studies laid out as specific obligations, within

the specified timeframe, the results of which shall form the basis of a reassessment of the benefit/risk profile.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Glivec in the treatment adult patients with Philadelphia chromosome (bcr-abl) positive chronic myeloid leukaemia (CML) in chronic phase after failure of interferon- alpha therapy, or in accelerated phase or myeloid blast crisis was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.

6. Extension of the indication: treatment of Gastrointestinal stromal tumours (GIST)

Gastrointestinal stromal tumours (GIST) are uncommon visceral sarcoma that arises predominantly in the gastrointestinal tract. A the time of this application, the MAH had established that malignant GIST was estimated to be affecting 0.06 in 10,000 persons in the EU.
The origin of GIST is not fully understood, but available histopathogenetic evidence links GIST cells with the interstitial cells of Cajal (ICC), gastrointestinal pacemaker cells that regulate gut peristalsis.

GIST are the most common subtype of GI sarcomas, which also include leiomyosarcomas, liposarcomas and other more rare histologic subtypes. GIST have been reported to represent about 3% of all malignant GI tumours.
GIST are most common in the stomach (60-70%), followed by small intestine (20-30%), colon and rectum (5%), and oesophagus (<5%). GIST primary in the omentum and mesentery have also been reported. Recurrence of disease after resection is predominantly intra-abdominal and involves the original tumour site, peritoneum and liver.

Recent advances in molecular and immunohistochemical analysis of GIST have identified that GIST cells are positive for CD117, a cell surface antigen localised on the extracellular domain of the transmembrane tyrosine kinase receptor KIT, the protein product of the proto-oncogene *c-KIT* and receptor for stem cell factor. It is hypothesized that virtually all malignant GIST harbour mutations of *c-KIT* as the driving factor of this disease, resulting in constitutive activation of KIT associated with the signal transduction pathway for cell division and tumour growth. KIT overexpression is determined by immunohistochemistry which are performed in standard practice.

The treatment of GIST so far has been almost uniquely surgical and there is no approved specific drug therapy. Whereas resection is potentially curative, especially in low-grade or borderline tumours, long-term outcome is dismal for patients with large, high-grade lesions, even with complete surgical extirpation. For patients who undergo complete resection there is high risk of recurrence within the abdomen. Median time to recurrence is in the range of 7 months to 2 years, with the probability of recurrence after re-excision approaching 100%. Most GIST do not respond to radiotherapy and/or chemotherapy and are ultimately lethal. There is no evidence that pre-operative or post-operative systemic therapy has a favourable impact on outcome.

The prognosis is poor largely due to the fact that there is no effective systemic therapy for unresectable or metastatic malignant GIST. Since treatment with any conventional cytotoxic chemotherapy is considered ineffective, current recommendations for these patients are to enter clinical trials. Response rates for true GIST to any conventional chemotherapy are much lower than for other sarcomas of non-osseous tissues and range from 0% to 5%. The estimated progression free survival for metastatic GIST is less than 2 months. The median survival of GIST patients for whom complete resection cannot be accomplished is in the range of 10 to 12 months.

Imatinib is a tyrosine kinase inhibitor that selectively inhibits the KIT-associated tyrosine kinase at an IC_{50} of approximately 100 nM which is similar to that required for inhibiting the tyrosine kinases associated with Bcr-Abl and the PDGF- receptor. A primary cell line established from a patient with GIST characterized by the point mutation K642E that results in autoactivation of the c-*KIT* protein product showed inhibition of cell growth by imatinib at concentrations of 0.1-1 μM. These results

provided the rationale for the clinical development of imatinib in the treatment of malignancies such as GIST that are completely or partially dependent upon the activity of wild type or mutant c-*KIT* for proliferation and/or survival.

Clinical aspects

This application is based on one pivotal phase II trial (B2222) and a publication (a phase I-II study performed by the EORTC, and a single patient case report)[1,2,3].

B2222 is a multi-center, randomised, phase II study. All patients included in B2222 trial had unresectable and/or metastatic GIST. The sample size was expanded from 36 to 200 in several amendments. Finally, 147 patients have been included. This interim analysis was not prospectively planned.
Patients included in the trial were randomly assigned to receive imatinib 400 mg or 600 mg daily.
The primary endpoint was objective response rate (complete response, CR plus partial response, PR), following the SWOG response criteria. These criteria are mainly based on bi-dimensional tumour size based on physical examination and imaging and are the standard criteria for phase II trials in this setting.
Secondary efficacy endpoints included duration of response, time to response, time to treatment failure (TTF) and overall survival. Failure was defined as either progressive disease, death due to any cause, or protocol treatment discontinuation for any reason other than "condition no longer requires therapy".

Pharmacokinetics

In study B2222, a full pharmacokinetics analysis was performed in a subset of GIST patients following continuous once daily oral administration for both imatinib doses (400 mg, n=10; 600 mg, n=9). Imatinib was rapidly absorbed after the first administration and there was an approximate 1.5-fold drug accumulation after one month. The $AUC_{(0\text{-}24h)}$ values indicate 1.2 times higher drug exposure for the 600 mg dose than for 400 mg at steady state. Considerable inter-patient variability of pharmacokinetics was observed and the coefficient of variation for AUC was about 40% at steady state. A population PK approach, on data from patients with full PK profiles (n=19) and those patients with limited PK sampling (n=54) identified albumin, WBC and bilirubin showing a statistically significant relationship with imatinib PK.
The PK of imatinib in GIST patients seem to differ from CML. Peak plasma concentrations and systemic exposure observed in GIST patients were higher than those observed in CML patients at 400 and 600 mg. This may have been related to differences in the liver function between the two populations (78.2% of GIST patients had liver metastases). In addition, patients with GIST had a higher percentage of biochemical abnormalities than CML patients at baseline for albumin, alkaline phosphatase, SGOT and SGPT. The cause of these differences in PK is unknown although hepatic impairment could be involved. The presence of hepatic metastases is related with hepatic insufficiency and this is in turn, expected to reduce metabolisms. The biochemical abnormalities observed in GIST patients (albumin, alkaline phosphatase, SGOT and SGPT) support this hypothesis. Additional factors such as some functional and anatomic abnormalities associated with GIST could also be involved. Intestinal surgery could influence drug absorption or hepatic surgery could decrease drug elimination. Therefore, the pharmacokinetics profile of imatinib in this population should be further investigated.

[1] Joensuu H, Roberts PJ, Sarlomo-Rikala M, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. New Engl J Med 2001; 344:1052-1056.
[2] Van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours, a phase I study. Lancet 2001; 358:1421-1423.
[3] Blanke CD, von Mehren M, Joensuu H, et al. Evaluation of the safety and efficacy of an oral moleculary-targeted therapy, STI571, in pts with unresectable or metastatic gastrointestinal stromal tumors (GIST) expressing c-KIT (CD117). Proc Am Soc Clin Oncol 2001; 20:1[a], (abstract 1).

Efficacy

Seventy-three patients received 400 mg of imatinib daily, and 74 received 600 mg daily for periods ranging from 7 days to up to 13 months. The mean duration of treatment was 7 months. At the time of the analysis, only 10 patients had received treatment with imatinib for ≥12 months.
The main reasons for treatment discontinuation (n=25, 17%) were progressive disease (7.5%), adverse events (3%), and death (3%).

No CRs were observed in the intent-to treat analysis. Fifty nine out of 147 patients achieved a PR. The overall response rate was 59/147 (40.1 %, 95%CI: 32.1 % - 48.5%). There was no difference in response rate between the two doses of imatinib. Sixty-one patients (41.5%) had stable disease (table 1).

Table 1: Best response for trial B2222

	400 mg	600 mg	All
Complete response	0	0	0
Partial response	27 (37.0)	32 (43.2)	59 (40.1)
Stable disease	33 (45.2)	28 (37.8)	61 (41.5)
Progressive disease	10 (13.7)	8 (10.8)	18 (12.2)
Not evaluable	3 (4.1)	4 (5.4)	7 (4.8)
Unknown	0	2 (2.7)	2 (1.4)
Total	73 (100)	74 (100)	147 (100)

The Kaplan-Meier estimate of patients who were free from treatment failure at 12 weeks was 80% and this estimate was 66% at 24 weeks . A difference between dose groups was not observed. At the cut-off date for analysis, 38 patients had failed therapy, mainly due to disease-related events. The median TTF has not yet been reached. Overall survival has not been analysed for the interim report due to the low number of deaths observed and the short follow-up period.
In a published dose-escalating phase I trial with 40 patients (of whom 36 had GISTs) who received imatinib at doses of 400 mg once daily (8 patients), 300 mg twice daily (8 patients), 400 mg twice daily (16 patients) or 500 mg twice daily (8 patients), 19/36 (52.8%) confirmed partial responses (RECIST criteria) were observed..
Two phase III studies (B2223 and B2224) comparing 400 vs 800 mg of imatinib in the treatment of GIST are ongoing. An update on patient recruitment planned availability of data and results from these studies will be provided as part of the specific obligations of the MAH.

Safety

The toxicity profile of imatinib in the pivotal trial in GIST patients was similar to that observed in CML patients. AEs with suspected relationship to study drug are reported in table 2. No major differences in toxicity were attributable to the imatinib doses given in the trial. Toxicity was observed in 66% of the patients and grade 3-4 toxicity was reported in < 3% of patients.

The most commonly reported adverse events were fluid retention, emesis, diarrhoea, muscle cramps, fatigue and skin rash (table 2). In comparison to CML studies, there was an increased frequency of oedema in GIST patients, which was characterised as either periorbital (47% of patients), lower limb (19% of patients) or facial (10% of patients) and that was of grade 3-4 severity in 1.4 % patients.

Table 2. AEs with suspected relationship to study drug (>10% at any dose)

	All doses (N=147)	
Preferred Term	**All Grades** (%)	**Grade 3-4** (%)
Any fluid retention	72.1	1.4
Superficial oedema	71.4	0.7
Other fluid retention events[1]	4.1	0.7
Nausea	51.0	1.4
Diarrhoea	41.5	2.0
Muscle cramps	34.0	0
Fatigue	29.9	0
Rash	28.6	2.0
Headache	24.5	0
Abdominal pain	23.1	0
Flatulence	19.0	0
Any haemorrhage	12.2	4.8
Tumour haemorrhage	2.7	2.7
Cerebral haemorrhage / subdural hematoma	0	0
Upper G-I tract bleeding/perforation	3.4	2.7
Vomiting	10.2	0.7

[1] Other fluid retention events included pleural effusion and ascites

There were 10 deaths reported, and none was attributed to the study drug.

Seventeen patients (11.6%) suffered SAEs related to imatinib treatment. Treatment was discontinued for drug-related AEs in 4/147 patients (3%) of patients. These included 4 patients that developed GI bleeding and 3 patients that developed intratumoral haemorrhage.
Clinical laboratory abnormalities related to liver and renal function were uncommon (grade 3: <5%, grade 4: <2%) and usually not related to imatinib.
Haematological toxicity was lower than in CML patients. In the data submitted as part of the MAA for the registration of Glivec in CML, grade 3 neutropenia and thrombocytopenia were reported in 25% and 16% of patients with chronic phase CML, respectively, as compared with less than 5% of the GIST patients in B2222. Grade 4 episodes of neutropenia and thrombocytopenia were 8% and 3% in CML patients and 0.4% and 0% in GIST patients, respectively.
The phase I study by the EORTC confirmed the safety findings of the pivotal trial. Dose- limiting toxicities (grade 3 emesis: 3 patients; grade 3 oedema: 1 patient; grade 3 dyspnoea: 1 patient) were observed at the dose of 500 mg twice daily, and 400 mg twice daily was shown as the maximum clinically feasible dose. Intratumoural bleeding (one with perforation to the abdomen) was seen in 3 patients.

Benefit/risk analysis

Overall, the efficacy data available demonstrate the ability of imatinib to induce tumour regressions and disease stabilisation in a range of GIST patients, where no available therapy exists.

The implications of such regressions on the natural history of the disease are unknown as yet, given the short follow up of the studies reported. Tumour regressions seem to be accompanied by tumour-related symptoms improvement, a clinically meaningful endpoint. Furthermore, the duration of response and TTF as compared to that reported in historic series (median TTF: 1.2 versus >6 months) suggest that imatinib affords, at least, effective palliation for these patients.

Imatinib appears to have an acceptable safety profile in patients with unresectable and/or metastatic, malignant GIST. Chronic daily administration is feasible and, though relatively frequent, AEs are

generally mild to moderate in severity and can be reasonably monitored and managed. Intratumoural haemorrhage is a potentially severe side effect that should be closely monitored.

According to the CPMP "Note for guidance on evaluation of anticancer medicinal products in man. CPMP/EWP205/95, Rev.1" non-comparator studies maybe acceptable in the circumstances of a proven outstanding anticancer activity and an acceptable and extensively documented toxicity profile. In this application for a new indication for imatinib in GIST patients it can be considered the these requirements set in the Note for guidance are met.

Furthermore, the MAH has committed to provide on an ongoing basis regular updates with longer follow-up on the trial B2222 (Response, Response Duration, TTF and survival data) and available data or update from the EORTC phase I/II trial. An update on accrual, efficacy and safety on the study status of the NCI and EORTC Phase III studies will be provided.

The MAH will also provide additional pharmacokinetic data on GIST patients, including the effect of liver dysfunction on imatinib pharmacokinetics. The effects of prior treatments (previous extensive gastric, bowel or liver surgery, embolisations, chemotherapy, etc) on the pharmacokinetics of imatinib in the GIST population should be investigated. A further assessment of PK relationship to prior surgery in the B2222 study will be performed.

With regard to safety, The MAH has committed to provide long term toxicity data from B2222, especially on intratumoural/ GI bleeding and fluid retention. This update will include a study on the impact of previous cardiac, renal, and hepatic function and prior treatments given on imatinib toxicity.

Recommendation

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Glivec in the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) was favourable and therefore recommended the granting of the additional indication.

7. Extension of the indication to patients with newly diagnosed Ph+ CML

Treatment of CML is usually initiated when the diagnosis is established, which is done by the presence of an elevated white blood cell (WBC) count, thrombocytosis, Philadelphia (Ph) chromosome, and splenomegaly. The standard therapeutic options include IFN-α(IFN), chemotherapy with hydroxyurea, low-dose cytarabine or, rarely, busulfan. CML is not currently curable with conventional chemotherapy or immunotherapy and, allogeneic bone marrow transplantation from related or unrelated donors in the chronic phase is the only known curative therapy, although it has a risk of mortality.

There is no consensus on what should be the initial therapy for patients with early chronic phase CML. At initial diagnosis, the possibility of curative therapy with bone marrow transplantation (BMT) is explored. IFN-based regimens are now considered as the standard therapy for newly diagnosed patients in chronic phase that are ineligible for allogeneic transplantation. Hematologic responses (control of the peripheral blood counts) have been reported in 50-80% of patients and, about 20-40% of the chronic-phase patients treated with interferon alpha have major cytogenetic remissions (MCR, defined as <35% Philadelphia chromosome-positive cells in the bone marrow). The achievement of both a haematological and an MCR with IFN has been shown to be associated with prolonged survival. However, the majority of patients treated with interferon still had molecular evidence of disease when assessed by the more sensitive polymerase chain reaction (PCR).

The combination of IFN and low-doses AraC has been investigated in phase II and phase III trials with the objective of maximising the antileukaemic effect of both drugs. It has been found that the combination of IFN at the standard "high dose" regimen and low-dose intermittent subcutaneous AraC

is more effective than IFN alone in inducing both hœmatologic and cytogenetic response, although the translation of this effect into a prolonged survival remains controversial. Thus, there is a clear need for a more effective and safer therapy.

The MAH applied for an extension of the imatinib indication, to the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML). Data presented in the dossier supporting this type II variation relates only to adult population. This extension of indication is mainly based on the results of a pivotal randomised phase III trial (0106) comparing Glivec as single agent given at 400 mg with interferon (IFN) plus cytarabine (Ara-C). Additional safety data paediatric and late chronic phase and advanced phase CML have also been provided.

The proposed dose for this indication is 400 mg/day. A dose increase from 400 mg to 600 mg (up to a maximum of 800 mg/d) is recommended in the absence of adverse drug reactions if assessments demonstrate an insufficient response to therapy.

7.1. Preclinical aspects

In view of the expected longer treatment duration of newly diagnosed CML patients, a carcinogenicity study program has been initiated. In addition, since the original submission an oral pre- and post-natal development study in rats has been now completed.

Carcinogenicity
A 2-year rat carcinogenicity study is presently ongoing. Protocol design was based on the ICH Harmonised Tripartite Guideline *S1C Dose selection for carcinogenicity studies of pharmaceuticals* and S1B *Testing for carcinogenicity of Pharmaceuticals*. A final study report is expected by mid 2005. In addition, a complementary carcinogenicity study in the p53 transgenic mouse model using gavage dosing is in planning. Therefore, the MAH is planning to:

- perform a 4-week DRF study in the p53 wild type strain, starting 3rd quarter 2002.
- initiate the main 26-week study in p53 mice, based on the results from the DRF study.

A final study report for this mouse carcinogenicity study is expected no later than by mid 2005.

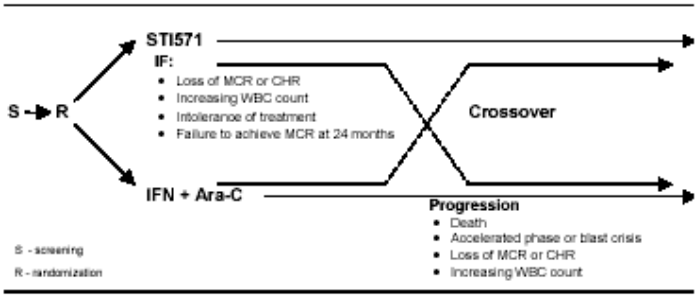
Pre- and post-natal development
Three groups of timed-pregnant F_0 female rats were administered orally the test compound from implantation of the embryo (gestation day 6) to the end of lactation (lactation day 20), at daily doses of 5, 15 and 45 mg/kg/day.
There was no maternal mortality. Red vaginal discharge was noted for 5 females in the 45 mg/kg/day group on day 14 - 15 of gestation. The significance of this finding is unknown since all of these females produced viable litters and none had significantly elevated post-implantation loss. The number of stillborn pups was slightly increased and the number of viable pups per litter was decreased at 45 mg/kg/day as was the number of pups dying between postpartum days 0 and 4. In the F1 offspring at the same dose level, mean body weights were reduced from birth until terminal sacrifice and the number of litters achieving criterion for preputial separation was slightly decreased. There were no other significant effects noted on developmental parameters or behavioural tests. F1 fertility was not affected, but reproductive effects were noted and included an increased number of resorptions and a decreased number of viable foetuses at 45 mg/kg/day. The no effect level for both the maternal animals and the F_1 generation was 15 mg/kg/day.

7.2. Clinical aspects

The claim is supported by one pivotal phase II trial (0106). Study 0106 is an open-label, controlled, multicentre, international randomised phase III study comparing treatment with either Glivec monotherapy or a standard combination of IFN+Ara-C in patients with CML within 6 months of their

initial diagnosis. Because of differing mode of administration (Glivec being orally available and both IFN and Ara-C requiring subcutaneous injections) and different safety profiles, a double-blind controlled design was considered impracticable by the applicant. On the basis of the efficacy seen with Glivec given as second-line therapy in patients in chronic phase CML failing prior IFN therapy in the phase II study 0110, the applicant considered a crossover to be an essential component of the study design. Patients showing lack of response (lack of CHR at 6 months, increasing WBC, no MCyR at 24 months), loss of response (loss of CHR or MCyR) or severe intolerance to treatment were allowed to crossover to the alternative treatment arm.

Study 0106. Study design



In the Glivec arm, patients were treated with 400 mg/day. In the IFN+Ara-C arm, patients were treated with the standard recommended target dose of IFN of 5 MIU/m2/day s.c., in combination with Ara-C 20 mg/m2/day s.c. for 10 days/month.

The primary efficacy endpoint of the study is progression-free survival and the study was designed to show superiority of first-line therapy with Glivec. Progression was defined as any of the following event: progression to AP or BC, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. MCyR was considered as the main endpoint for this first interim analysis. Haematological response, time to AP or BC, survival and PCR analysis of MRD are main secondary endpoints.

The management of the study was supported by a Study Management Committee (SMC) of 4 investigators authorised to review (in a blinded fashion) requests for crossovers related to either intolerance to treatment or increasing WBC. This aspect of the study was essential to guarantee that all measures recommended by the protocol had been taken before actually crossing over. Patients safety and general monitoring of the study conduct was overseen by an Independent Data Monitoring Board (IDMB) which has conducted two data reviews, a safety review of the first 500 patients randomised (April 2001) and an analysis of both safety and efficacy on all data collected up to a cut-off date of 31 July 2001, i.e. 6 months after the last patient had been randomised. On the basis of early evidence for a consistent and significant superiority of the Glivec arm in terms of efficacy together with a superior safety profile, the IDMB recommended that the data be released and the protocol amended to allow crossover also for patients not achieving a CHR at 12 months, patients not achieving a MCyR at 12 months (instead of 24 months) and for patients refusing to continue treatment with IFN. This amendment was implemented after the cut-off for the present "12-months" analysis.

Between 16 June 2000 and 30 January 2001, a total of 1106 patients were randomised from 177 centres in 16 countries, 553 to each arm. The baseline characteristics of these patients were well balanced between the two arms and are described in the following table.

Table 1.: Patients characteristics in Study 0106

	Glivec N=553	IFN + Ara-C N=553
Age (years)	50 (18-70)	51 (18-70)
Sex (% male / female)	62%/38%	56%/44%
Diagnosis		
Time since diagnosis (months)	2.14 (0-10.4)	1.77 (0-8)
Sokal risk group at diagnosis	N=383 (69.2%)	N=394 (71.2%)
Low	52.5%	48.2%
Intermediate	29.0%	29.6%
High	18.5%	22.4%
Hasford risk group at diagnosis	N=374 (67.6%)	N=387 (70%)
Low	45.5%	44.9%
Intermediate	44.4%	45.6%
High	10.2%	9.9%
Baseline characteristics		
Spleen ≥10 cm	33 (6%)	33 (6%)
Hepatomegaly	57 (10.3%)	46 (8.3%)
WBC ($10x^9$/L)	17.9 (1.6-421.3)	20.2 (2-500)
Platelets ($10x^9$/L)	336 (47-2950)	340.5 (18-3412)
Hemoglobin (g/dL)	13 (6.2-17.5)	12.8 (6.6-19.4)
Basophils in PB (%)	3 (0-39)	3 (0-26)
Blasts in PB ≥3%	3.9%	5.7%
Blasts in BM ≥5%	12.5%	12.7%
Other chromosomal abnormalities	70 (12.7%)	44 (8.0%)

Data expressed as median and range unless otherwise indicated, PB: peripheral blood
Source: CSR Text tables 7-11, 7-12, 7-13, 7-14, 7-15, 7-16

The median follow-up for all patients the cut-off for this analysis was 14 and 13 months in the Glivec and IFN arms, respectively. 90% of patients randomised to Glivec are still receiving first-line treatment. As a consequence of high rates of both discontinuation and crossover, only 30% of patients randomised to IFN+ara-C are still on first line treatment. Discontinuation of first line therapy was more frequent in the group of patients randomised to IFN+ara-C, the most frequent reason being withdrawal of consent (13.4%). In addition, considerably more patients treated with IFN+ara-C crossed-over to the alternative therapy than those randomised to treatment with Glivec, the most frequent reason for crossover in the former group being intolerance to treatment.
The SMC examined a total of 424 requests for crossovers for 267 patients randomised to IFN+ara-C. Out of the 227 requests for intolerance, 140 were approved (61.6%), but only 126 patients had crossed over at the time of cut-off. Likewise, the SMC examined requests for crossover due to increasing WBC for 40 patients, and approved 29 of them (72.5%). Only 25 of them were implemented at the time of cut-off.

Efficacy results

Haematological response
The rate of CHR was significantly higher in the Glivec arm. In addition, CHRs were achieved faster with Glivec (median time to CHR of 1 month) than with IFN (2.5 months). Duration of response was also significantly longer in the Glivec arm, with an estimated proportion of patients with continuing response at 12 months of 98% compared to 79.7% in the IFN arm.
However, this analysis may underestimate the response to IFN because of the high rate of crossovers or discontinuations. As an example a patient crossed over because of intolerance might be counted as a non-responder in this analysis. To compensate for this bias, the data were further analysed with the Kaplan-Meier method, in which patients who crossed over or discontinued for reasons other than progression were censored. Using this approach, the estimated rate of CHR at 12 months in the Glivec arm was minimally affected (95.9%) whereas it increased from 54.6% (Table 6) to 66.6% in the IFN arm. The difference between the two arms remained significant ($p<0.001$).

Of interest, the rate of CHR to second line Glivec for the 218 patients who crossed over was 83.5%, ie. very similar to the reported rate of 88% in the phase II study 0110. When CHR was analysed using the ITT principle, the rate of CHR in the Glivec arm (94.6%) remained significantly higher than that in the IFN arm (76.5%, p<0.001).

Cytogenetic response

During first line treatment, 83% of patients achieved an MCR in the Glivec arm, compared to 20% in the IFN arm. Sixty eight percent of patients randomised to Glivec achieved a CCR, compared with only 7% in the IFN arm. Major responses were achieved faster with Glivec (median 3 months) compared to IFN (median 5.8 months). At the cut-off, a higher proportion of responding patients had lost their MCyR in the IFN arm (n=9, 8%) compared to the Glivec arm (n=7, 1.5%). Out of the responding patients, three (0.6%) progressed to AP or BC in the Glivec arm and three (2.6%) in the IFN arm.

As with haematologic response, the rates of MCR and CCR responses were further estimated using a Kaplan-Meier approach in order to compensate for the higher rate of discontinuation and crossovers in the IFN arm. Using this conservative approach, the estimated rates of MCyR at 12 months were 84.1% in the Glivec arm as compared to 29.8% in the IFN arm. This difference remained highly statistically significant (p<0.001). For the 218 patients who crossed over from IFN, the rate of MCyR to second line Glivec therapy was 53.2%. This was again very similar to the rate of 49.4% reported in the initial report of study 0110, at a time when the follow-up in that study was similar to the follow-up currently available for study 0106.

Interestingly, even when cytogenetic response was further analysed using the ITT principle where the crossover effects were ignored, the rate of MCyR for patients randomised to Glivec was still statistically significantly higher (82.6%) than in patients initially randomised to IFN (39.8%)(p<0.001).

Table 2. Haematological and cytogenetic response to first line therapy

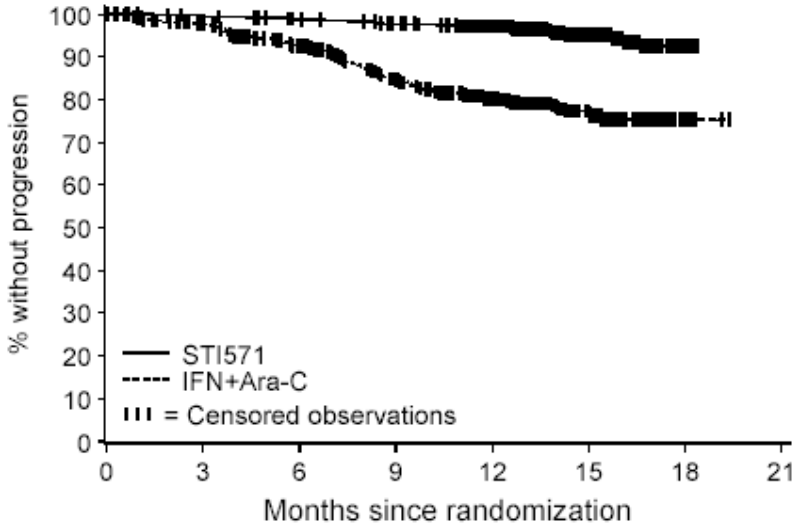
(Best response rates)*	Glivec n=553	IFN+Ara-C n=553
Hematologic response		
CHR rate n (%)	522 (94.4%)*	302 (54.6%)*
[95% CI]	[92.1%, 96.2%]	[50.4%, 58.8%]
Cytogenetic response		
Major response n (%)	457 (82.6%)*	112 (20.3%)*
[95% CI]	[79.2%, 85.7%]	[17.0%, 23.8%]
Complete CyR n (%)	375 (67.8%)*	41 (7.4%)*
Partial CyR n (%)	82 (14.8%)	71 (12.8%)

Source: CSR In text tables 9-2, 9-6
* best response at any time during first-line therapy
** p<0.001, Fisher's exact test
Hematologic response criteria (all responses to be confirmed after ≥4 weeks): WBC<10 x10^9/L, platelet <450 x10^9/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils<20%, no extramedullary involvement
Cytogenetic response criteria: complete (0% Ph+ metaphases), partial (1-35%), minor (36-65%) or minimal (66-95%). A major response (0-35%) combines both complete and partial responses [1].

Time to progression

Time to progression (TTP) was analysed for first-line treatment, second-line treatment and using the ITT principle regardless of crossover. Only the most conservative ITT analysis is presented in this report. There were more progression events in the IFN arm (18.6%) than in the Glivec arm (4.3%). The difference between the two arms is highly statistically significant using either the Logrank or the Wilcoxon test (p<0.001, Figure 2). The estimated rate of progression-free survival at 12 months is 97.2% in the Glivec arm and 80.3% in the control arm. Given the known activity of Glivec as second line therapy in study 0110, this ITT analysis represents an overestimate of the rate of progression to IFN (the estimated 12 months rate on first line therapy is 75.3%, CI95% 70-80%).

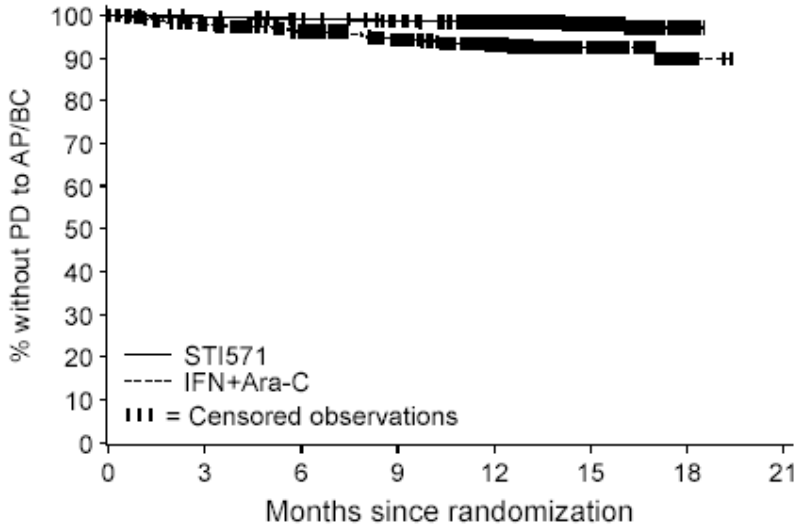
Figure 1. Study 0106: Time to progression (ITT principle)



Time to AP or BC

There was a statistically significantly higher 12-months rate of patients without progression to AP or BC in the Glivec arm (98.5%) as compared to the IFN arm (93.1%, $p<0.001$).

Figure 2. Time to progression to AP or BC (ITT principle)



In the IFN arm, in addition to the 32 patients with progression to AP or BC as first progression event (29 during first line therapy, 3 during second-line therapy), there were 4 patients who progressed to AP or BC after having lost a CHR, giving a total of 36 patients. In contrast, in the Glivec arm, in addition to the 8 patients with progression to AP or BC as first progression event (all during first line therapy), 2 patients progressed to AP/BC after either loss of MCyR or increasing WBC giving a total of 10 patients.

Survival

With the follow-up currently available, there were a total of 31 deaths: 11 in patients randomised to Glivec (1 of them after crossover to IFN) and 20 on the IFN arm (4 of them after crossover to Glivec and another 5 who received Glivec after progression under the extension protocol). Five and 13 of them were reported as related to CML in the Glivec and IFN arms, respectively. None were considered drug-related. These differences were not significant.

Prognostic factors analysis

In a multivariate analysis, treatment group remained the strongest significant factor, followed by the Sokal risk group (and to a lesser degree the Hasford score).

Table 3. Haematological and cytogenetic response by Sokal risk groups

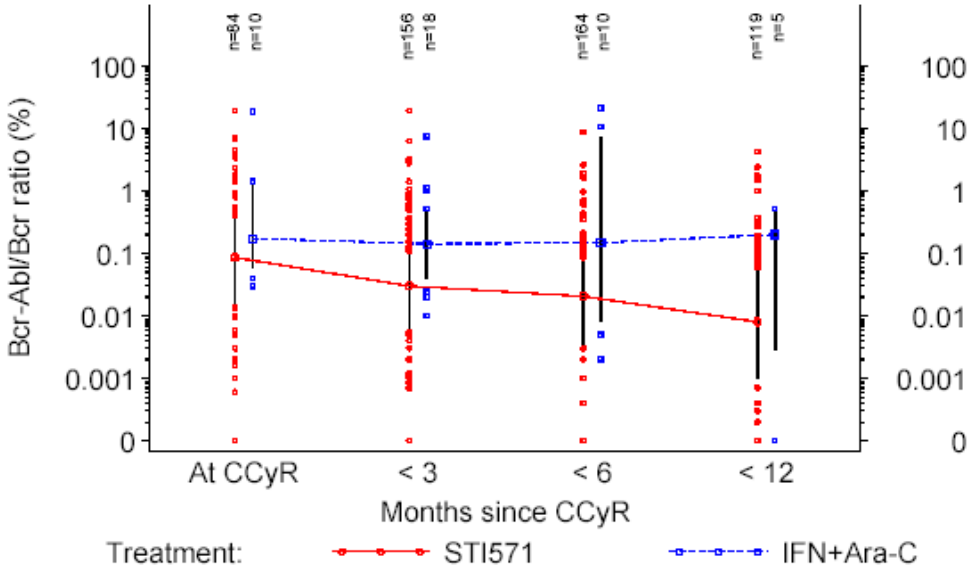
Risk group (Sokal score)	Glivec (n=383)*	IFN+Ara-C (n=394)*
CHR		
Low	95%	61%
Intermediate	99%	57%
High	92%	41%
MCyR		
Low	88%	27%
Intermediate	84%	20%
High	63%	11%

*patients with data available at diagnosis to calculate the Sokal score

Minimal residual disease (RT-PCR)

The degree of MRD achieved after a CCyR on first-line therapy was assessed. Samples were taken at baseline, within 3 months of achieving a CCyR, and every three months thereafter. MRD was assessed by quantitative RT-PCR and expressed as the ratios of the number of Bcr-Abl transcripts over the number of normal Bcr transcripts. At the time of analysis, at least one sample taken either at or after the achievement of a CCyR was available for 285 of 416 of patients with CCyR. In the Glivec arm, 677 samples were available for 257 responding patients; in the IFN arm, 71 samples were available for 28 patients. The median follow-up with PCR samples after the achievement of a CCyR was 5.7 months in the Glivec arm (up to 15.2 months) and 2.8 months in the IFN arm (up to 11.2 months). The baseline Bcr-Abl/Bcr ratios were similar in the two groups (median of approximately 25%). At the time of CCR, the median ratios were reduced to a median of 0.09% and 0.17% in the Glivec and IFN arms, respectively ($p<0.001$). Importantly, after the achievement of a CCR, the ratios continued to decrease in the Glivec arm to a median of 0.008% more than 6 months after the achievement of a CCR (ie. more than one log reduction compared to the values at CCR, and >3 logs compared to baseline).

Figure 3. Bcr-Abl/Bcr ratios at or after CCR



When considering the Bcr-Abl/Bcr ratios observed at 12 months, and keeping in mind the different durations of follow-up related to the different kinetics of time to cytogenetic response with Glivec and

IFN, there were more patients with very low levels of MRD (ratio equal or below 0.001%) in the Glivec arm as compared to the IFN arm.

Table 4. Study 0106: Molecular response obtained after 12 months

Bcr-Abl/Bcr ratio in %	Glivec N=207* (%)	IFN+Ara-C N=20* (%)
Below detection limits	22 (10.6)	1 (5.0)
≤ 0.001%	30 (14.5)	0 (0)
≤ 0.01%	45 (21.7)	2 (10.0)
≤ 0.1%	71 (34.3)	6 (30.0)
≤ 1%	32 (15.5)	6 (30.0)
> 1%	7 (3.4)	5 (25.0)

* patients in CCyR and with a PCR assessment at 12 months
Source: Table 8-3 (PCR report)

Safety

Patient exposure
In Study 0106, in contrast to nearly 90% of the patients randomised to Glivec, only 30% of the patients randomised to IFN+Ara-C are still on their first line treatment. The median duration of first-line treatment was 14 months in the Glivec arm, as compared to 8 months in the IFN arm.
For the 218 patients who crossed over from IFN+Ara-C to Glivec at a median of 5.6 months after randomisation, the median duration of their second-line therapy with Glivec was 7.8 months. Whereas the median daily dose of Glivec was 400 mg as intended, the median dose of IFN was 4.9 MIU/day. If this dose is lower than the intended target dose of IFN, it is in line with the delivered dose in published phase IIIstudies. In the IFN arm, Ara-C was started in 71.2% of patients, who received a median of 4 cycles. In addition, more patients in the IFN+Ara-C arm required additional hydroxyurea (74.3%) for a longer period of time (median of 30 days) compared to the Glivec arm (44.6% patients, median duration of 15 days). Considerably more patients required dose-reduction or dose interruption in the IFN+Ara-C arm (75.6% and 54.2%) compared to the Glivec arm (33% and 28.1%). The main reasons were AEs or laboratory abnormalities.
At the cut-off date of 31 July 2001, the median follow-up in study 0110 was 18 months and 86.7% of patients were still on treatment. Treatment was given for more than 12 months in 90.1% of patients.

Adverse clinical events
All safety analyses were performed on all patients who have received at least one dose of study medication. The most striking difference in the safety profile between the two groups is illustrated by a considerably higher rate of crossovers related to severe intolerance to therapy in the IFN arm (22.7% vs. 0.7%). An additional 5.6% of patients discontinued treatment with IFN because of AEs not qualifying for crossovers, in contrast to only 2% in the Glivec arm. Lastly, there was a 13.4% rate of withdrawal of consent (compared to 1.8% in the Glivec arm).
The frequency of reported AE in both arms was consistent with previous data with both regimens. In particular, there were no new unexpected findings in the Glivec arm.
In the Glivec arm, the most frequent AEs were superficial edemas, nausea, muscle cramps and skin rashes. However, as in the previous phase II studies, these events were mostly of grade 1-2 severity and only a minority were considered as severe (grade 3-4). Nausea was less frequent than in the phase II study 0110, a difference which may be related to the fact that drug was taken with food in study 0106 but not in study 0110. The main AE leading to treatment discontinuation were skin rash and abnormal liver tests. The safety profile of second-line Glivec for those patients who crossed over from IFN to Glivec was similar. The updated safety analysis of the preceding phase II studies, and in particular study 0110, revealed no new findings. In the IFN arm of study 0106, the most frequent events were typical of IFN therapy: fatigue (severe in 24% of patients), nausea, anorexia, rigors and myalgias. There was a slightly higher frequency of severe depression (12.4%) as compared to published data. Psychiatric disorders were the most frequent reason for crossover related to intolerance (29.3% of the 126 patients who crossed over due to intolerance).

Table 5. Most frequently reported AEs in Study 0106

Adverse event (preferred term)	All grades		CTC grades 3/4	
	Glivec N=551 (%)	IFN+Ara-C N=533 (%)	Glivec N=551 (%)	IFN+Ara-C N=533 (%)
Fluid retention	54.1	10.1	0.9	0.9
- Superficial edema	53.2	8.8	0.9	0.4
- Other fluid retention events	3.4	1.5	0	0.6
Nausea	42.5	60.8	0.4	5.1
Muscle cramps	35.4	9.9	1.1	0.2
Musculoskeletal pain	33.6	40.5	2.7	7.7
Rash	31.9	25.0	2.0	2.1
Fatigue	30.7	64.7	1.1	24.0
Diarrhea	30.3	40.9	1.3	3.2
Headache	28.5	41.8	0.4	3.2
Joint pain	26.7	38.3	2.2	6.8
Abdominal pain	23.4	22.9	2.0	3.6
Myalgia	20.9	38.6	1.5	8.1
Nasopharyngitis	19.2	7.7	0	0.2
Hemorrhage	18.9	19.9	0.7	1.3
Dyspepsia	15.1	9.0	0	0.8
Vomiting	14.7	26.6	0.9	3.4
Pharyngolaryngeal pain	14.2	11.4	0.2	0
Dizziness	13.2	23.1	0.5	3.4
Cough	12.5	21.6	0.2	0.6
Upper respiratory tract infection	12.5	7.9	0.2	0.4
Pyrexia	11.8	38.6	0.5	2.8
Weight increased	11.6	1.5	0.7	0.2
Insomnia	11.4	18.4	0	2.3
Depression	8.9	34.7	0.5	12.4
Constipation	7.6	13.9	0.7	0.2
Liver failure	7.6	15.8	3.1	4.3
Rigors	6.9	33.8	0	0.8
Anxiety	6.5	10.9	0.2	2.6
Dyspnea	6.5	14.4	1.3	1.7
Pruritus	6.5	11.3	0.2	0.2
Influenza like illness	6.4	18.4	0	1.1
Night sweats	6.4	15.0	0.2	0.4
Anorexia	4.7	31.3	0	2.4
Sweating increased	3.3	14.4	0	0.4
Alopecia	2.2	14.6	0	0.2
Weight decreased	2.2	16.9	0	1.1
Asthenia	1.6	10.9	0	1.9
Dry mouth	1.6	10.3	0	0.2
Mucosal inflammation	0.7	10.1	0	3.2

All AE regardless of drug relationship, reported in at least 10% of patients in either the IFN or the Glivec arm

Clinical laboratory evaluations

Severe myelosuppression in the Glivec arm was significantly less frequent as compared to the IFN arm and also less frequent than in study 0110 in late chronic phase. In addition, the frequency of grade 3-4 neutropenia and thrombopenias were slightly higher with second line Glivec (22.5% and 10.1%, respectively). In the Glivec arm, the median time to grade 3-4 neutropenia and thrombopenia were 44 days (range 7-463) and 43 days (8-421 days), respectively.

The incidence of severe transaminitis (elevation of SGOT and/or SGPT) was also significantly higher in the IFN arm (7.1% vs. 4.2%, p=0.0357). Transaminitis occurred earlier in the IFN arm (median 85 days) than in the Glivec arm (median 141 days).

Table 6. Grade 3/4 hematologic and biochemistry toxicity during first-line therapy

Parameter	Glivec N=551		IFN+ARA-C N=533	
	Grade 3 %	Grade 4 %	Grade 3 %	Grade 4 %
Hematology				
- Anemia	2.7	0.4	4.1	1.9
- Leukopenia	7.8	0	12.0	0.7
- Neutropenia*	9.6	2.2	20.3	4.3
- Thrombocytopenia*	6.9	0.2	15.8	0.6
Biochemistry				
- SGOT	2.9	0.2	3.8	0.4
- SGPT	3.1	0.4	5.6	0
- Total bilirubin	0.2	0.5	0.4	0
- Alkaline phosphatase	0.2	0	0.9	0
- Creatinine	0	0	0.4	0

Source: CSR In-text Table 10-16, 10-22
*p<0.001

Discussion of efficacy

Overall, the results of study 0106 demonstrate that Glivec is clearly superior to the combination of IFN+Ara-C in terms of both haematological and cytogenetic responses. Time to response is also shorter with Glivec than with the comparative treatment. This effect has shown to be consistent across risk groups. In addition, although data are limited due to the short follow up, there is some evidence showing that Glivec also significantly reduces and delays disease progression, even when considering only AP and BC as relevant events and under the more conservative ITT approach. In a prognostic factor analysis, in each of the three Sokal risk groups, the treatment differences favouring the Glivec arm remained large and significant for either haematologic response, MCyR or TTP.
However, it is difficult to assess the influence that the high rate of crossover may have had on the lower rate of response observed in the control arm. The MAH will provide further details on the timing of patient's crossover due to safety reasons (most of crossovers) and their baseline demographics and disease-related characteristics.

The relationship of response rate with survival with Glivec remains to be investigated. In this sense, the findings of the effect of Glivec on disease progression and on the persistence of MRD seem to indicate that Glivec might have a relevant impact on the major objective of the treatment of the disease: to prolong survival. However, long-term data correlating these facts with a prolonged survival are still lacking. In addition, relevant questions as the time to reach a plateau of major cytogenetic response and the assessment of long-term treatment escapes are considered of utmost importance in order to determine the optimal treatment duration and the time to withdrawal in case of absence of major cytogenetic response. Today, the only available curative treatment for CML is bone marrow transplantation. It is supposed that Glivec is intended as first line treatment for patients with CML who are not candidates for BMT. Nevertheless, it cannot be ruled out that patients initially treated with Glivec can eventually be transplanted. There is no available data to assess whether Glivec might have a potentially beneficial, neutral or deleterious effect on the outcome of an ulterior BMT. This is an important issue and the applicant is committed to closely monitor this issue and provide data to the CPMP on an annual basis.

Discussion of safety

Overall, Glivec appears to have an acceptable safety profile and, as expected from previous data, compares favourably with IFN based regimens. However, it is important to highlight that the control arm, although harbouring a presumably higher antineoplastic activity than IFN monotherapy, is considerably more toxic regarding both clinical and laboratory adverse events. This can be regarded as one of the reasons of the high crossover rate of patients to Glivec arm. Anyway, Glivec appears to be a reasonable well tolerated drug on the long-term basis. As already requested in the initial application for Glivec, the applicant should monitor the impact of fluid retention and weight gain associated with Glivec therapy

Benefit/risk ratio

The clear benefit of Glivec, superior to the combination of IFN+Ara-C, in patients newly diagnosed of Philadelphia chromosome positive CML has been demonstrated in terms of both haematological and cytogenetic responses and is consistent across risk groups. Although the data are limited due to the short follow up, there is sufficient evidence showing that Glivec also significantly reduces and delays disease progression, even when considering only AP and BC. Glivec appears to have an acceptable safety profile and, as expected from previous data, compares favourably with IFN based regimens. The data submitted do not show any effect of Glivec on survival. The effect of Glivec on disease progression and on the persistence of MRD seems to indicate that Glivec might have a relevant impact on survival. However, long-term data correlating these facts with a prolonged survival are still lacking. There is no available data to assess whether Glivec might have a potentially beneficial, neutral or deleterious effect on the outcome of an ulterior BMT. This is considered an important issue, and the applicant must provide any data available on this issue and commit to closely monitor patients treated with Glivec.

The CPMP recommend the approval of the indication for Glivec in patients newly diagnosed of Philadelphia chromosome positive CML. The MAH committed to fulfil a number of follow-up measures ;

- The design and follow-up of the trial does not allow showing any effect of Glivec on survival. The achievement of a cytogenetic response has been demonstrated to have clinical relevance regarding survival in the studies with IFN. However, for Glivec this correlation has not been validated yet. The MAH will submit any further information available on this issue.
- The study design makes difficult the interpretation of the results, as it is difficult to assess the influence that the high rate of crossover may have had on the lower rate of response observed in the control arm. In this sense, the MAH will give further details on the timing of patient's crossover due to safety reasons (most of crossovers) and their baseline demographics and disease-related characteristics.
- The MAH will update the CPMP with information on the present status of study 0106 after the last amendment has been implemented.
- The MAH will commit to provide annual updates of study 0106 in order:
- To monitor treatment escapes,
- To determine the optimal duration of Glivec administration,
- To assess the potential impact of Glivec therapy on BMT.
- To monitor minimal residual disease (MRD).
- The MAH will further assess the time to reach a plateau (if any) of major cytogenetic response to clearly define the time to treatment withdrawal in case of absence of major cytogenetic response
- In order to identify responding and non-responding patients, the MAH will further assess the predictive factors of response to Glivec. This remains an important issue, especially when considering the better efficacy of allogeneic transplantation when it is performed in the first year following the diagnosis.
- The MAH will further assess the potential impact of fluid retention and weight gain associated with long-term Glivec therapy.
- The MAH should commit to provide annual updates of the study 0106 in order to monitor unexpected long-term side effects.

Recommendation

On the basis of the above commitments agreed with the MAH, the CPMP considered that the benefit/risk of Glivec for the treatment of patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment, is positive.

8. Extension of the indication in paediatric patients with CML

The initially approved indication for Glivec was: "Treatment of adult patients with Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase after failure of interferon-alpha therapy, or accelerated phase, or blast crisis. Glivec is also indicated for the treatment of adult patients with Kit (CD 117) positive unresectable and/or metastasic malignant gastrointestinal stromal tumours (GIST). The indication was extended to newly diagnosed patients with CML (see section 7 of the EPAR) and in a parallel application the MAH proposed to extend the indication in order to include paediatric patients with CML.

8.1. Clinical aspects

The current type II variation for the extension of the CML indication to the use in children is based on efficacy, pharmacokinetic (PK) and safety data from two Phase I studies (study 0103 -Pivotal and study 03 001, see table 1). Additional safety data were provided from approximately 92 children treated in a compassionate case program.

Table 1. Clinical studies in paediatric population

Study No.	Patient population	Purpose	n	Daily dose of Glivec
0103 (Phase I)	CML or Ph+ acute leukaemia	Safety, PK, efficacy	31	260, 340, 440 and 570 mg/m2/day
03 001 (Phase I)	CML or Ph+ acute leukaemia	Safety, PK, efficacy	8	173 to 362 mg/m2/day

Main Study 0103.

This study was a phase I open, non-controlled, dose-escalation study conducted by the Children's Oncology Group (COG), a NCI supported clinical co-operative group, in the US, Canada and Australia. Study Participants were male and female patients younger than 22 years old with Ph+ leukaemia:

- CML, which was either recurrent after stem cell transplantation or resistant to prior IFN therapy in either late chronic phase or blast crisis
- Refractory or relapsing Ph+ acute lymphoblastic (ALL) or myeloblastic (AML) leukaemia.

Glivec was administered at doses of 260, 340, 440 and 570 mg/m^2/day once daily or b.i.d. if the dose was > 800 mg/day, for 28 days during course 1, and for 28 additional days during course 2. After completion of the two 28-day treatment courses, eligible patients could receive further courses of therapy.

As a dose escalation study, the starting dose was 260 mg/m^2/day, which was extrapolated from the efficacious dose of 400 mg in the adult population. Dose levels for subsequent groups of patients were based on escalation in increments of 30% up to a dose of 570 mg/m^2/day.

This study aims to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of imatinib to characterise the pharmacokinetics in children and to preliminarily define efficacy.

Endpoints were:
Haematological response. A complete haematological response for chronic phase CML patients is defined as a reduction in the white-cell count to less than 10.000 per cubic millimetre and in platelet count to less than 450,000 per cubic millimetre, maintained for at least four weeks.
Bone marrow response in acute phase patients were defined as follows: M1: 0-5% bone marrow blast cells. M2: >5-25% bone marrow blast cells. M3: >25% bone marrow blast cells.
Cytogenetic response is defined in terms of the percentage of Ph chromosome positive metaphases in bone marrow. Complete cytogenetic response is defined as 0% Ph+ cells, a major response: 0-35% Ph+ cells, minor with >35-65% Ph cells, minimal with >65-95% Ph cells and none with >95-100% Ph cells. For chronic phase CML patients, best cytogenetic response as given by the investigator was listed. In addition, it was checked if this best response was confirmed after at least four weeks. Data on cytogenetic response were not obtained for acute leukaemia. No PCR bcr-abl results were obtained for patients with complete cytogenetic response.
Adverse events were identified using the Common Toxicity Criteria (CTC).

Recruitment
A total of 31 patients with either chronic phase CML (n=15) or CML in blast crisis or Ph+ acute leukemias (n=16) were enrolled over a 17 months period between 26 February 2000 and 4 September 2001 in 23 centres. Data collected up to 19 March 2002 have been analysed. Patients' characteristics are presented in table 2.

Table 2: Study 0103 patients' characteristics.

Patients enrolled	**N=31**
Median age (years, range)	14 (3-20)
Sex (M/F)	23/8
Disease	
CML chronic phase failing prior IFN	15 (48.4%)*
CML myeloid blast crisis	4 (12.9%)
ALL	9 (29.0%)
AML	3 (9.7%)
Prior BMT	14 (45.2%)
Prior multi-agent chemotherapy	21 (67.7%)
Dose cohort	
260 mg/m^2/day	6
340 mg/m^2/day	11
440 mg/m^2/day	8
570 mg/m^2/day	6

* Including one patient diagnosed with testicular involvement of CML qualifying for blast crisis

Table 3. Number of patients in each dose cohort by age group (Study 0103 CML chronic phase)

Dose (mg/m2)	**2-12 years**	**12-18 years**	**> 18 years**	**All ages**
260	0	2	1	3
340	1	3	1	5
440	2	2	1	5
570	0	1	1	2
All doses	3	8	4	15
CML acute phase (CML, ALL, AML)				
Dose (mg/m2)	**2-12 years**	**12-18 years**	**> 18 years**	**All ages**
260	2	1	0	3
340	4	1	1	6
440	1	2	0	3
570	2	2	0	4
All doses	9	6	1	16

Supportive study 03 001

This study was a phase I open, non-controlled, dose-escalation study conducted in the US (3 Centres). The study population consisted on adult and paediatric patients with either CML in the chronic phase, resistant to or intolerant of IFN, or Ph+ acute leukaemia (myeloid or lymphoid blast crisis, or Ph+ ALL or AML). Glivec was administered at doses of 175 mg/m^2/day once daily for 28 days during course 1, and for 28 additional days during course 2. After completion of the two 28-day treatment courses, eligible patients could receive further courses of therapy. Eight paediatric patients 5 to 17 years old were enrolled under amendment 6 of the protocol in one centre, 3 with CML in chronic phase failing prior IFN (two cytogenetic failures, one haematological failure) and 5 with ALL (n=4) or lymphoid blast crisis (n=1). Their median age was 9 years.

Table 4. Patients by age groups in studies 0103 and 03 001

	CML (n=18*)	**Acute leukaemia** (n=21**)
2 - <12 years	5 (27.8%)	13 (61.9%)
12 - <18 years	9 (50%)	7 (33.3%)
18 - 22 years	4 (22.2%)	1 (4.8%)

* 15 patients in study 0103 and 3 in 03 001. ** 16 patients in study 0103 and 5 patients in study 03 001

Clinical pharmacokinetics

The pharmacokinetics of imatinib in paediatric patients have been investigated in a total of 33 children (27 children enrolled in study 0103 and 6 children enrolled in the phase I study 03 001).
Plasma concentrations of imatinib were determined by a high-performance liquid chromatography MS/MS method (LC/MS/MS). Blood samples were collected from all patients enrolled on day 1 of course 1 and at the following time points following drug administration:
- Single dosing at 0.5, 1, 1.5, 2, 4, 8, 24 and 48 hours (only for day 8) post drug administration.
- b.i.d. dosing at 1, 2, 3, 4, 10, 12, 13, 16, 24 and 48 hours (only for day 8) post drug administration.
The basic pharmacokinetics parameters of imatinib and its main metabolite (CGP 74588) were to be summarised by dose using descriptive statistics.
Whenever feasible, the following non-compartmental parameters were calculated from the plasma concentration-time profiles (t_{max}, C_{max}, λ_z, $t_{1/2}$, AUC_{τ}, $AUC_{(0-\infty)}$, Vz/F and Cl/F. Phamacokinetic parameters were determined using WinNonlin Pro (Version 3.2.).

Absorption
As in adult patients, imatinib was rapidly absorbed after oral administration. It was detectable in plasma 30 minutes after oral administration (the first sampling time), t_{max} was approximately 3.7 hours. There was considerable inter-patient variability in the PK and the coefficient of variation for $AUC_{(0-24)}$ at steady state ranged from 21% (260 mg/m^2) to 68% (570 mg/m^2). The comparison of $AUC_{(0-24)}$ at steady state and at Day 1 following treatment at 340 mg/m^2 revealed similarly a 1.7 fold drug accumulation after daily dosing. The comparison of the relationship between AUC and dose in relation to either body surface area (m^2) or body weight (kg) at steady state showed that dosing based on body weight did not reduce inter-patient variability of AUC.

Metabolism
The kinetics of the main metabolite CGP 74588, the N-desmethyl derivative of the parent compound was investigated. In most patients, CGP 74588 could be detected in plasma 30 minutes after the oral administration of imatinib. As in adult patients, the plasma AUC(0-24) for CGP 74588 is approximately 20% of the AUC for imatinib.

Comparison between children and adult populations

As shown in the figures, the mean plasma concentration curve and AUC at steady state in children following once daily dosing with 260 mg/m^2 and 340 mg/m^2 were comparable to the exposure in adults at daily doses of 400 mg and 600 mg, respectively.

Figure 1. Comparison of mean plasma concentrations at steady state in children (study 0103) and adults (study 03 001)

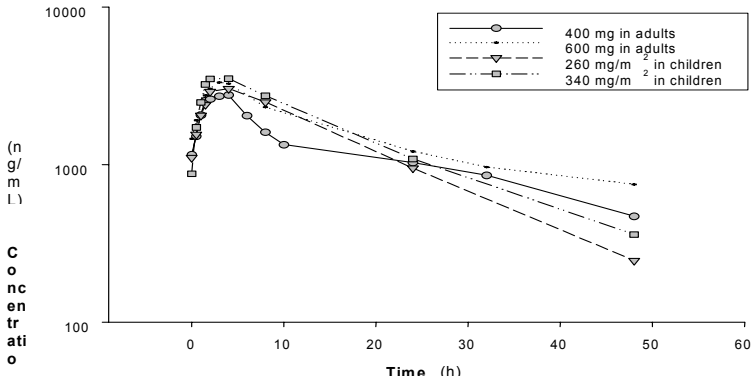
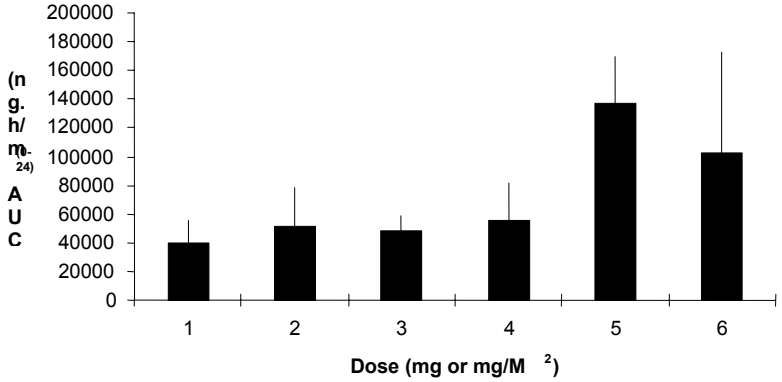


Fig. 2. Comparison of $AUC_{(0-24)}$ ±SD in adults and in children



Legend: - Adults from study 03 001 treated at (1) 400 mg or (2) 600 mg

- Children in study 0103 treated at (3) 260 mg/m^2, (4) 340 mg/m^2, (5) 440 mg/m^2 and (6) 570 mg/m^2.

Relationship between plasma concentration and effect

Pharmacodynamic (PD) effects were explored by examining the relationship between WBC counts after one-month treatment and drug exposure (AUC). The lowest AUC was above 20000 ng.h/ml, which is almost 3 times higher than the EC_{50} estimated from adult data (7000 ng.h/mL), at which level of AUC 87.5% of the maximum WBC reduction effect of Glivec is to be expected. On the basis of these limited data and despite substantial between-patient variability, it can be concluded that the lowest dose of 260 mg/m^2 evaluated in this study is associated with a drug exposure already above the maximal effect level and is predicted to result in normalization of WBC counts in all patients.

Dose - response

In study 0103, the starting dose of 260 mg/m^2 was extrapolated from the dose of 400 mg/day, which was found to be both safe and effective in clinical trials in adult patients with chronic phase CML. Subsequent dose levels were defined as 30% dose escalation steps (340, 440 and 570 mg/m^2/day). Data from study 0103 indicate that a daily dose of 260 mg/m^2 in children is associated with a similar PK exposure and a comparable efficacy and safety in comparison with a dose of 400 mg in adults. A higher dose of 340 mg/m^2 daily is similarly safe and yields a drug exposure comparable to a dose of 600 mg in adults. In this study, no MTD was characterised up to 570 mg/m^2/day.
A modelling of the relationship between drug exposure and pharmacodynamic response measured by WBC at day 28 indicate that the maximum effect on WBC is already achieved at the dose of 260 mg/m^2. On this basis, it can be concluded that imatinib at doses of 260 to 340 mg/m^2 is safe and effective. However, the total daily dose should not exceed the doses recommended in adults, ie. 400 and 600 mg respectively. As recommended for adults, escalation of the dose to 340 and 440 mg/m^2/day can be considered in selected patients with insufficient response or loss of response.

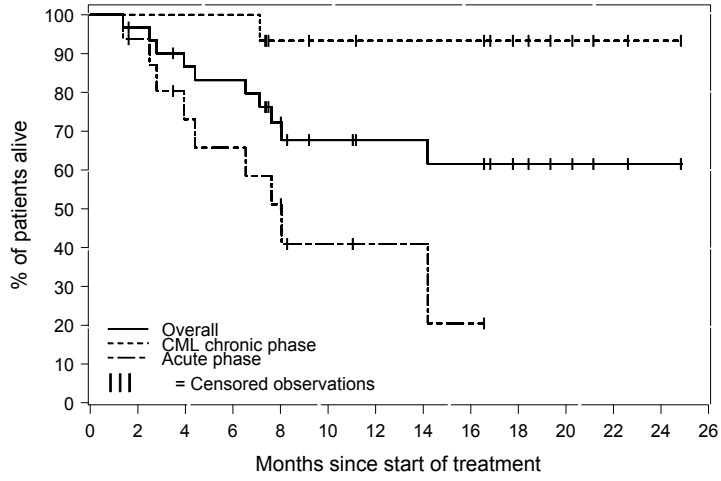
Efficacy results

Study 0103

- Chronic phase CML failing prior IFN therapy

Among the 14 patients with confirmed late chronic phase CML, all **(100%)** achieved a complete haematological response with WBC <10 x10^9/L and platelets <450 x10^9/L on two consecutive visits (8 had elevated WBC and/or platelet counts at baseline).
Out of 13 patients with chronic phase CML and cytogenetic data available, major cytogenetic response rate (MCR) was **84.6%**, thereof 7 (54%) and 4 (31%) achieved a complete and partial cytogenetic response respectively. After the database lock for this analysis, communication with the principal investigator revealed that two of the 4 patients with a partial response subsequently achieved also a complete cytogenetic response (CCR). Glivec was effective at all doses tested.
The estimated 12-months rate of survival for the 15 patients reported to be in chronic phase CML was **93.3%** (95%CI 80.7 – 100). However, the only patient who died in the chronic phase cohort is the patient who had testicular disease at study entry and therefore fulfilled the criteria for blast crisis. None of the 14 patients with confirmed chronic phase CML have died.

Study 0103: Survival by disease phase



- Acute leukaemia

The haematological response of patients with acute leukaemia was evaluated on bone marrows only. Overall, the rate of M1 marrow response (ie. with up to 5% blasts) was **60%** (9 out of 15 patients). Out of the six patients evaluable for response and with an acute leukaemia with a myeloid phenotype,

three (50%) achieved a M1 marrow. In contrast, six (67%) of the 9 patients with a lymphoid phenotype achieved a M1 marrow.
For cytogenetic response, no summary is provided in the acute phase patients due to incomplete data.
The estimated 12-months rate of survival for the 16 patients with either blast crisis or acute leukaemia was **40.9%** (95%CI 13.4 – 68.5). Median survival was 8 months.
The results are not described separately for patients with CML in blast crisis, ALL and AML.

Study 03 001.
Chronic phase CML failing prior IFN therapy. From the 3 patients, two of them (aged 11 and 13 years) achieved a CCR and were still on treatment at 463 and 590 days on study at the time of cut-off. The third patient did not achieve a cytogenetic response but stayed on study for 675 days. Of the 5 advanced phase patients, only the one with CML lymphoid blast crisis achieved a complete response in both blood and bone marrow.

Comparison of response in children and adults

Rates of MCyR in late chronic phase CML

Paediatric N = 16 (Studies 0103 + 03 001)	Adult N = 454 (Study 0110)
81.3%*	60%

* Patients with MCR: 11/13 in study 0103 and 2/3 in study 03 001

In patients with either CML in BC or Ph+ acute leukaemias, the level of bone marrow response (≤5% blasts in marrow regardless of peripheral blood counts) seen in children in studies 0103 and 03 001 is also similar to previous findings in adults enrolled in study 03 001 in which haematologic response was evaluated using similar response criteria. However, as seen in adult trials, these responses were usually short and many patients discontinued study because of progressive disease.

Rates of marrow response (≤5% blasts) in blast crisis or Ph+ ALL

Paediatric n = 20 (Studies 0103 + 03 001)	Adult** n = 20 (Study 03 001 ALL+ LBC)
55***%	55%

** sum of patients with either a CHR or a marrow response ≤5% in adults enrolled in study 03 001
*** Patients with a M1 marrow (blasts ≤5%): 9/15 in study 0103 and 2/5 in study 03 001

Clinical safety

Patient exposure
It is estimated that approximately 131 children with Ph+ leukemias have been treated with Glivec either in clinical trials (39 patients in studies 0103, 03 001), in the expanded access program (30 patients in trials 0113, 0114, 0115) or in a specific paediatric compassionate case program (program 0116 and other local mechanisms involving 62 children). There is no post-marketing experience with paediatric patients.
The majority of the 18 children with CML enrolled in both study 03 001 and 0103 with chronic phase CML were in the adolescent group. The median age of the patients with chronic phase CML in study 0103 was 14 years.
In contrast, the majority of patients with acute leukaemias were in the children category as expected given the epidemiology of ALL in children. No infants below 3 years of age have been enrolled in these trials.

Patients by age groups in studies 0103 and 03 001

	CML (n=18*)	Acute leukaemias (n=21**)
≥2 - <12 years	5 (27.8%)	13 (61.9%)
≥12 - <18 years	9 (50%)	7 (33.3%)
≥18 years	4 (22.2%)	1 (4.8%)

* 15 patients in study 0103 and 3 in study 03 001.

** 16 patients in study 0103 and 5 patients in study 03 001

Study 0103

At the time of cut-off for analysis, 13 (86.7%) and 1 patients (6.3%) with chronic phase CML and acute leukemias were still on study, respectively.

The main reasons for discontinuation were progressive disease for 5 patients (4 with acute leukemias), relapse for 8 patients (7 with acute leukemias) and transfer to a BMT program (2 patients with acute leukemias).

The median duration of exposure was 16.6 months for the chronic phase patients (ranging from 2.6 to ≥24.8 months) and 2 months for acute leukaemia patients (ranging from 0.9 to ≥11.0 months).

The median dose-intensities in each dose cohort were almost identical to the intended dose.

Only one 3-year-old patient treated at 260 mg/m^2 had to have the capsules opened and the contents suspended in a beverage. According to the expert report, this patient experienced no remarkable AEs and his PK profile was not different from the profile of the other patients enrolled in this cohort. However, in the final study report, it is mentioned that this patient experienced several dose reductions from 250 to 25 mg/day. This finding is not adequately described and the applicant justifies that, from the data available, it was not possible to assess the nature of the toxicity, which led to dose reduction in this patient.

Study 03 001

Among the 8 children enrolled in this study, 3 received a dose of 173 to 200 mg/m^2/day, four a dose of approximately 260 mg/m^2, and one a dose of 360 mg/m^2/d. The median duration of treatment was 9.8 months (range 1.6 to 22.2 months). The three patients with chronic phase CML were treated for ≥15.2, ≥19.4 and 22.2 months, respectively (the first two were still on treatment at the time of analysis). The five advanced phase CML or ALL patients were on treatment for 1.6, 1.9, 2.6, 5 and 14.6 months.

Additional data

It is estimated that approximately 62 children have received Glivec under the 0116 compassionate case program up to 31 January 2002, including one 13-month-old infant treated with accelerated phase (Guilhot, personal observation).

Thirty patients were enrolled in the expanded access program (6 with chronic phase CML in study 0113, 13 in study 0114 including 4 ALL and 7 accelerated phase CML, and 11 in study 0115 including 2 AML and 9 blast crisis). Their median age was 15 years (range 3 to 17 years).

From both the compassionate case program and the expanded access program trials, only safety data on SAEs are available.

Safety results

A maximal tolerated dose (MTD) was not formally established during the first 28 days of therapy, as specified in the protocol. However, with continued daily treatment beyond the first month, the highest dose of 570 mg/m^2 appeared to be somewhat less well tolerated in acute phase patients though many "dose-limiting toxicities" may have represented complications of the underlying disease (all occurred in patients with acute leukaemia). The study therefore did not formally characterise a MTD, in line with the corresponding study in adults.

The most frequently reported drug-related AEs in study 0103 are shown in the table. The most frequent AEs reported in chronic phase CML were mild nausea/vomiting, diarrhoea, abdominal pain

and skin disorders. In patients with acute leukaemia, most frequent AEs were mild nausea and vomiting. The incidence of grade 3-4 drug-related AEs was low.
The pattern of AEs seen in this study is similar to previous studies in adults, with the exception of a much lower incidence of musculoskeletal events and oedema. Muscle cramps were never reported during the study and only three patients (10%) complained of myalgia. There were also no reports of periorbital or lower limb oedema and only two patients experienced events possibly related to fluid retention: one patient with a pericardial effusion though in association with a pericarditis that may have had an infectious origin, and a second patient with marked weight gain (from 71.4 to 78.6 kg) during the first month of therapy without overt signs of fluid retention. This was judged to be a dose-limiting toxicity (DLT) and the dose of study drug was reduced by 30%. A single episode of cerebral haemorrhage occurred in a patient with myeloid blast crisis and a grade 4 thrombopenia who was also receiving heparin.

Study 0103: most frequent drug-related AEs by disease group

(≥10% overall, all grades)	**Chronic phase CML**	**Acute phase**	**All patients**
Total no. of patients treated n (%)	15 (100)	16 (100)	31 (100)
Total no. of patients with any AE	15 (100)	12 (75.0)	27 (87.1)
Total no. of patients with any AE (excl. laboratory)	14 (93.3)	11 (68.8)	25 (80.6)
Adverse event			
Vomiting NOS	4 (26.7)	8 (50.0)	12 (38.7)
Nausea	6 (40.0)	3 (18.8)	9 (29.0)
Diarrhoea	5 (33.3)	1 (6.3)	6 (19.4)
Abdominal pain NOS	4 (26.7)	1 (6.3)	5 (16.1)
Skin desquamation NOS	4 (26.7)	1 (6.3)	5 (16.1)
Febrile neutropenia	1 (6.7)	2 (12.5)	3 (9.7)
Dyspepsia	2 (13.3)	1 (6.3)	3 (9.7)
Pyrexia	1 (6.7)	2 (12.5)	3 (9.7)
Infection NOS	1 (6.7)	2 (12.5)	3 (9.7)
Myalgia	2 (13.3)	1 (6.3)	3 (9.7)
Fatigue	2 (13.3)	0	2 (6.5)
Catheter related infection	0	2 (12.5)	2 (6.5)
Bone pain	2 (13.3)	0	2 (6.5)
Hypotension NOS	0	2 (12.5)	2 (6.5)
Weight decrease	1 (6.7)	1 (6.3)	2 (6.5)
Headache	1 (6.7)	1 (6.3)	2 (6.5)

In general, within the range of doses evaluated and keeping in mind the limitations of small numbers of patients, there was no clear evidence of any dose-relationship in terms of AEs, grade 3-4 AEs, and SAEs. When considering the three different age groups, there was again no obvious difference with the exception of a slightly higher incidence of drug-related diarrhoea and abdominal pain in patients older than 12 years.
A total of 10 deaths have been reported in this study, all in patients with blast crisis or acute leukemias, all were related to a progression of the underlying disease.
Examination of the safety data from the 8 children enrolled in study 03 001 revealed no additional findings.

Laboratory findings
In study 0103, in comparison with adult studies, there was a higher incidence of grade 3-4 myelosuppression (neutropenia and thrombopenia). This may relates in part to the population of patients enrolled (51.6% with acute leukaemia, and heavily pre-treated population). However, it is more probably related to “aggressive” protocol guidelines for dose adjustment. Indeed, the protocol required no dose adjustment for thrombocytopenia and required temporary interruption of dosing only in case of grade 4 neutropenia persisting for more than 3 days. Although 87% of chronic phase CML patients developed grade 3/4 haematological toxicity in this current study, no severe episodes of febrile neutropenia or bleeding were reported.

Study 0103: grade 3/4 hematologic AEs

	Chronic phase CML	Acute phase	All patients
Total no. of patients treated n (%)	15 (100)	16 (100)	31 (100)
Total no. of patients with any hematologic AE grade 3/4	13 (86.7)	11 (68.8)	24 (77.4)
Adverse event			
ANC	12 (80.0)	10 (62.5)	22 (71.0)
Haemoglobin	3 (20.0)	8 (50.0)	11 (35.5)
Platelets	4 (26.7)	9 (56.3)	13 (41.9)
WBC	6 (40.0)	7 (43.8)	13 (41.9)

With regards to biochemistry abnormalities, grade 3-4 elevation of liver transaminases were reported in only 2 patients (6.5%) in study 0103. It was reported also in two children in study 03 001, however attributed to a GVHD in one patient, whereas the other patient had already grade 1-2 transaminases at baseline, probably related to the underlying disease.

In study 0103 as well as in study 03 001, no patients discontinued therapy because of AEs.

Additional data: compassionate case and expanded access programs
Patients were eligible to the compassionate case program (protocol 0116) if they were below 18 years of age and had either a Ph+ ALL or a CML in blast crisis, accelerated phase, or chronic phase failing prior IFN. No data were collected from this program with the exception of SAE. The dosing recommendations were with either 260 or 340 mg/m^2 daily.
In addition, a few children have been treated as special exemptions in one of the three adult expanded access protocols 0113 (chronic phase CML failing IFN), 0114 (accelerated phase) or 0115 (blast crisis and Ph+ ALL or AML).
There are no additional studies that are ongoing at the time of application in the indication of paediatric CML.
Altogether, up to 31 January 2002, SAEs have been reported to the MAH in a total of 13 children with Ph+ leukemias less than 18 years old treated either in one of the three expanded access clinical trials, the compassionate case program, or as spontaneous reports. Only 6 of them (6.5% out of the estimated denominator of at least 92 patients) were considered to have a suspected relationship to drug therapy and are listed in the table.

Additional drug-related SAEs in Ph+ leukemias (patients aged <18 years)

Study (Case number)	Age	Disease	Event
0114 (PHHO2001BR03304)	17	AP	Mucosal inflammation, neutropenia
Compassionate* (PHHO2001BR05402)	4	BC	Neutropenia, progressive disease, hepatic failure, elevated bilirubin, cholestasis, sepsis*
Spontaneous report (PHEH2001US08947)	2	CML	Intestinal perforation, infection, abdominal pain (patient treated after BMT, and with concomitant GVHD)
Spontaneous report (PHBS2001JP13085)	5	BC	Drug interaction with fluconazole, elevated bilirubin
Spontaneous report (PHBS2001JP13071)	9	BC	Elevated creatinine and urea, oliguria, renal disorder (all thought to be related to both Glivec, vancomycin and amphotericin B), pneumonia
Spontaneous report (PHEH2001US08299)	13	CML	Relapse of CML, aspergillosis, diarrhoea, skin lesions, oedema, pulmonary haemorrhage (patient with history of BMT)

* Only the neutropenia was considered as potentially drug related. The other events occurred after additional chemotherapy with vincristine, etoposide and cytarabine given for progressive disease
CML-AP: accelerated phase. CML-BC: blast crisis. GVHD: graft versus host disease

Discussion on clinical efficacy

CML is very rare in children. The clinical course and outcome of the disease in children appears essentially similar to adults. Even though the safety and effectiveness of BMT may be slightly superior, the toxicity and mortality related to the transplant procedure remain substantial.
In this variation application for paediatric use, the main evidence comes from two phase I dose finding studies which only included 39 children and out of them, only 18 were of an age from 3 to 12 years old, which is the most representative subgroup of a paediatric population. In the limited data available, the efficacy of imatinib in children has been demonstrated. In the chronic phase, the response rate, including cytogenetic response, was very high and it was maintained during the duration of the study. The rate of MCR observed in the 16 children with late chronic phase CML and evaluable cytogenetic data enrolled in the two studies (13 in study 0103, 3 in study 03 001) was 81.3% (95%CI 54.4–96.0, with 11 patients in study 0103, and 2 patients in study 03 001). A complete cytogenetic response was achieved in 9 patients (56.5%). These results also include 5 patients of an age between 18 and 22 years old. In patients with acute leukaemia, the response rate was high (60%) but of a very short duration with a median survival of approximately 8 months. In general, the efficacy of Glivec in this paediatric population was similar to adult studies in terms of haematological response, cytogenetic response and survival.

The recommended dose is acceptable as the results of these studies show a pharmacokinetic profile that seems to be similar to data previously obtained in adult studies. However, provided that the studies involved a very limited number of patients, an analysis of PK data according to age subgroups should be performed, especially for the 3-12 years subgroup. Moreover, it has to be underlined that no data regarding children under 3 years old are yet available.

Concerning the treatment approach of CML in children, it should be taken into account that BMT is considered as “first line” treatment due to being potentially curative of the disease. The impact of imatinib treatment on the outcome of ulterior BMT should be discussed. Detailed data on clinical experience in patients receiving BMT that had been treated with Glivec previously should be provided.

A number of methodological issues have been discussed during the assessment. The total number of patients included in the studies submitted is very low, even considering the circumstances of the low incidence of CML in children. It should be noted that only 18 patients younger than 12 years have been included in the studies. The youngest patient was 3 years old. A very high proportion of patients had received prior BMT (45.2% of the patients) or prior multi-agent chemotherapy (67.7%). The age groups considered are in accordance with the ICH recommendations for paediatric studies; however, it would be interesting to have a more detailed description of the patient characteristics, particularly in the subgroup of 2 to 12 years. An important part of the patients included were adolescents or adults of an age from 18 to 22 years old. The MAH presented data to justify the choice of 22 years as the upper limit for a paediatric population and reanalysed the results of the studies (pharmacokinetics, efficacy and safety) through the age subgroups included in the population investigated.

In spite of the limitations, the results show that the pharmacokinetics of imatinib, including exposure and metabolism, in children seems to be similar to that in the adult population. The inter-individual variability was high as it was previously described in former studies. The plasma concentrations of imatinib obtained in these investigations seem to be in the target concentration. However, each finding should be carefully analysed in every age range and compared with adults. The dosage is justified by a similar drug exposure to that in the adult experience, which is acceptable taking into account the pharmacokinetic/pharmacodynamic relationship described for Glivec. This similarity was observed for the two lower doses but the trial had been designed to determine the maximum tolerated dose. The dose finding approach is acceptable. It cannot be taken for granted that doses lower than those proposed are also efficacious but, as safety was tolerable, the doses proposed can be recommended for further use in children.

Furthermore, concerning the treatment approach of CML in children, the impact of imatinib treatment on the outcome of ulterior BMT should be described and discussed. Detailed data on clinical experience in patients receiving BMT that had been treated with Glivec previously should be provided. Long term safety data of children treated with imatinib should be provided.

Discussion on Safety

With more than 130 children with Ph+ leukemias (CML or acute leukaemia) treated with Glivec in clinical trials or as compassionate cases, the available data suggest a similar safety profile in children compared to adults. In clinical trials, children have been treated for up to 25 months, with apparent no late onset toxicities. No data are available to date with regards to the effect (or absence of effect) of long-term treatment on growth. The safety results have not been analysed separately in the different age subgroups. The 3-year-old patient experienced several dose reductions from 250 to 25 mg/day. This finding is not adequately described and should be further discussed The results of the compassionate case and expanded access programs should be described in more detail In adults, Glivec has previously been shown to be reasonably safe as second-line treatment for all stages of CML. As the clinical course of the disease and response to IFN therapy in paediatric CML is similar to adults, it can be expected that Glivec will have a safety and efficacy profile also comparable to adult data.

Benefit / risk ratio

The data presented in this report in children with Ph+ leukemias are very limited but they indicate that imatinib at the proposed dosing regimen appears safe and effective in a paediatric population.
In late chronic phase CML, 14 children failing to IFN were treated with imatinib with a very high response rate that was sustained during at least 12 months. All of them obtained an haematological response and 85% of them a cytogenetic response. In this population, the efficacy was similar to that reported in adults. Regarding CML in blast crisis, it is recognised that the incidence of this situation is low and its prognosis poor, but the clinical experience in paediatric population that is submitted is limited to 5 cases, which makes difficult to make an adequate benefit/risk assessment.

It should be taken into account that the therapeutic situation is similar in both adults and children, therefore extrapolation from adult efficacy data may be appropriate considering the pharmacokinetic and safety results. Concerning the treatment approach of CML in children, it should be taken into account that BMT is considered as “first line” treatment due to being potentially curative of the disease. The impact of imatinib treatment on the outcome of ulterior BMT should be described and discussed. Detailed data on clinical experience in patients receiving BMT that had been treated with Glivec previously should be provided.

In the available data, imatinib seems to have a similar safety profile in children compared to adults. Moreover, in additional safety data from children in compassionate and expanded access programs treated, the safety was acceptable, although long-term results are not yet available.

Recommendation

On the basis of the commitments of the MAH to provide additional data, the use of Glivec is indicated for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. Glivec is also indicated for the treatment of patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. The effect of Glivec on the outcome of bone marrow transplantation has not been determined.

9. Update on Drug interactions

Imatinib undergoes important hepatic metabolization as described in section 4 of the EPAR. There is a potential for significant drug-interactions when Glivec is administered concomitantly with drugs known to be inducers of cytochrome CYP3A4, resulting in a decrease in the exposure to imatinib. An interaction study to investigate the effects of rifampin (a semisynthetic antibiotic derivative of

rifamycin B, potent inducer of the cytochrome P-450 hepatic enzyme system) on the pharmacokinetics of Glivec (substrate of CYP450 3A4).with Rifampin, a potent inducer of the cytochrome P-450 hepatic enzyme system, has been performed in order to assess this issue and to provide guidelines for the co-administration with this class of drugs.

9.1 Clinical aspects

Study CSTI571B2102, a single centre, open-label, single-sequence, crossover study, has been developed to assess the clinical relevance of the interaction of Glivec with a CYP3A4 inducer in fourteen healthy subjects. During the first treatment period, baseline oral Glivec PK were established. The second treatment period consisted of oral Glivec PK following 8 days of oral rifampin administration. Rifampin administration was maintained throughout the PK sampling period for an additional 3 days to prevent any reduction in CYP3A4 induction. The ratio of 6beta-hydroxycortisol to cortisol excreted in the urine was measured on study days –1, 10, 14 and 18 as proof of induction of CYP3A4. The primary objective of the study was to investigate the effect of the co-administration of rifampin on the pharmacokinetics of Glivec. The secondary objetive was to assess the tolerability of Glivec alone and in combination with rifampin. Safety was assessed by recording all adverse events (AEs) reported during the course of the study, regular monitoring of clinical laboratory parameters, vital signs and ECG recordings.

Pharmacokinetics results
13 male and 1 female participants were enrolled and completed the study. Two subjects were CYP 2D6 poor metabolisers. The main pharmacokinetic parameters of imatinib and the main metabolite, CGP74588 for the 14 healthy subjects determined by non-compartmental analyses are listed in Tables 1 and 2. The mean and standard deviation for each parameter are given for the two treatment periods in which Glivec was administered.

Table 1 Imatinib PK parameters following oral administration of 400 mg Glivec alone and combined with oral administration of 600 mg rifampin

	Glivec plus rifampin	**Glivec alone**
T_{max} (h) *	2.5 (1.0 – 2.5)	2.5 (2.0 – 4.0)
C_{max} (ng/mL)	727±173	1563±285
$t_{½}$	8.8±0.7	16.7±3.1
$AUC_{(0-24)}$ (ng.h/mL)	5331±1369	16301±3475
$AUC_{(0-inf)}$ (ng.h/mL)	5996±1631	22992±5607
V_z/F (L)	921±303	436±96
CL/F (L/h)	72.0±21.5	18.7±6.0

all unflagged values are mean ± SD
* = median (range)

Table 2 Metabolite (CGP 74588) PK parameters following oral administration of 400 mg Glivec alone and combined with oral administration of 600 mg rifampin

	Glivec plus rifampin	Glivec alone
T_{max} (h)*	1.8 (1.0-2.5)	2.5 (1.5-4.0)
C_{max} (ng/mL)	330±76	174±33
$t_{½}$	35.2±9.9	38.8±11.3
$AUC_{(0-24)}$ (ng.h/mL)	2285±580	1820±351
$AUC_{(0-inf)}$ (ng.h/mL)	3669±955	4115±923

all unflagged values are mean ± SD

* = median (range)

Figure 1 Mean plasma concentrations of imatinib following oral administration of Glivec alone (A) and combined with rifampin (B)

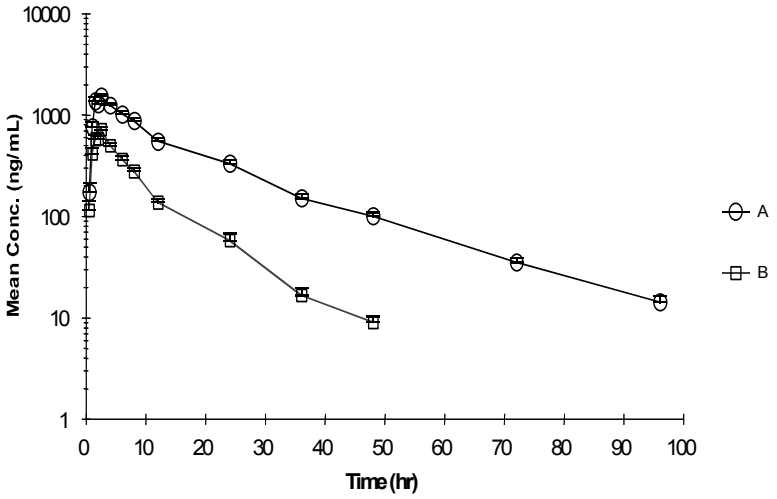
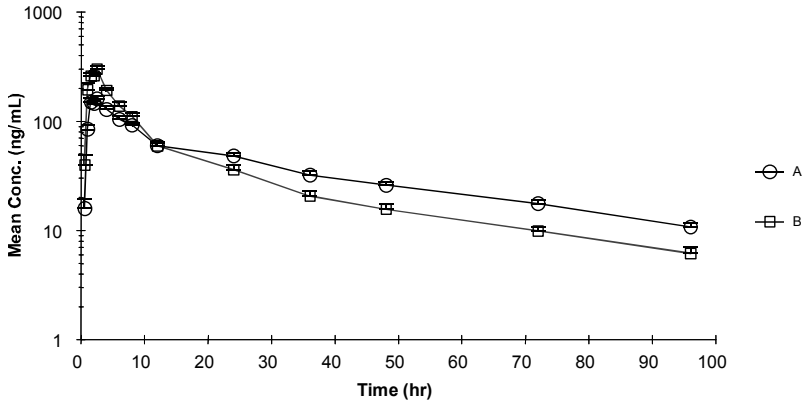


Figure 2 Mean plasma concentrations of the metabolite following oral administration of Glivec alone (A) and combined with rifampin (B)



Following rifampin co-administration, the mean imatinib Cmax, AUC(0-24) and AUC(0-inf) decreased significantly by 54% , 68% and 74% respectively. When expressed as the ratio of the value of imatinib with rifampin over the value without rifampin, co-administration of rifampin reduces Cmax to 46.1% (90% confidence interval: 40.8% to 52.1%), AUC(0-24h) to 32.4% (29.5%-35.6%), and AUC(0-inf) to 26.0% (23.5%-28.7%) of the respective values without rifampin treatment. There was a statistically significant increase in CL/F with a mean 4-fold increase.

With regard to metabolites, the mean Cmax and AUC (0-24) of CGP74588 increased significantly by 88.6% and 23.9% after rifampin treatment. However, the AUC (0-inf), decreased by 11.7%. With the exception of AUC (0-inf) of the metabolite, which meets the formal equivalence criteria, the ratios for the other PK parameters are far from the ideal value of 1. Thus, a pharmacokinetics interaction between Glivec and Rifampin exists. The ratio of 6-β-hydroxycortisol to cortisol increased by 10-fold on day 18 after continuous administration of rifampin, indicating that CYP3A4 induction did occur.

Safety and tolerability

Mild or moderate adverse events were reported in five (36%) of the fourteen subjects during the study, but none of them was suspected to be related to the study drug and all resolved within one to two days during the study period. Thirteen of the patients presented deviations from the normal range for at least one biochemical and/or haematological/urinalysis parameters (being cholesterol plasma concentrations and ALT elevations the most frequent). The Investigator did not consider any of these abnormalities as clinically significant nor related to study drug. The monitoring of vital signs did not reveal any abnormalities related to study drug.

9. 2. Discussion

The design of the study is considered appropriate to assess the influence of a potent CYP 3A4 inducer of the pharmacokinetic profile of Glivec. The study population is adequate, the inclusion of healthy subjects is acceptable due to the safety profile of Glivec. The inducer of CYP 3A4 (Rifampin) and its dosage regimen is considered sufficient for maximum induction and pharmacokinetic evaluation. The definition of a confidence interval (0.75-1.33), an extension of the confidence interval accepted for bioequivalence, for concluding that no clinically relevant interaction is found has not been justified on terms of dose-response, although taking into account the results of the study it is not relevant. The data analysis follows the CPMP Note for guidance on the investigation of drug interaction (CPMP/EWP/560/95).

For parent drug, both AUCs and Cmax showed a very marked decrease under coadministration of Glivec and rifampin (68% AUC 0-24, 74% AUC o-inf and 54% Cmax), as compared to administration of Glivec alone. This decrease was consistent for all subjects. Cl/F and V/F show a similarly consistent and marked increase (3.8-fold). These results have been explained by the induction of the hepatic metabolism of Glivec by CYP3A4 and also by induction of the pre-hepatic metabolism in the gut. The applicant's explanation seems plausible.

The AUCs for the metabolite showed and increase of the AUC 0-24 (23.9%) but a decrease of the AUC o-inf (11.7%). The mean Cmax also increased significantly by 88% after rifampin treatment. These results are less consistent (not all subjects followed this trend) than those seen for the parent drug. The increase in the concentrations of the metabolite was only mild. This disproportional change is claimed to be due to the increased rate of formation of other metabolites mediated by CYP3A4 not determined in this study. The applicant's explanation seems plausible The imatinib exposure in the two poor CYP2D6 metaboliser was not significantly increased, thus confirming the in vitro findings, i.e. CYP2D6 is not the main P450 enzyme involved in the microsomal biotransformation of Glivec. The reduction in the plasma concentrations of Glivec following the co-administration of rifampin was statistically significant and clinically relevant and therefore, may result in subtherapeutic plasma levels of Glivec (the plasma drug exposure is directly related to haematologic response). So that, it seems reasonable to extrapolate these findings to other potent inducer of CYP3A4 and translating it in a recommendation in the SPC. The proposed recommendation is acceptable.

The coadministration of Glivec and Rifampin has been well tolerated. No unexpected adverse events have appeared. The AEs were considered no drug related in the investigator's opinion, although most of them have been described in the SmPC as common adverse events.

The result clearly show that the concomitant use of Glivec and Rifampin may result in a significant and marked drug-interaction. Following Rifampin coadministration the mean imatinib Cmax, AUC0-24 and AUC0-inf decrease by 54%, 68% and 74%, respectively. The Cl/F increase nearly 4-fold.

The results of this study are consistent with the in vitro finding and the in vivo observations suggesting that Imatinib is a substrate of CYP3A4, the main enzyme involved in the microsome biotransformation of imatinib.

The reduction of plasma concentration of imatinib resulting from the concomitant use of CYP3A4 inducer may result in subtherapeutic plasma levels of Glivec. It is reasonable to extrapolate the results to other potent 3A4-inducers.
Therefore, the above findings were translated to adequate recommendations in the SmPC.

10. Update on Clinical Safety post-authorisation

A number of adverse reactions had been already included in the SPC following the assesment of the extensions of indication described above. These reactions were: exfoliative dermatitis, bullous eruption, erythema exudativum multiform including Stevens Johnson syndrome, toxic epidermal necrolysis,, vesicular rash, psoriasis, hepatitis and hepatic failure.
Following the assessment of the 2nd PSUR the following additional reactions were included under section 4.8 of the SPC as rare: pericardial effusion, pulmonary fibrosis, interstitial pneumonitis, glaucoma and arthralgia.

Furthermore, with the review of the 3rd PSUR the following reactions were added as rare: pericardial effusion, pulmonary fibrosis, interstitial pneumonitis, glaucoma, arthralgia, ileus, intestinal obstruction, pericarditis, thrombosis, embolism, pancreatitis, vitreous haemorrhage, tumour haemorrhage, tumour necrosis, confusion and convulsion.

Incorrect statement on possible interaction was deleted from sections 4.4 and 4.5. In section 4.5 of the SPC, in the paragraph on "drugs that may have their plasma concentration alterated by Glivec" the sentence *"and patients should be warned to avoid or restrict the use of over the counter and prescription medicines containing paracetamol"* is erroneous.

Paracetamol is metabolised by conjugation enzymes (glucoronide and sulfate formation). Paracetamol is also oxidised by hepatic cytochrome P450. At therapeutic doses, this pathway is a minor one. With large doses, the importance of paracetamol oxidation increases. The two P450 isoforms appear to be the principal catalysts of paracetamol oxidation are CYP2A1 and CYP2E1. No one of these two P450 cytochrom isoenzymes appear to be involved in the metabolism of imatinib. In vitro studies has shown that imatinib is mainly transformed by CYP3A4 and competitively inhibits CYP2C9, CYPD6 and CYP3A4/5. It is concluded that a metabolic interaction between imatinib and paracetamol at the level of CYP'S appear to be unlikely. The above sentence is now deleted. The statement *"One patient, who was taking paracetamol regularly for fever, died of acute liver failure. Although the aetiology is currently unknown, caution should be exercised when using paracetamol*" is deleted from section 4.4 of the SPC.

Regarding hepatic disorders the sentence in section 4.8 of the SPC that reads "…However, one patient with accelerated phase died of acute liver failure in which drug interaction with high doses of paracetamol could not be formally ruled out (see section 4.5)" should be replaced by"…There have been cases of cytolytic and cholestatic hepatitis and hepatic failure; in some of them outcome was fatal". This is in accordance with the CPMP recommendation.

Regarding the statement "on fluid retention reactions" the relevant paragraph has been modified.
"Miscellaneous adverse reactions such as pleural effusion, ascites, pulmonary oedema and rapid weight gain with or without superficial oedema may be collectively described as "fluid retention". These reactions can usually be managed by withholding Glivec temporarily and with diuretics and other appropriate supportive care measures. However, some of these reactions may be serious or life threatening and several patients with blast crisis died with a complex clinical history of pleural effusion, congestive heart failure and renal failure".

The Package Leaflet was updated accordingly.