30 May 2013
EMA/CHMP/161314/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Glivec

International non-proprietary name: IMATINIB

Procedure No EMEA/H/C/000406/II/0080

Note

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

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 8 June 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Glivec	IMATINIB	See Annex A

The following variation was requested:

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

The MAH applied for an extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC.

The Package Leaflet was updated in accordance.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0028/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0028/2012 was completed.

The PDCO issued an opinion on compliance for the PIP P/0028/2012.

Information relating to orphan market exclusivity

Similarity

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Arantxa Sancho-Lopez **Co-Rapporteur: Pierre Demolis**

Submission date:	8 June 2012
Start of procedure:	24 June 2012
Rapporteur's preliminary assessment report circulated on:	31 August 2012
Joint Rapporteur's updated assessment report circulated on:	14 September 2012
1st Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	22 November 2011
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 January 2013
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	17 January 2013
MAH's responses submitted to the CHMP on:	15 February 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	4 March 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	15 March 2013
3rd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	26 April 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 May 2013
Rapporteur's final assessment report on the MAH's responses circulated on:	24 May 2013
Upon request of the CHMP, the PDCO provided an opinion on the paediatric data with regard to the safety and efficacy (Appendix 01):	15 March 2013
The CHMP adopted a report on similarity of Glivec with Atriance, Evoltra, Novapurine and Sprycel (Appendix 02):	20 September 2012
CHMP opinion:	30 May 2013

2. Scientific discussion

2.1. Introduction

Problem statement:

Acute leukaemia, the most common form of cancer in children, comprises approximately 30%of all childhood malignancies, with acute lymphoblastic leukaemia (ALL) being five times more common than acute myeloid leukaemia. Philadelphia positive acute lymphoblastic leukaemia (Ph+ ALL) is characterised by the presence of the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)) resulting in the fusion of the break cluster region (bcr) gene on chromosome 22 with c-abl gene sequences translocated from chromosome 9 and the expression of the BCR-ABL protein. BCR-ABL fusion proteins are constitutively active tyrosine kinases that can alter multiple signalling pathways, which contribute to tumour growth and proliferation. Ph+ALL accounts for 15-30% of adult ALL and up to 5% of paediatric ALL.

Survival rates for ALL have improved dramatically since the 1980s, with a current five-year overall survival rates estimated at greater than 85 percent. In children, long-term survival rates are approximately 80%. This improvement in survival is due to treatment of a large number of children on sequential standardised research protocols.
Unfortunately, with chemotherapy alone, only 20–30% of children with Ph+ ALL are cured. Allogeneic hematopoietic stem cell transplantation (HSCT) with a closely matched donor in first complete remission cures 60% of patients. A review of 326 documented cases of Ph+ ALL diagnosed and treated by ten study groups and institutions from 1986 to 1996 described estimated 5 year disease-free survival ranging from 49% to 20%, for patients with the best and worst prognosis, respectively (Arico, 2000).

Treatment of children with ALL involves administration of a multidrug regimen that is divided into several phases (ie, induction, consolidation, and maintenance) and includes therapy directed to the central nervous system (CNS). Most treatment protocols take two to three years to complete, although the specific regimen varies depending upon immunophenotype and risk category.

Induction therapy is the initial phase of treatment and is designed to place the patient in remission. More than 90% of children and adolescents with ALL enter CR at the end of induction therapy regardless of their initial risk grouping. Induction therapy usually involves weekly administration of vincristine for three to four weeks, daily corticosteroids (prednisone, prednisolone, or dexamethasone), and asparaginase, either in its pegylated form or as 6 to 12 doses of L-asparaginase. A fourth agent such as an anthracycline (eg, doxorubicin or daunorubicin) may be added to the three-dose regimen, particularly for high-risk patients. Early clearance of lymphoblasts from the bone marrow and the presence of minimal residual disease (MRD) at day 15 and the end of induction therapy are the best indicators of outcome. Patients who respond rapidly to the induction regimen appear to have a more favorable outcome, whereas those who have a slow response or who fail induction therapy have a more guarded prognosis. Induction failure, which occurs in fewer than 5%of cases, is defined by the persistence of leukemic blasts in the blood, bone marrow, or any extramedullary site after four to six weeks of remission-induction therapy. Induction failure has historically been considered a particularly ominous sign and an indication for allogeneic hematopoietic cell transplantation (HCT).

Leukemic involvement of the CNS at the time of diagnosis is an uncommon finding, occurring in fewer than 5% of patients. However, before the use of preventive CNS therapy, up to 80 percent of children with ALL who were in complete bone marrow remission relapsed with "leukemic meningitis". The routine use of preventive CNS therapy is a major therapeutic advance in the treatment of childhood ALL. CNS treatment usually begins during the induction phase and continues throughout the remainder of the treatment regimen.

Consolidation or intensification therapy is the second phase of ALL treatment and is initiated soon after attainment of CR. Ongoing treatment is required because small numbers of leukemic lymphoblasts

(referred to as MRD) remain in the bone marrow despite histologic evidence of CR after induction therapy. In such cases, relapse occurs quickly if therapy is not continued.
The goal of post-induction chemotherapy is to prevent leukemic regrowth, reduce residual tumour burden, and prevent the emergence of drug-resistance in the remaining leukemic cells.
Consolidation therapy usually lasts from four to six months. It commonly involves the use of several different drug combinations and drugs with mechanisms of action that differ from those used during the induction phase. The MRD status is one of the most important predictor of disease-free and overall survival. Patients with detectable MRD have an increased risk of relapse after conventional therapy. As a general rule, the higher the risk for treatment failure, the more aggressive the intensification therapy plan.
Selected patients with high-risk disease have an increased incidence of relapse during intensification chemotherapy (eg, Philadelphia chromosome positive ALL, severe hypodiploid ALL (less than 46 chromosomes), infants with ALL, and those who have failed initial induction therapy). These patients are candidates for receiving HCT during first remission.

In the maintenance therapy, the overall treatment duration for most children with ALL is 24 to 36 months. After completion of the consolidation or intensification phase of therapy, patients often receive a less intensive continuation regimen using daily oral 6-mercaptopurine (6-MP) and weekly methotrexate with periodic intrathecal therapy.

Approximately 20 to 25 percent of children with ALL fail initial treatment. Patients with relapsed ALL require aggressive reinduction therapy and intensification, often using agents not administered in the original treatment protocol. Nelarabine and clofarabine have been used for the treatment of relapsed ALL. Although patients in first relapse usually attain a second remission with induction chemotherapy, they often relapse after short periods despite aggressive treatment. These patients are candidates for HCT once they have attained second remission

About the product

Imatinib is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the BCR-ABL1 tyrosine kinase (TK) and of several other receptor TKs, including KIT, the stem cell factor (SCF) receptor, the discoidin domain receptors (DDR1 and DDR2), the colony stimulation factor receptor (CSF-1R) and the platelet-derived growth factor receptors α and β (PDGFR-α and PDGFR-β). The inhibitory effects of imatinib on primary ALL blasts expressing p190BCR-ABL are similar to those observed on primary chronic myeloid leukaemia (CML) blasts expressing p210BCR-ABL.

Glivec is currently approved in over 110 countries for the treatment of both haematological malignancies and solid tumours. Glivec is already approved in a paediatric indication (paediatric patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy) at a recommended dose of 340 mg/m2 daily. Glivec is currently approved in the EU for the treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy at a recommended dose of 600 mg/day. Glivec is also approved in the EU for the treatment of adult patients with relapsed or refractory Ph+ ALL.
The present application is intended to seek approval for the following indication: “Glivec, integrated with chemotherapy, is indicated for the treatment of newly diagnosed paediatric patients with Philadelphia chromosome positive acute lymphoblastic leukaemia”.

A Paediatric Investigation Plan (PIP) was developed in accordance with Article 8 of the European Regulation (EC) 1901/2006. A final opinion from the EMA PDCO was received on 27 January 2012 on the acceptance of a modification of an agreed paediatric investigation plan for imatinib mesilate (Glivec) (EMEA-000463-PIP01-08-M03).

In the context of the PIP, the Company was asked to submit the results of three studies:

- Study 1: Open-label, multi-centre, non-randomised, dose-escalation trial to evaluate safety and efficacy of chemotherapy, haematopoietic stem cell transplantation and imatinib in children from 1 year to less than 18 years (and young adults) with acute lymphoblastic leukaemia.

- Study 2: Open-label, multi-centre, randomised trial to evaluate safety, activity and efficacy of imatinib on top of chemotherapy and in combination with haematopoietic stem cell transplantation in children from 1 year to less than 18 years with acute lymphoblastic leukaemia.
- Study 3: Development and validation of an integrated physiology-based pharmacokinetic (PBPK) and population pharmacokinetics model

Overall, the PIP agreed by the PDCO has been followed and the PDCO has issued an opinion that the studies were completed in compliance with the PIP and that the timelines have been respected.

The Company has submitted the three studies.

2.2. Non-clinical aspects

No new non-clinical studies were submitted.

2.2.1. Ecotoxicity / environmental risk assessment

The maximum anticipated daily dose foreseen for imatinib in paediatric patients is 600 mg.

Imatinib is rapidly absorbed after oral administration and is a substrate of CYP3A4, resulting in one main metabolite, the N-demethylated piperazine derivative, with similar pharmacological activity as the parent substance. Excretion of imatinib as unchanged parent substance accounts for 25% with 5% and 20% excreted in urine and faeces, respectively. Results from a new study on toxicity to sediment-dwelling organisms (OECD219) have been reported and a Tier B assessment was conducted.

Summary of main study results

Substance (INN/Invented Name): Imatinib/Glivec			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.5	Not potential Persistent, Bioaccumulative and Toxic (PBT)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.5	not B
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	3	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =4200-6100 cm^3/g	Study No. 486001
Ready Biodegradability Test	OECD 301B	9.0-12.0%	Not readily degradable. Study No. 270258
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ whole\ system}$ = 83-137 days $DT_{90,\ whole\ system}$ = 309-552 days	Study No. 486002
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	0.96	mg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC	5.6	mg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	10	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10} EC_{50}	65.0 232.0	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OCED 219	27d-NOEC	1.8	mg/L	Larvae of *Chironomus riparius*

2.2.2. Discussion and conclusion on non-clinical aspects

The pharmacologic properties and the toxicological profile of imatinib mesylate have been adequately described and assessed in previous applications. No additional non-clinical studies are considered necessary.

Imatinib mesylate is not a PBT substance. The calculation of the PECsediment using the equation R16-35 and the study following the OECD219 guidance are considered appropriate. A risk for sediment organisms has been identified. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see SmPC sections 5.3, 6.6).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study No. / Analysis	Patient population	Supporting data	n (evaluable)	Total daily dose
Pivotal study STI571I2301	Newly diagnosed ALL VHR patients (Ph+ ALL and Ph- ALL)	Efficacy, safety	Ph+ ALL: 92 Ph- ALL: 65 (safety only)	340 mg/m^2
studies and analyses				
Supportive study STI571AIT07	Newly diagnosed, Ph+ ALL patients (good and poor risk)	Safety	Good risk: 90 Poor risk: 70	300 mg/m^2
Pooled popPK STI571A0103, STI57103001, STI571A2108 STI571A2110	Ph+ CML, Ph+ ALL, other hematologic disorders	PK	67 (46 CML, 12 Ph+ ALL, and 9 other hematological disorders)	90 to 606 mg/m^2
Physiologically based PK (PBPK) model	Pediatric patients from 1 to 18 years	PK	Not applicable	340 mg/m^2
Ph-ALL: Philadelphia chromosome negative Acute Lymphoblastic Leukemia Source: [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]				

2.3.2. Pharmacokinetics

Imatinib is available as two different dosage forms: hard gelatin capsules and film-coated tablets. For paediatric patients who are unable to swallow the capsules, the capsules may be opened and the contents should be dissolved either in water or in apple juice. For paediatric patients who are unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of mineral water or apple juice per instruction of SmPC.

2.3.2.1. Methods – analysis of data submitted

This application included two modelling study reports [pooled population pharmacokinetic modelling report update] and [PBPK modelling report update]. The pooled population pharmacokinetic analysis was conducted in paediatric patients aged 2 to 18 years with haematological disorders including CML, Ph+ALL, or other imatinib indicated haematological disorders in four clinical studies: CSTI571A0103, CSTI57103001, CSTI571A2108, and CSTI571A2110. Since the 100 mg and 400 mg tablet formulations were bioequivalent with the 100 mg hard gelatin capsule, it is appropriate to pool PK data from the above 4 studies into a single popPK analysis.

- [CSTI571A2108] was a phase II non-randomised single arm study to determine the response rate of imatinib in paediatric CML and delineate its toxicity and PK in paediatric patients. Imatinib was administered orally, at 340mg/m2, rounded to the nearest 100 mg increment, once daily. In the absence of dose-limiting toxicities, there was no planned interruption of therapy. Each 28-day period was considered a treatment course.
- [CSTI57103001] was a phase 1 dose-finding study to determine the safety, tolerability, PK and PD profiles of imatinib in patients with CML resistant to interferon-alpha (IFN). Six children received 175 to 260 mg/m2 daily dose and had evaluable PK data for the popPK analysis.
- [CSTI57A10103] was a phase 1 dose-finding study to determine the safety, tolerability, PK/PD and efficacy of imatinib in paediatric patients with Ph+ leukaemia. The starting dose was 260 mg/m2 daily and dose was escalated to 340, 440, 570 mg/m2.
- Study [CSTI571A2110] was a non-randomised, open-label study in which patients diagnosed with CML, Ph+ ALL or other imatinib indicated haematological disorders between the ages of 1 to 4 years were administered a daily dose of STI571 ranging from 260 mg/m2 to 340 mg/m2. The duration of this study was a maximum of 21 days, during which 2 sets of PK profiles were collected from each patient. This study was discontinued early as agreed by PDCO due to the lack of patient population and accrual.

Pooled Population Pharmacokinetics Modeling

Experimental methods and data: Data from subjects between 2 and 18 years of age were pooled from studies CSTI571A2110, CSTI571A2108, CSTI57103001, and CSTI5710103. Plasma concentrations were measured for imatinib and the major pharmacologically active metabolite CGP74588.

Data analysis and modeling methods: Nonlinear mixed-effects models for the popPK of imatinib and CGP74588 were developed using NONMEM Version VI Level 2.0 with METHOD=1 INTERACTION. The likelihood function and diagnostic plots were used to assess goodness of fit and to suggest refinements to the model.

As part of the model validation, the final model was refitted by excluding the subjects younger than 4 years. The parameter estimates were compared to the corresponding estimates from the full dataset.

The concentration-time course of the 9 excluded subjects was predicted and compared to the observed concentrations.

The final model was used to assess clearance across body surface area (BSA), body weight and age. The clearance relationship with body weight from the final model was compared to a previously reported adult model.

The final model was then used to simulate PK parameters and related PK exposure measures (AUC, Cmax, Cmin) for the proposed paediatric doses of 260 and 340 mg/m2, as well as for various alternative dosing schemes, including those designed to match the AUC for children with adults.

The target exposures used in the model-based simulations for dosing schemes MODELAUC40 and MODELAUC60 were derived from previous population PK analysis in adult CML patients. The previous adult CML patient modeling suggested that CL is approximately 10 L/h and AUCs were approximately 40 and 60 h×mg/L for adult 400 mg and 600 mg dose, respectively, from an integrated popPK report in adult patients.

Physiologically-based PK (PBPK) Modeling Report

PBPK model reflects current knowledge about pharmacological processes that are known to be well characterised. Therefore poor characterisation of some physiological or pharmacological process with respect to imatinib in younger children aged 1-2 years may lead to a sub-optimal estimation of PK behaviour of imatinib in this age group. Therefore it is important to consider the validity of some model assumptions and uncertainty of model parameters when one interprets the results from PBPK modelling.

Objectives:

- To predict pediatric AUC at steady-state using PBPK approach based on imatinib clearance in adult population, then compare the results with the experimentally observed AUC values, with specific focus on children age 1 year and older.
- To predict imatinib plasma concentration-time profiles in plasma and tissue in pediatric subjects, and to assess the effect of pediatric growth processes using a PBPK model
- To evaluate factors influencing imatinib exposure in pediatric patients

Experimental methods and data: Paediatric growth database was obtained from the literature, such as organ size, blood flow, enzyme and plasma protein maturation. No clinical data were used for model-based simulation. Clinical data from pooled studies were used as references to compare with model predictions.

Data analysis and modeling methods: A PBPK model previously developed for imatinib was used, and the model parameters were modified using growth and maturation database obtained from the literature. Clearance range observed in phase III trial in adult population was used as reference for paediatric scaling. Two separate approaches were employed: 1) steady-state (SS-Model) approach scaling only clearance to predict steady-state AUC, and 2) dynamic (Dyn-Model) PK simulation to assess the imatinib concentration-time profile within a dosing interval. The effects of body size and blood perfusion on the PK profiles were evaluated in addition to maturation in clearance. The model evaluations were conducted by comparing the predicted steady-state AUC and predicted imatinib concentration-time profile with noncompartmental AUC computed by the trapezoidal rule and observed data from the pooled clinical studies, respectively. Dyn-Model simulation was performed with SimuSolv on a VAX cluster.

2.3.2.2. Results

Pooled Population Pharmacokinetics Modeling

The popPK of imatinib was characterised by a one-compartment model with zero- order absorption and first-order elimination. The model was parameterised in terms of apparent clearance (CL/F), apparent volume of distribution (V/F), and duration of zero-order input (D1). Inter-individual variability in CL/F and V/F were characterised by lognormal distributions and the residual error by a combined error model. Analysis of covariate effects revealed that CL/F and V/F increased with body surface area (BSA). After correcting for the BSA effect, the following covariates were not found to have clinically significant effects on the exposure of imatinib: age, gender, race, WBC, hemoglobin, body weight, BMI, and disease type. The clearance for a subject whose BSA=1.73 m2 was 9.06 L/h, which corresponds with the estimates from previous works in adult populations.

There was no statistically significant difference in imatinib clearance among disease types Ph+ CML, Ph+ ALL and Other (Figure 01). Clearance for patients with Ph+ ALL were estimated to have an imatinib clearance 9.7% (SE=15.9%) less than that for Ph+ CML.

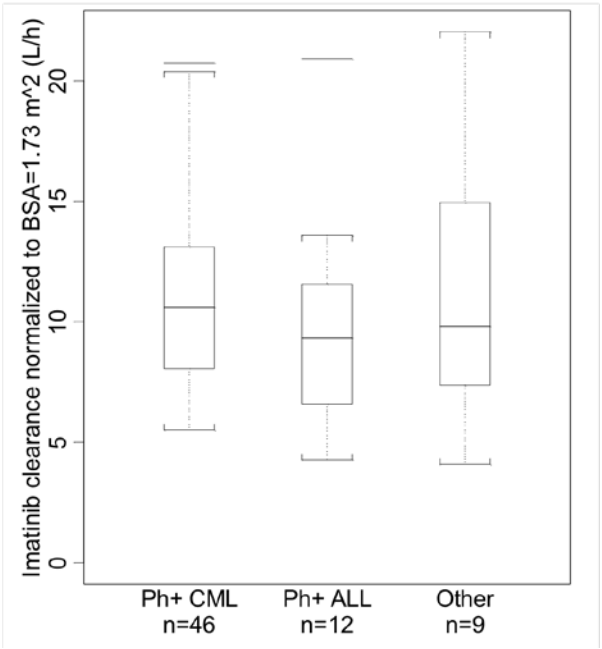


Figure 01: Imatinib clearance normalized to BSA=1.73m^2 by disease type (N=67)

Comparison of the relation between clearance and body weight in the final model with a previously developed adult model shows that the models are consistent with each other for body weights of 60 kg and higher. Refitting the final model without the subjects younger than 4 years led to similar parameter estimates. Prediction of concentration-time profiles for the excluded subjects showed that the observed concentrations were generally within the predicted 90% variability bands. The popPK model was used to extrapolate AUC for one year old children. The uncertainty was greater for one year than two year old. Slightly lower exposures were observed for 1 year old as compared to 2 year and above.

The popPK of CGP74588 was characterised by a two-compartment model parameterised in terms of apparent clearance (CLM/F), apparent volumes of the central compartment (VCM/F) and peripheral compartment (VPM/F), and the apparent inter-compartmental clearance (QM/F). The fraction of imatinib metabolised to CGP74588, a scaling factor in parent/metabolite modeling, was fixed to 0.13 or 13%. The final popPK model for CGP74588 includes BSA as a covariate with clearances and volumes increasing with BSA.

The exposure of 18-year old subjects (dosing scheme of 340 mg/m2 not to exceed 600 mg) was simulated using the adult model by Schmidli et al. (2005). As can be seen in Figure 02, the exposure of children in different age groups (simulated from the final popPK model in this report) for 340 mg/m2 capped at 600 mg corresponds closely to the exposure of adults simulated using the model by Schmidli et al. (2005).

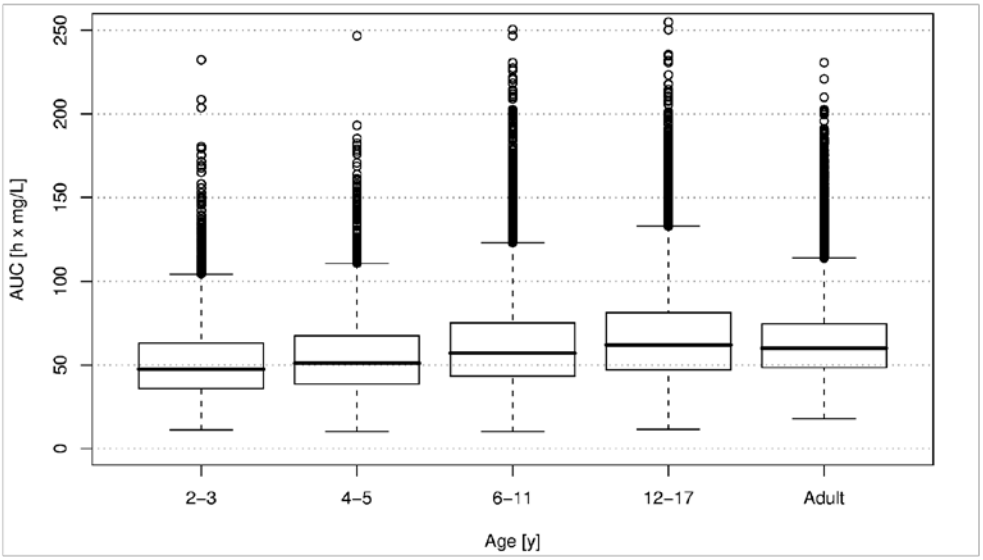
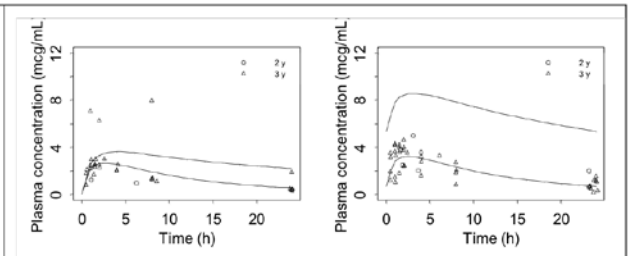
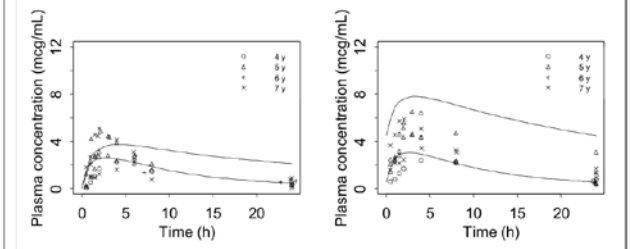
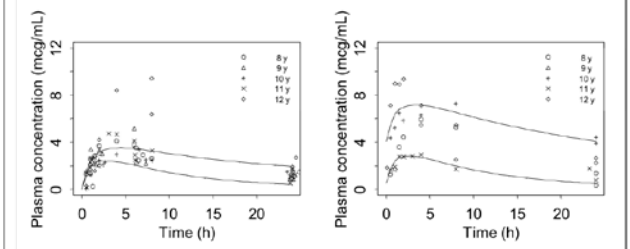
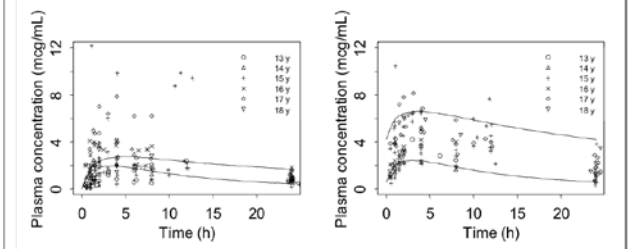


Figure 02: Simulated AUC by age group for 304 mg/m^2 not to exceed at 600 mg dose, compared against adults simulated with the adult model receiving 600 mg fixed dose

Model-based simulation of various dosing schemes showed that doses of 260 mg/m2 not to exceed 400 mg or 340 mg/m2 not to exceed 600 mg lead to relatively constant exposures (AUC, Cmax, and Cmin) across the range of observed body surface areas and ages. The AUCs achieved by these doses are similar to adult AUCs.

Physiologically-based PK (PBPK) Modeling Report

The SS-Model simulations showed that the majority of actual steady-state AUC values (94%; 29/31) normalised to 340 mg/m2 in paediatric patients fell within the 0.5 and 99.5 percentiles of model projected range scaled from adult measurements. Based on the Dyn- Model, the predicted plasma concentration-time profiles were generally in good agreements for most paediatric subjects, except for younger subjects ≤ 2 years old, for which the exposure appeared to be over-predicted. The predicted deviation from adult was higher for the first dose than at steady state (Day 28). The largest deviation was observed for Cmax. The predicted age effect on AUC and trough (Cmin) were less than that on Cmax. The differences in predictions of children and adults seem to be the mixed results of changing distribution volume and blood circulating turnover, in addition to clearance maturation with age. Improvement of model prediction could be achieved for the young subjects by refining certain model assumptions or parameters, such as assuming different plasma protein maturation in cancer patients from healthy subjects, or a lower extent of oral absorption for those age groups instead of a complete absorption, considering the immaturity of the gastrointestinal tract. Nonetheless, taking a “conservative approach” for the model assumptions, the prediction was only 1.5-fold of the adult value at 1 year age, suggesting a safe application of PBPK approach in scaling imatinib clearance down to children at 1 year of age.

2 year old simulation; 0.5 and 99.5 percentile on Day 1(left) and 28 (right); plots are 2 years (circle) and 3 years (triangle)	
5 year old simulation; 0.5 and 99.5 percentile on Day 1 (left) and 28 (right); plots are 4 years (circle), 5 years (triangle), 6 years (+), and 7 years (×)	
10 year old simulation; 0.5 and 99.5 percentile on Day 1 (left) and 28 (right); plots are 8 years (circle), 9 years (triangle), 10 years (+), 11 years (×), and 12 years (diamond)	
15 year old simulation; 0.5 and 99.5 percentile on Day 1 (left) and 28 (right); plots are 13 years (circle), 14 years (triangle), 15 years (+), 16 years (×), 17 years (diamond), and 18 years (inverted triangle)	

Source: PBPK modeling report, 2011

Figure 03: PBPK modelling: comparison of model simulated plasma imatinib concentration and the measurement from four clinical syudies (N=67 patients with concentrations normalized to 340mg/m² dose)

2.3.3. Discussion and conclusion on clinical pharmacology

The dosing scheme for paediatric Ph+ ALL derives from the pooled population pharmacokinetic analysis, the physiologically-based pharmacokinetic modelling analysis, experience from paediatric CML population and extrapolation from adult Ph+ ALL population. To achieve comparable exposures in paediatric patients corresponding to target exposure in adult patients, body surface area (BSA) based dosing should be employed in the dose administration of imatinib in paediatric patients with Ph+ ALL. The proposed posology of 340 mg/m^2 in paediatric patients from 1 to 18 years of age seems appropriate.

2.4. Clinical efficacy

Studies STI571I2301 (Schultz et al. 2008; Schultz et al., 2009) and STI571AIT07 supporting this application were conducted and monitored by cooperative groups in the US and Europe, respectively.

2.4.1. Main study

A Children's Oncology Group pilot study for the treatment of very high risk (VHR) acute lymphoblastic leukaemia in children and adolescents (COG AALL0031, STI571I2301).

Methods

Study participants

The study population consisted of paediatric patients with VHR ALL, defined as those patients who have an expected 5-year EFS of < 45% (Schultz et al., 2007. Criteria identified for VHR were:

- Ph+ ALL identified by
  - BCR-ABL expression by PCR or fluorescence in-situ hybridisation (FISH)
  - t(9;22)(q34;q31) by cytogenetics
- Hypodiploidy (chromosomes <44) by cytogenetics
- DNA index <0.81 by flow cytometry
- MLL gene rearrangement with slow early response (SER); SER is defined as M3 (>25% blasts) bone marrow (BM) on day 7 (high risk patients) or an M2 (5%-25% blasts) /M3 (>25%) marrow on day 14 (standard risk patients) of induction.

Other patients presumed to have a poor outcome and classified as VHR were those with persistent measurable disease following induction in a frontline study defined by bone marrow and MRD status at the end of induction.

Eligibility for entry into the COG AALL0031 protocol for VHR ALL required a central confirmation of Ph+ ALL, hypodiploidy or MLL rearrangement with slow early response (SER).

Patients were included who met the following criteria:

- Male or female patients, aged 1 to < 22 years, who themselves or the legally authorised representatives have given informed consent
- Ph+ ALL:
  - BCR/ABL by FISH or RT-PCR
  - t(9;22)(q34;q11) detected by cytogenetics
- Chromosomes < 44 by cytogenetics
- DNA index < 0.81 by flow cytometry

- Any rearrangement of chromosome 11 that resulted in disruption of MLL (gene 11q23) by cytogenetics and slow early response (SER).
- Induction failures were defined prior to study entry as:
  - Patients with a bone marrow (BM) status of M3 (> 25% blasts) at the end of standard induction therapy, enrolled within 42 days of diagnosis
  - Patients with a BM status of M2 (5-25% blasts) or MRD ≥ 1% (by flow cytometry) at the end of induction therapy who still had M2 (or M3) or MRD ≥ 1 % at the end of extended induction, enrolled within 14 days of their last day of extended induction therapy

Those who failed induction therapy or extended induction therapy were allowed to enrol into this study, irrespective of haematological values provided there was no active infection or immediate life-threatening organ malfunction.
Patients were enrolled after receiving a 3 - 4 drug Induction regimen either on, or identical to, a frontline COG, POG, or CCG trial for ALL. These induction regimens included intravenous (iv) vincristine, a corticosteroid such as prednisone or dexamethasone p.o., L-asparaginase (either native or pegylated) iv, and with or without an anthracycline such as daunorubicin iv. Additionally, patients received intrathecal therapy with methotrexate, with or without cytarabine, and with or without a corticosteroid such as hydrocortisone.

Removal of patients from therapy or assessment

The Study Chair of COG was to be contacted prior to removing any patient from protocol therapy for toxicity.
The following criteria for removal from protocol treatment were pre-defined:

• M2 (5-25%) or M3 (> 25% blasts) bone marrow at the end of Consolidation 2
• Relapse (BM, CNS, testicular or other) at any site, during the study
• Secondary malignancy during the study
• Refusal of further protocol therapy

After removal from protocol therapy (chemotherapy with imatinib or HSCT with imatinib), patients went into study follow-up. The following criteria for removal from study follow-up, referred to as "off study" were pre-defined in the protocol:

• Confirmed as lost to follow-up
• Withdrawal of informed consent for further follow-up
• Entry into another COG therapeutic study
• Death

Treatments

Overall, the chemotherapy treatments administered consisted of the following per treatment block:

- Consolidation 1 (3 weeks) Etoposide (VP-16), Ifosfamide, MESNA, Filgrastim (Granulocyte Colony Stimulating Factor (G-CSF)), Triple IT Therapy, IT Methotrexate (MTX), Imatinib (for Ph+ ALL), radiation to testes (if indicated)
- Consolidation 2 (3 weeks) MTX, Leucovorin, Triple IT therapy, Cytarabine (Ara-C), G-CSF, Imatinib (for Ph+ ALL)
- Reinduction 1 (3 weeks) Vincristine (VCR), Daunorubicin (DAUN), Cyclophosphamide (CPM), PEG-ASP, GCSF, Triple IT therapy, Dexamethasone (DEX), Imatinib (for Ph+ ALL)
- Intensification 1 (9 weeks) MTX, Leucovorin, Triple IT therapy, VP-16, CPM, MESNA, G-CSF, ARA-C, Lasparaginase (L-ASP), Imatinib (for Ph+ ALL)
- Reinduction 2 (3 weeks) VCR, DAUN, CPM, PEG-asparaginase (PEG-ASP), G-CSF, Triple IT therapy, DEX, Imatinib (for Ph+ ALL)
- Intensification 2 (9 weeks) MTX, Leucovorin, Triple IT therapy, VP-16, CPM, MESNA, G-CSF, ARA-C, LASP, Imatinib (for Ph+ ALL)
- Maintenance (8-week cycles): Cycles 1-4 MTX, Leucovorin, Triple IT therapy, VCR, DEX, 6-mercaptopurine (6-MP), VP-16, CPM, MESNA, G-CSF, Imatinib (for Ph+ ALL)
- Maintenance (8-week cycle): Cycle 5 VCR, DEX, 6-MP, MTX, Imatinib (for Ph+ ALL), cranial radiation
- Maintenance (8-week cycles): Cycle 6-12 VCR, DEX, 6-MP, MTX, Imatinib (for Ph+ ALL)

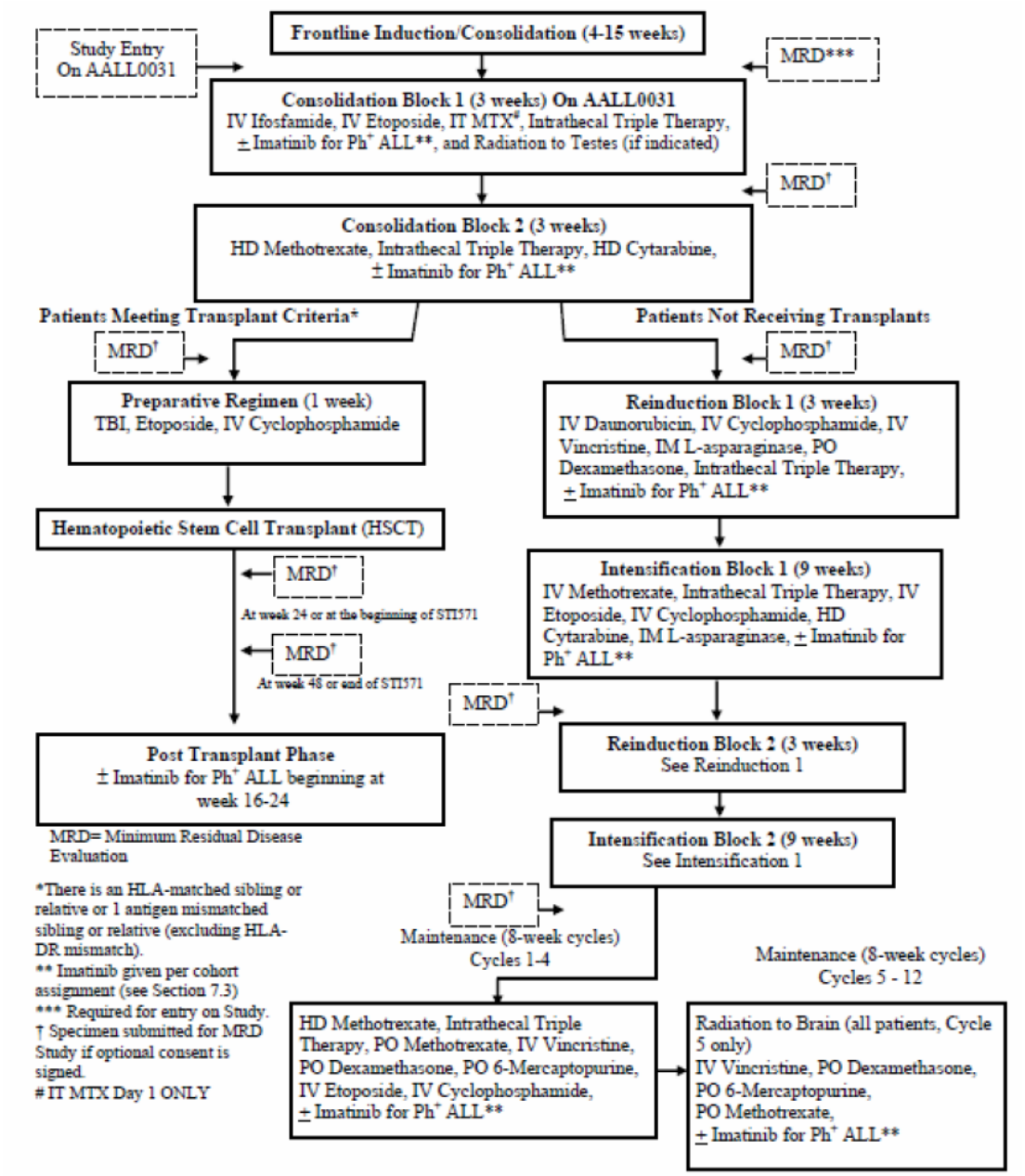


Figure 04: Study Design

Imatinib was supplied as 100 mg tablets in polyethylene bottles and was given orally. Imatinib was given on a daily dosing schedule for 21 days or continuously, depending on the cohort and treatment blocks. Treatment blocks started when the following criteria were met: ANC ≥ 750/µL; platelets ≥ 75,000/µL; ALT < 20x the upper limit of normal; direct bilirubin and creatinine normal for age. After count recovery was met, then patients continued the next treatment block and resumed imatinib.

The tolerability of the addition of imatinib to the chemotherapy regimen was unknown prior to the start of the trial. Thus, the tolerability of imatinib was assessed by incorporating it into 5 sequential cohorts of patients that incorporated it both earlier in the course of treatment and during more treatment blocks. (Figure 2, see below). The duration of imatinib increased from 42 days (cohort 1) to 210 days (cohort 5) prior to maintenance cycles.

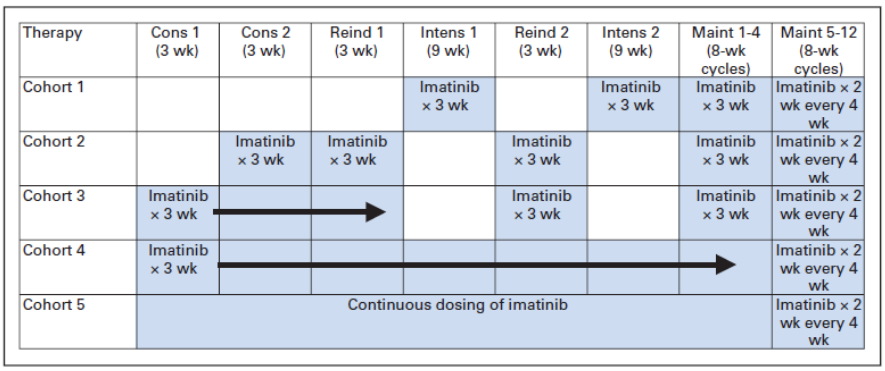


Fig 2. Integration of imatinib into successive blocks of therapy. Imatinib was given at 340 mg/m^2/d (blue blocks) for 21 days (cohorts 1 to 4). Maintenance Blocks 1 through 4 consisted of 3-week blocks and Maintenance Blocks 5 through 12 consisted of 2-week blocks every 4 weeks. In cohort 5, dosing was continuous except for 2 weeks every 4 weeks during Maintenance Blocks 5 through 12. All boxes shaded blue received imatinib during that cycle of therapy. Cons, Consolidation Block; Reind, Reinduction Block; Intens, Intensification Block; Maint, Maintenance Block.

Dose selection

The imatinib dose selection was made based on results from a previous phase I study (Champagne et al., 2004). In this study oral imatinib was administered daily at dose levels ranging from 260 to 570 mg/m2. There were 31 children who received 479 courses of imatinib and a maximum tolerated dosage was not defined. The authors concluded that daily oral imatinib was well tolerated in children at doses ranging from 260 to 570 mg/m2. Doses of 260 and 340 mg/m2 provided systemic exposures similar to those of adults who were treated with daily doses of 400 and 600 mg, respectively.

The imatinib dose given was 340 mg/m2/d or 230 mg/m2/d. Paediatric doses were calculated according to body surface area. The dosing increment of 50 mg, as was the case for the 150 mg and 250 mg doses, was accomplished by dividing a divisible 100 mg film-coated tablet.

Table 01: Doses of imatinib (340 mg/m2/dose)**

Body Surface Area	Daily dosage	100 mg tablets	Range of actual dose given
0.37 – 0.51 m^2	150 mg/day	1 ½	(405 – 294 mg/m^2)
0.52 – 0.66 m^2	200 mg/day	2	(385 – 303 mg/m^2)
0.67 – 0.80 m^2	250 mg/day	2 ½	(373 – 313 mg/m^2)
0.80 – 1.02 m^2	300 mg/day	3	(370 – 300 mg/m^2)
1.02 – 1.32 m^2	400 mg/day	4	(388 – 303 mg/m^2)
1.33 – 1.61 m^2	500 mg/day	5	(376 – 311 mg/m^2)
1.62 – 1.91 m^2	600 mg/day	6	(370 – 314 mg/m^2)

Table 02: Doses of imatinib (230 mg/m2/dose)**

Body Surface Area	Daily dosage	100 mg tablets	Range of actual dose given
0.36 – 0.54 m^2	100 mg/day	1	(278 – 185 mg/m^2)
0.55 – 0.76 m^2	150 mg/day	1 ½	(273 – 197 mg/m^2)
0.77 – 0.97 m^2	200 mg/day	2	(260 – 206 mg/m^2)
0.98 – 1.19 m^2	250 mg/day	2 ½	(255 – 210 mg/m^2)
1.20 – 1.52 m^2	300 mg/day	3	(250 – 197 mg/m^2)
1.53 – 1.95 m^2	400 mg/day	4	(261 – 205 mg/m^2)
1.96 – 2.39 m^2	500 mg/day	5	(255 – 209 mg/m^2)
2.40 – 2.50 m^2	600 mg/day	6	(250 – 240 mg/m^2)

According to Table 2.1 in the CHMP Reflection paper: Formulations of choice for the pediatric population, July 2006, a body surface of 0.41 m^2 correlates with an age of 1 year. By that the dosing schemes provided above were covering the pediatric target population.

Imatinib dose adjustments

The individual imatinib dose of 340 mg/m2/d was reduced to 230 mg/m2/d for patients who could not tolerate 340 mg/m2/d. In addition, the decision to reduce the dose from 340 mg/m2/d to 230 mg/m2/d was taken at interim monitoring, if dose limiting toxicities (DLT) were observed within a cohort or within a specific treatment block. According to the protocol, a DLT was monitored continuously and administered imatinib was to be decreased by 30% (230 mg/m2/d) if grade 3 or 4 nonhematopoietic toxicity was observed in 2 of the first evaluable 6 patients within a cohort. If at any time for the remaining patients in the cohort, the percentage of DLT for the full group of evaluable patients reached 33%, this also resulted in dose modification. If DLTs were observed within a specific

treatment block, then reduction of dose would only apply to that specific treatment block where unacceptable toxicity had been observed.

Imatinib treatment post-HSCT

Per protocol HSCT was performed by a COG-approved HSCT/ Bone Marrow Transplant (BMT) center. The HSCT regimen consisted of a 1-week preparative regimen including Total Body Irradiation (TBI), CPM, etoposide, and GVHD prophylaxis (of MTX and cyclosporine). Patients with an HLA-matched related donor could proceed with HSCT after Consolidation 2.
Imatinib (230 mg/m2/d) started between weeks 16-24 post-HSCT when ANC ≥ 750/µL, platelet count ≥ 75,000/µL, and non-haematological toxicities had resolved to ≤ Grade 1. Imatinib dose increased to 340 mg/m2/d between weeks 20-28 post-HSCT, after no toxicities of ≥ Grade 3 toxicities were observed (Table 03). The total duration of imatinib treatment post-HSCT was 24 weeks.

Table 03: Imatinib dose schedule for patients undergoing HSCT

Dose Levels	Dose	Dose escalation schedule post HSCT days
Dose level 1	230 mg/m^2	Once daily starting between week 16-24 post HSCT
Dose level 2*	340 mg/m^2	Once daily starting between weeks 20-28 post HSCT
* Patients were escalated to dose level 2 if no grade 3 or 4 toxicity X 28 days Imatinib therapy continued from the time of initiation for a total of 24 weeks.		

HSCT
In this study, patients with HLA-matched related donors or 1 antigen mismatched (excluding HLA-DR mismatch) related donors were eligible to receive HSCT after the two initial consolidation chemotherapy blocks if a matched related donor was available.
At any time during the protocol therapy, patients and their families had an option to be removed from protocol treatment to obtain off protocol HSCT (that did not meet per protocol HSCT criteria).

Objectives

The primary objective of this study as defined by the COG in the actual protocol was to determine the feasibility of patient accrual and toxicity of an intensified chemotherapeutic regimen (including imatinib for Ph+ ALL patients) for treatment of children and adolescents with VHR ALL. Over time it was apparent that both patient accrual and the toxicity profile were feasible. It was observed that the Ph+ ALL patients appeared to have improved EFS compared to what the expected outcome was based on historical control data from clinical trials performed by COG and its precursor organisations. Thus the primary focus of the trial shifted to assess the efficacy and safety of the combination of imatinib and chemotherapy for patients with Ph+ ALL

For this report, in order to evaluate the effect of imatinib integrated into an intense chemotherapy regimen in Ph+ ALL patients the following objectives were defined:

Primary objective
The primary objective was to assess the event-free survival (EFS; events defined as relapse at any site, secondary malignancy, or death from any cause) in Ph+ ALL paediatric patients in cohort 5, from study entry, including the option of HSCT treatment.
Secondary objectives
The secondary objectives were:
• To assess the overall survival (OS; event: death from any cause) in Ph+ ALL patients, from study entry, including the option of HSCT treatment.
• To evaluate the exposure-response of imatinib per cohort, and combined cohort groups, at endpoints EFS and OS.
• To compare EFS and OS in patients receiving chemotherapy plus imatinib in cohort 5 versus all patients undergoing HSCT (on and off protocol), including and excluding induction failures in all groups
• To evaluate the safety and tolerability of adding imatinib to intensive chemotherapy in Ph+ ALL patients (including HSCT), specifically in cohort 5; stating the impact of imatinib in addition to chemotherapy.

• To compare the safety profile in patients receiving intensive chemotherapy plus imatinib versus patients undergoing per protocol HSCT.

Additional exploratory evaluations (i.e. EFS and OS from start of diagnosis; prognostic effect of MRD, etc.) and sensitivity analyses (i.e. EFS including induction failure as an event) were performed.

Outcomes/endpoints

The primary endpoint is event free survival for both the COG analyses (Schultz et al 2007b, Schultz et al 2009) and the Novartis analyses. EFS, defined as the time between study entry and the earliest of the following events: leukemic relapse (BM, CNS, testicular, or other) at any site, secondary malignancy, or death. OS, a secondary endpoint, was defined as the time between study entry and death due to any cause. However, there is some variation in the definition of EFS used by COG and Novartis, in terms of inclusion/exclusion of patients who failed induction therapy and considering induction failure (IF) as an 'event.' Table 04 shows how data from induction failures were handled in different documents.

Study STI571I2301 included patients failing induction therapy as well as patients who responded to initial induction treatment, whereas the historical control group did not include any induction failures. Novartis conducted EFS analyses including induction failure patients and provided the results in two ways: first, by not treating these patients as having had an event and second, by treating these patients who failed induction treatment as having an event. This latter definition of EFS was aligned with the analysis performed by Schultz et al (2009).

Table 04: Handling of patients who failed induction treatment in EFS analyses (STI571I2301)

Document	Definition of EFS	Handling of induction failures within the analyses
Schultz et al (2009)	Includes Induction failures as events	• Exclusion of all induction failures for comparison of cohort 5 with historical control • Comparison of induction failures versus non-induction failures in cohort 5
Study STI571I2301	Primary and secondary analyses include patients who failed induction but do not define them as EFS events. Sensitivity analysis of EFS includes induction failures as events (per PDCO request)	• Main analysis includes induction failure patients but not as events • Comparison of induction failures versus non-induction failures • Inclusion of induction failures considering them as events as requested by PDCO
Study STI571I2301-Appendix 16.5	Defines EFS including patients who failed induction but does not define them as EFS events	• All analyses include induction failure patients in the analysis but not as events

The predictive value of MRD (by multi-parameter flow cytometry) to EFS was also an exploratory endpoint. MRD was assessed at study entry (after induction) and after the first and second blocks of consolidation. Measurements were performed at a single central reference laboratory.

Sample size

Sample size considerations were based on practical grounds such as recruitment time. It was planned to recruit 12 patients into each of the 5 cohorts. Accrual into Cohort 1 was stopped at 7 patients because data became available that showed that imatinib could be administered in combination with high-dose methotrexate in the Hyper-CVAD regimen. Cohort 5 was expanded to accrue a total of 50 patients in order to provide a more precise estimate of outcome once it became clear that the combination of imatinib and chemotherapy was tolerable and appeared to be improving patient outcome based on the improved EFS observed in Cohorts 3 plus 4 compared to Cohorts 1 plus 2. According to the COG original protocol the estimation of precision was as follows: with the original cohort size of 12, a 90% confidence interval provides a half-width of approximately 24% that was the

true EFS result could be 24% higher or lower depending upon the observed estimate. Increasing the size of the final cohort to 50 patients reduced the half-width of the confidence interval to 12% to provide reasonable precision.

Randomisation

N/A

Blinding (masking)

The study was open-label

Statistical methods

The analyses described in this section are those performed for the purpose of the analysis of Ph+ ALL patients who received imatinib integrated into the chemotherapy regimen as defined in the protocol for this study designed by COG for VHR ALL patients

Data cut-off

A snapshot of the data as of 5-Sep-2009 was received from COG and used for the analyses presented in this report. Last patient last visit (LPLV) for Ph+ ALL patients who completed protocol treatment occurred on 8-Jan-2009, hence all protocol treatment visits were included. In addition, the follow-up data for patients in the study follow-up period (up to the data cutoff date of 5-SEP-2009) was included in this dataset.

Populations

The following analysis sets were defined and are based on all Ph+ patients who consented to participate in this study:

- Enrolled set: All eligible Ph+ patients enrolled into the study. Data of one Ph+ patient from cohort 1 was inevaluable according to COG, because this patient was inadvertently dosed with imatinib during consolidation 1. Per protocol, patients in cohort 1 do not receive imatinib in consolidation 1. According to COG, very limited information was entered by the site. COG decided to remove patient's data from their analyses and did not provide this patient's data to Novartis.
- Safety set: All patients from the enrolled set who received at least one dose of chemotherapy and/or imatinib starting at Consolidation 1.
- Efficacy set: All patients from the safety set qualified for the efficacy analyses

Definition of primary efficacy endpoint

The primary endpoint was EFS calculated as the time (months) from the date of first treatment with study medication in Consolidation 1 (study entry) to first event or last contact (assuming that the date of last contact is equivalent to the last disease assessment), where an event was defined as: relapse at any site, secondary malignancy, death from any cause.

Patients who did not fail were censored as of the date of last EFS assessment, which was the date of last contact, since it was assumed that relapse was assessed at every visit. Table 03 summarises the definition of EFS and the censoring algorithm.

Table 05: Definition of primary event-free survival

Situation	Date of Event or Censoring	Outcome
Relapse, second malignancy or death*	Earliest of event dates	Not censored
No event*	Last contact date as reported in the CRF	Censored
*Events and censored times occurring after HSCT are included in this analysis		

The primary objective was to show efficacy of chemotherapy plus imatinib with the option of HSCT. A secondary objective was to evaluate efficacy on chemotherapy plus imatinib alone.

Efficacy analysis

The analysis of EFS was conducted on the efficacy population using data received from COG (with data cut-off date of 05-Sep-2009). All efficacy analyses were performed on the efficacy set and in subgroups as indicated. The primary patient group for efficacy was cohort 5.

There was no formal comparison with the historical control data because COG did not provide the individual patient data. Instead, COG provided the respective results for the efficacy endpoint, by sending the yearly estimated EFS rates with 95% confidence intervals (based on Kaplan Meier method) to Novartis. The historical control data (n=120) were from previous POG studies (ALinC 14: POG 8602, ALinC15: POG 9005 and 9006, ALinC16: POG 9201, 9405, 9406 and 9605). Historical control data that were obtained consisted of Ph+ ALL patients treated with chemotherapy with or without HSCT between 1988 and 1995. Only estimated EFS rates were provided to Novartis; no data on OS or other subgroup data from the historical control was provided by COG.

The following comparisons for EFS and OS were performed as appropriate (including induction failures for the main analyses if not otherwise stated).

- by cohort: cohort 5 vs. cohorts 1+2, cohort 5 vs. cohorts 3+4, and cohort 5 vs. cohorts 1 to 4
- by HSCT: cohort 5 chemotherapy + imatinib vs. per protocol HSCT and vs. off protocol HSCT; cohort 5 chemotherapy + imatinib vs. overall HSCT (per protocol and off protocol HSCT)
- by risk groups:
    - NCI risk group: standard risk vs. high risk
    - Baseline age: < 10 vs. ≥ 10 years
    - WBC at diagnosis: < 50,000/µL vs. ≥ 50,000/µL; < 100,000/µL vs. ≥ 100,000/µL
    - Induction failure: no vs. yes
    - MRD at study entry: ≤ 0.01% vs. > 0.01%; ≤ 0.1% vs. > 0.1%; ≤ 1.0% vs. > 1.0%.

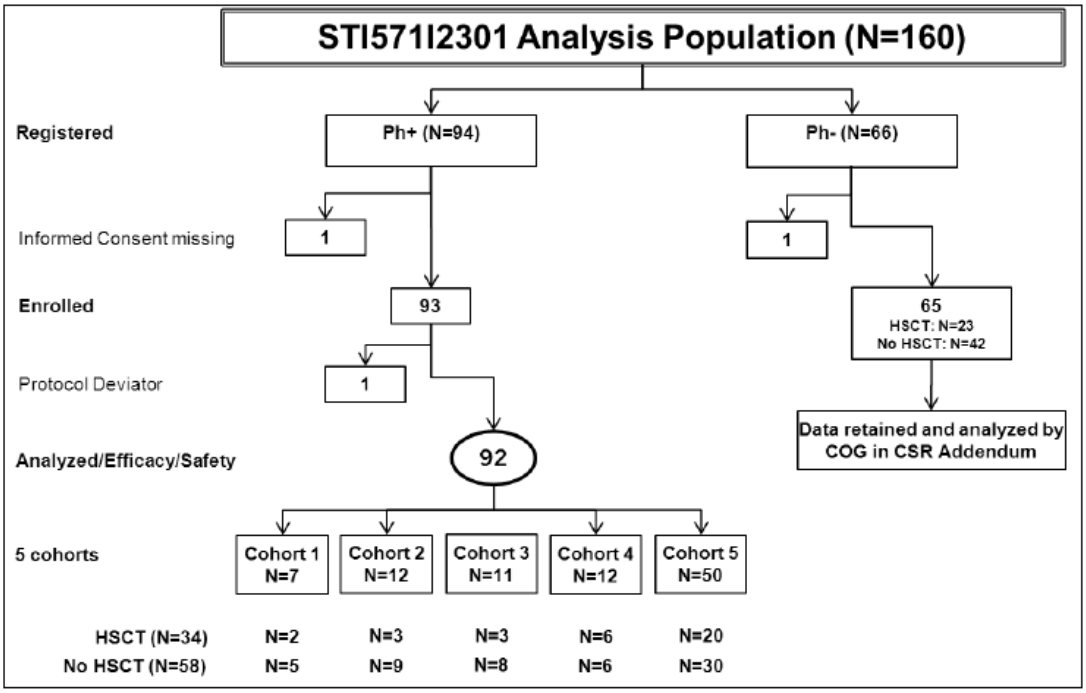
The primary endpoint analysis was performed on all patient data for cohort 5; no comparison was foreseen for the primary endpoint. Therefore, respective results were presented using descriptive statistics only. The EFS rates were calculated from date of study entry. Cohort 5 efficacy results (estimated EFS rates) were presented side by side with the historical control estimated EFS rates including 95 % confidence intervals. No induction failures were included in the historical control data; however, cohort 5 included patients who failed induction therapy.

Overall survival was calculated in months from the date of study entry (as the start date) to the date of death (due to any cause) or date of last contact (for those who are still alive). For any comparisons the log-rank test was applied

Results

Participant flow

A total of 160 paediatric VHR ALL patients were enrolled in this study between 14-Oct-2002 and 20-Oct-2006. Ninety-three (93) were Ph+ patients and received imatinib in addition to the chemotherapy regimen. There was one Ph+ patient from cohort 1 that COG considered not evaluable because this patient was inadvertently dosed with imatinib during consolidation 1. Per protocol, patients in cohort 1 do not receive imatinib in consolidation 1. Data for this patient was not provided to Novartis because very limited information was entered by the site when COG decided to remove this patient from all study analyses. Hence 92 patients were included in this analysis.



Source: [STI571I2301 Table 14.1-1.8]

Figure 05: Patient population in Study STI571I2301

Fifty-seven (62.0%) patients received previous chemotherapy induction treatment (no imatinib) in one of the CCG, POG, or COG frontline studies; the remaining 35 (38%) patients underwent a similar induction therapy as that defined in the protocol including vincristine, asparaginase, and prednisone/dexamethasone, with or without daunorubicin.

	Cohort 1 N=7 n (%)	Cohort 2 N=12 n (%)	Cohort 3 N=11 n (%)	Cohort 4 N=12 n (%)	Cohort 5 N=50 n (%)	Overall N=92 n (%)
Patients from frontline studies	1 (14.3)	2 (16.7)	5 (45.5)	11 (91.7)	38 (76.0)	57 (62.0)
Patients from similar induction therapy	6 (85.7)	10 (83.3)	6 (54.5)	1 (8.3)	12 (24.0)	35 (38.0)
Induction failures	1 (14.3)	2 (16.7)	0	1 (8.3)	6 (12.0)	10 (10.9)
Non-induction failures	6 (85.7)	10 (83.3)	11 (100)	11 (91.7)	44 (88.0)	82 (89.1)
HSCT	2 (28.6)	3 (25.0)	3 (27.3)	6 (50.0)	20 (40.0)	34 (37.0)
Per protocol HSCT	2 (28.6)	1 (8.3)	1 (9.1)	4 (33.3)	13 (26.0)	21 (22.8)
Off protocol HSCT	0	2 (16.7)	2 (18.2)	2 (16.7)	7 (14.0)	13 (14.1)
Non-HSCT	5 (71.4)	9 (75.0)	8 (72.7)	6 (50.0)	30 (60.0)	58 (63.0)
Completed protocol treatment	2 (28.6)	6 (50.0)	5 (45.5)	5 (41.7)	27 (54.0)	45 (48.9)
Discontinued protocol treatment	5 (71.4)	6 (50.0)	6 (54.5)	7 (58.3)	23 (46.0)	47 (51.1)
No follow-up	0	0	0	2 (16.7)	3 (6.0)	5 (5.4)
Follow-up ongoing	2 (28.6)	4 (33.3)	7 (63.6)	6 (50.0)	38 (76.0)	57 (62.0)
Follow-up discontinued	5 (71.4)	8 (66.7)	4 (36.4)	4 (33.3)	9 (18.0)	30 (32.6)

Source: PT-Table 14.1-1.1, PT-Table 14.1-1.8

Recruitment

Conduct of the study

The study protocol was amended seven times. The main amendments were:

- Amendment 1 (13-Jul-2003) modified the AALL0031 design for Ph+ patients to investigate a more accelerated integration of imatinib into the therapeutic blocks. Also, the overall number of cohorts of Ph+ patients was reduced. Following the implementation of this amendment, four cohorts of Ph+ patients (cohorts 2-5) were studied, and the last of these cohorts (if reached) was to use “continuous” dosing with imatinib (i.e., given in each of the blocks: Consolidation 1 and 2, Reinduction 1 and 2, Intensification 1 and 2, and each Maintenance cycle).
- In Amendment 5B (23-May-2005) the following changes were implemented:
    - an expanded definition of patient categories eligible for the study (MLL patients with a slow early response determined by day 15 marrow or end induction MRD), and a modification of the low hypodiploid criterion to be those with < 44 chromosomes,
    - an extended study duration by approximately 16 months in order to expand the last cohort of Ph+ patients,

Baseline data

Table 06: Demographics at baseline by cohort (Efficacy set)

	Cohort 1 N=7	Cohort 2 N=12	Cohort 3 N=11	Cohort 4 N=12	Cohort 5 N=50	Overall N=92
Baseline age (years)						
n	7	12	11	12	50	92
Mean	9.29	9.33	10.64	11.25	9.52	9.84
SD	5.992	4.119	5.573	5.119	5.418	5.221
Minimum	2	4	3	3	1	1
Median	7.0	9.0	11.0	10.5	9.0	9.5
Maximum	17	17	19	19	21	21
Age-groups - NCI risk classification						
<10 years	4 (57.1%)	6 (50.0%)	4 (36.4%)	6 (50.0%)	26 (52.0%)	46 (50.0%)
>=10 years	3 (42.9%)	6 (50.0%)	7 (63.6%)	6 (50.0%)	24 (48.0%)	46 (50.0%)
Age-group - ICH guidelines						
1-<2 years	0	0	0	0	2 (4.0%)	2 (2.2%)
2-<12 years	4 (57.1%)	8 (66.7%)	6 (54.5%)	6 (50.0%)	28 (56.0%)	52 (56.5%)
12-<18 years	3 (42.9%)	4 (33.3%)	4 (36.4%)	5 (41.7%)	16 (32.0%)	32 (34.8%)
18 years or more	0	0	1 (9.1%)	1 (8.3%)	4 (8.0%)	6 (6.5%)
Sex						
Male	6 (85.7%)	9 (75.0%)	5 (45.5%)	9 (75.0%)	30 (60.0%)	59 (64.1%)
Female	1 (14.3%)	3 (25.0%)	6 (54.5%)	3 (25.0%)	20 (40.0%)	33 (35.9%)
Race						
White	6 (85.7%)	9 (75.0%)	11 (100%)	9 (75.0%)	34 (68.0%)	69 (75.0%)
Black	1 (14.3%)	0	0	0	4 (8.0%)	5 (5.4%)
Other	0	3 (25.0%)	0	3 (25.0%)	12 (24.0%)	18 (19.6%)
Baseline weight (kg)						
n	7	12	11	11	50	91
Mean	32.81	37.09	40.16	47.95	41.86	41.07
SD	18.081	18.114	17.303	27.331	28.436	25.141
Minimum	14.1	16.0	15.7	18.2	10.8	10.8
Median	24.40	32.45	46.00	33.90	31.90	33.70
Maximum	64.0	68.0	63.8	94.3	150.0	150.0
Baseline height (cm)						
n	7	12	11	11	50	91
Mean	134.99	137.43	139.87	149.69	136.55	138.54
SD	33.974	25.030	27.212	29.583	31.197	29.693
Minimum	87.4	107.4	97.0	100.3	79.0	79.0
Median	123.00	131.45	150.00	148.10	141.75	144.30
Maximum	174.0	168.0	176.0	187.0	185.4	187.0
Baseline BSA (m^2)						
n	7	12	11	11	50	91
Mean	1.10	1.18	1.24	1.39	1.23	1.23
SD	0.433	0.396	0.394	0.528	0.531	0.488
Minimum	0.6	0.7	0.7	0.7	0.5	0.5
Median	0.90	1.09	1.37	1.19	1.11	1.17
Maximum	1.8	1.8	1.8	2.2	2.8	2.8

Source: PT-Table 14.1-3.1

Median age was higher (11.0 years) in patients who had any HSCT (per or off protocol) compared to patients in cohort 5 with chemotherapy plus imatinib excluding HSCT (8.0 years).

Table 07: Baseline characteristics by cohort (Efficacy set)

	Cohort 1 N=7	Cohort 2 N=12	Cohort 3 N=11	Cohort 4 N=12	Cohort 5 N=50	Overall N=92
NCI risk group						
Standard risk	1 (14.3%)	5 (41.7%)	1 (9.1%)	3 (25.0%)	13 (26.0%)	23 (25.0%)
High risk	6 (85.7%)	7 (58.3%)	10 (90.9%)	9 (75.0%)	37 (74.0%)	69 (75.0%)
WBC (1000/µL) at diagnosis						
n	7	12	11	12	50	92
Mean	121.3	77.1	152.5	58.9	404.7	265.1
SD	117.7	110.6	180.5	675.3	163.5	121.2
Minimum	3	1	3	4	1	1
Median	98.0	360.0	95.0	22.5	18.0	30.0
Maximum	360.0	361.0	534.0	200.0	9200.0 *	9200.0
<50,000/µL	2 (28.6%)	8 (66.7%)	4 (36.4%)	8 (66.7%)	33 (66.0%)	55 (59.8%)
>=50,000/µL	5 (71.4%)	4 (33.3%)	7 (63.6%)	4 (33.3%)	17 (34.0%)	37 (40.2%)
<100,000/µL	4 (57.1%)	10 (83.3%)	6 (54.5%)	9 (75.0%)	37 (74.0%)	66 (71.7%)
>=100,000/µL	3 (42.9%)	2 (16.7%)	5 (45.5%)	3 (25.0%)	13 (26.0%)	26 (28.3%)
Induction failure						
No	6 (85.7%)	10 (83.3%)	11 (100%)	11 (91.7%)	44 (88.0%)	82 (89.1%)
Yes - M3	1 (14.3%)	1 (8.3%)	0	1 (8.3%)	6 (12.0%)	9 (9.8%)
Yes - M2/M2	0	1 (8.3%)	0	0	0	1 (1.1%)
MRD status at study entry						
<=0.01%	0	0	2 (18.2%)	3 (25.0%)	18 (36.0%)	23 (25.0%)
>0.01%	5 (71.4%)	9 (75.0%)	6 (54.5%)	8 (66.7%)	26 (52.0%)	54 (58.7%)
<=0.1%	1 (14.3%)	4 (33.3%)	3 (27.3%)	5 (41.7%)	24 (48.0%)	37 (40.2%)
>0.1%	4 (57.1%)	5 (41.7%)	5 (45.5%)	6 (50.0%)	20 (40.0%)	40 (43.5%)
<=1%	2 (28.6%)	4 (33.3%)	4 (36.4%)	7 (58.3%)	34 (68.0%)	51 (55.4%)
>1%	3 (42.9%)	5 (41.7%)	4 (36.4%)	4 (33.3%)	10 (20.0%)	26 (28.3%)
Missing	2 (28.6)	3 (25.0)	3 (27.3)	1 (8.3)	6 (12.0)	15 (16.3)
Blasts (%) in peripheral blood at diagnosis						
n	7	12	11	12	50	92
Mean	73.14	48.92	63.27	57.83	41.00	49.34
SD	29.902	32.335	33.109	36.777	34.451	34.974
Minimum	12.0	0	0	0	0	0
Median	80.00	57.00	70.00	67.50	39.50	53.00
Maximum	97.0	88.0	97.0	96.0	97.0	97.0
CSF WBC (/µL) at diagnosis						
n	7	12	11	12	50	92
Mean	1.00	0.58	0.55	4.58	36.26	20.52
SD	1.826	0.669	0.688	12.781	240.219	177.177
Minimum	0	0	0	0	0	0
Median	0	0.50	0	1.00	0.50	0.50
Maximum	5.0	2.0	2.0	45.0	1700.0	1700.0
CSF RBC (/µL) at diagnosis						
n	7	12	11	12	50	92
Mean	1.00	20.08	57.36	5838.08	355.92	964.48
SD	2.236	57.521	143.946	20205.768	1447.883	7355.765
Minimum	0	0	0	0	0	0
Median	0	2.00	1.00	0.50	1.00	1.00
Maximum	6.0	202.0	479.0	70000.0	8000.0	70000.0
Down Syndrome						
Yes	0	0	0	0	0	0
No	7 (100%)	12 (100%)	11 (100%)	12 (100%)	50 (100%)	92 (100%)

	Cohort 1 N=7	Cohort 2 N=12	Cohort 3 N=11	Cohort 4 N=12	Cohort 5 N=50	Overall N=92
Spleen size						
not enlarged	3 (42.9%)	9 (75.0%)	4 (36.4%)	6 (50.0%)	34 (68.0%)	56 (60.9%)
enlarged, not below umbilicus	2 (28.6%)	3 (25.0%)	7 (63.6%)	4 (33.3%)	11 (22.0%)	27 (29.3%)
enlarged, below umbilicus	2 (28.6%)	0	0	2 (16.7%)	4 (8.0%)	8 (8.7%)
unknown	0	0	0	0	1 (2.0%)	1 (1.1%)
Lymph node status						
normal	2 (28.6%)	8 (66.7%)	5 (45.5%)	7 (58.3%)	31 (62.0%)	53 (57.6%)
enlarged < 3 cm	4 (57.1%)	4 (33.3%)	6 (54.5%)	4 (33.3%)	19 (38.0%)	37 (40.2%)
unknown	1 (14.3%)	0	0	1 (8.3%)	0	2 (2.2%)

Standard risk = patients < 10 years of age, < 50,000 /µL WBC
High risk = patients ≥ 10 years, ≥ 50,000 /µL WBC

* One patient (758270) presented with an abnormally high WBC count, which appeared to be a data entry error. Patient was in the study for 5 months, then discontinued protocol due to patient's/ family's choice

Source: PT-Table 14.1-3.4

Table 08: **Disease characteristics by cohort (Efficacy set)**

	Cohort 1 N=7	Cohort 2 N=12	Cohort 3 N=11	Cohort 4 N=12	Cohort 5 N=50	Overall N=92
Anterior mediastinal mass						
none	7 (100%)	12 (100%)	11 (100%)	12 (100%)	49 (98.0%)	91 (98.9%)
>1/3 thoracic diameter at level of T5	0	0	0	0	1 (2.0%)	1 (1.1%)
Testicle size						
normal	6 (85.7%)	8 (66.7%)	5 (45.5%)	9 (75.0%)	30 (60.0%)	58 (63.0%)
female, not applicable	1 (14.3%)	3 (25.0%)	6 (54.5%)	3 (25.0%)	20 (40.0%)	33 (35.9%)
unknown	0	1 (8.3%)	0	0	0	1 (1.1%)
Baseline CNS status						
CNS1	6 (85.7%)	10 (83.3%)	10 (90.9%)	11 (91.7%)	44 (88.0%)	81 (88.0%)
CNS2	0	2 (16.7%)	1 (9.1%)	1 (8.3%)	3 (6.0%)	7 (7.6%)
CNS3	1 (14.3%)	0	0	0	3 (6.0%)	4 (4.3%)
CD2						
positive	1 (14.3%)	4 (33.3%)	1 (9.1%)	0	8 (16.0%)	14 (15.2%)
negative	3 (42.9%)	6 (50.0%)	8 (72.7%)	8 (66.7%)	31 (62.0%)	56 (60.9%)
not done	3 (42.9%)	2 (16.7%)	2 (18.2%)	4 (33.3%)	11 (22.0%)	22 (23.9%)
CD7						
positive	1 (14.3%)	4 (33.3%)	1 (9.1%)	2 (16.7%)	11 (22.0%)	19 (20.7%)
negative	5 (71.4%)	7 (58.3%)	9 (81.8%)	9 (75.0%)	35 (70.0%)	65 (70.7%)
not done	1 (14.3%)	1 (8.3%)	1 (9.1%)	1 (8.3%)	4 (8.0%)	8 (8.7%)
CD10						
positive	7 (100%)	12 (100%)	1 (100%)	12 (100%)	47 (94.0%)	89 (96.7%)
negative	0	0	0	0	2 (4.0%)	2 (2.2%)
not done	0	0	0	0	1 (2.0%)	1 (1.1%)
CD19						
positive	7 (100%)	12 (100%)	11 (100%)	12 (100%)	49 (98.0%)	91 (98.9%)
negative	0	0	0	0	1 (2.0%)	1 (1.1%)
not done	0	0	0	0	0	0
Time since initial diagnosis (days)						
n	7	12	11	12	50	92

Mean	38.86	37.50	39.18	41.17	38.14	38.63
SD	6.842	4.232	3.894	5.813	5.245	5.197
Minimum	28.0	29.0	30.0	33.0	28.0	28.0
Median	41.00	37.00	40.00	41.50	38.50	39.00
Maximum	48.0	44.0	44.0	54.0	55.0	55.0

Source: PT-Table 14.1-3.7

Numbers analysed

Outcomes and estimation

Primary efficacy results

Continuous exposure to imatinib improved the outcome in cohort 5 patients. Fourteen patients in cohort 5 showed any event for EFS: 9 patients had a relapse at any site; and 5 patients died (without a relapse prior to death). Of these 5 patients who died, 4 underwent HSCT and 1 patient received chemotherapy plus imatinib.

Table 09: Event-free survival in cohort 5 (Efficacy set – STI571I2301) and in historical control

	Cohort 1+2	Cohort 3+4	Cohort 5	Historical control*
	N=19	**N=23**	**N=50**	**N=120**
Patients with events n (%)	12 (63.2)	10 (43.5)	14 (28)	91 (75.8)
Patients censored** n (%)	7 (36.8)	13 (56.5)	36 (72.0)	29 (24.2)
% Event-free probability estimates (95% CI)* for EFS**				
12 Months	78.9 (53.2,91.5)	91.3 (69.5,97.8)	89.8 (77.3,95.6)	60.0 (50.7, 68.1)
24 Months	52.1 (28.0,71.6)	71.0 (46.3,85.9)	81.6 (67.6,90.0)	40.8 (32.0, 49.5)
36 Months	46.3 (23.2,66.7)	65.9 (41.4,82.2)	77.4 (62.9,86.8)	35.0 (26.5, 43.6)
48 Months	34.7 (14.5,56.0)	60.4 (36.0,78.0)	69.6 (53.8,80.9)	31.6 (23.4, 40.1)
Comparison vs. cohort 5				
p-value (log-rank test)	0.0101	0.5292		<0.0001
Hazard ratio (95% CI)	0.38 (0.17,0.82)	0.76 (0.32,1.81)		0.28 (0.16, 0.49)

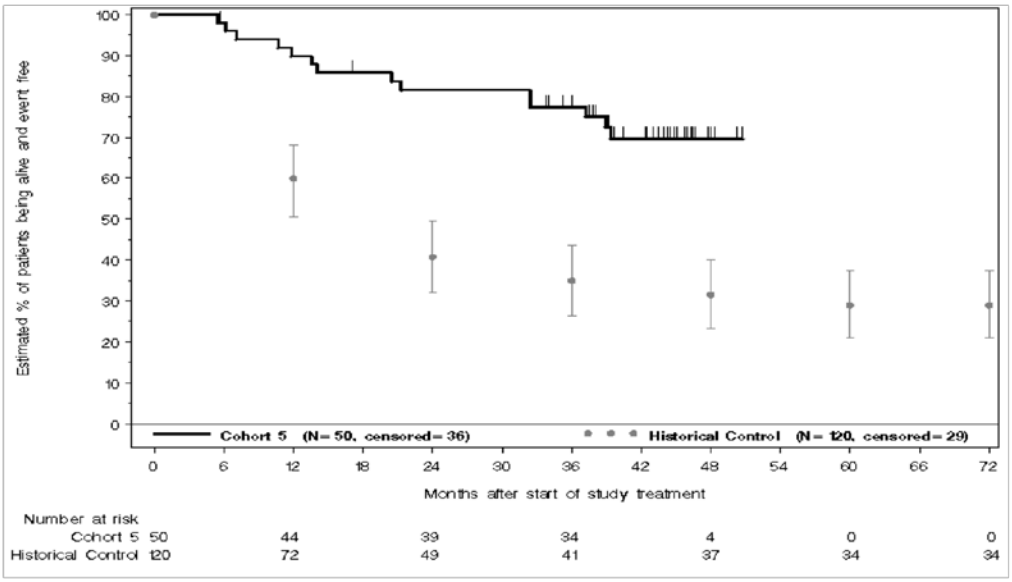
*The results for historical control and the analysis comparing cohort 5 with historical control were provided by COG [STI571I2301-Appendix 16.5 Table 14.2-1.8].

**Patients were censored when they did not show an event at the time of last assessment or discontinued treatment prematurely without prior event.

***The % Event-free probability estimate is the estimated probability that a patient will not have an event prior to the specified time point. The % Event-free Probability Estimates, and associated CIs are obtained from the Kaplan-Meier survival estimates for all cohort groups; Greenwood formula is used for CIs of KM estimates.

Source: [STI571I2301-Table 14.2-1.1]

Figure 06: **Kaplan Meier curve of event-free survival comparing cohort 5 (Efficacy set – STI571I2301) and historical control**



Historical control figures are presented as estimated yearly rates with 95% confidence intervals according to the results in Table 2-5. The exact curve could not be presented for the historical control group due to unavailability of individual data for the historical control group.

Source: [STI571I2301-Figure 14.2-1.2] and [STI571I2301-Table 14.2-1.1]

Table 10: **Event-free survival by cohort (Efficacy set – STI571I2301)**

	Cohort 1 N=7	Cohort 2 N=12	Cohort 3 N=11	Cohort 4 N=12	Cohort 5 N=50
Patients with event (%)	6 (85.7)	6 (50.0)	5 (45.5)	5 (41.7)	14 (28.0)
Patients censored (%)	1 (14.3)	6 (50.0)	6 (54.5)	7 (58.3)	36 (72.0)
% Event-Free Probability Estimates (95% CI)*					
12 Months	71.4 (25.8,92.0)	83.3 (48.2,95.6)	100 (100,100)	83.3 (48.2,95.6)	89.8 (77.3,95.6)
24 Months	42.9 (9.8,73.4)	57.1 (25.4,79.6)	70.0 (32.9,89.2)	72.9 (36.8,90.5)	81.6 (67.6,90.0)
36 Months	28.6 (4.1,61.2)	57.1 (25.4,79.6)	60.0 (25.3,82.7)	72.9 (36.8,90.5)	77.4 (62.9,86.8)
48 Months	14.3 (0.7,46.5)	47.6 (18.2,72.4)	60.0 (25.3,82.7)	62.5 (27.6,84.2)	69.6 (53.8,80.9)
Comparison vs. Cohort 5					
P-value (Log-Rank Test)	0.0008	0.1947	0.5650	0.6838	
Hazard Ratio (95% CI)	0.22 (0.08,0.58)	0.53 (0.20,1.40)	0.72 (0.24,2.20)	0.79 (0.26,2.43)	

*% Event-Free Probability Estimates and associated CIs are obtained from the Kaplan Meier survival estimates for all cohort groups; Greenwood formula is used for CIs of KM estimates.

All p-values and hazard ratios refer to comparisons of cohort 5 with the group in the respective column heading.

N: Total number of patients included in the analysis

Source: [STI571I2301-Table 14.2-1.3]

Secondary efficacy results

Overall survival

Table 11: Overall survival (months) - overall summary by cohort group (Efficacy set)

	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50
Patients with event (%)	9 (47.4)	5 (21.7)	8 (16.0)
Patients censored (%)	10 (52.6)	18 (78.3)	42 (84.0)
Percentiles (95% CI)			
25 %	23.0 (10.1, 26.2)	42.5 (16.3, NE)	NR
Median	34.9 (23.0, NE)	NR	NR
75 %	NR	NR	NR
% Event-Free Probability Estimates (95% CI) +			
12 Months	94.7 (68.1,99.2)	100.0 (100.0,100.0)	91.9 (79.8,96.9)
24 Months	67.7 (41.6,84.0)	85.0 (60.4,94.9)	85.7 (72.2,92.9)
36 Months	49.2 (24.8,69.8)	80.0 (55.1,92.0)	83.6 (69.8,91.4)
48 Months	49.2 (24.8,69.8)	74.7 (49.4,88.6)	83.6 (69.8,91.4)
Comparison vs. Cohort 5			
P-value (Log-Rank Test)	0.0091	0.5949	
Hazard Ratio (95% CI)	0.30 (0.12,0.78)	0.74 (0.24,2.26)	

+ % Event-Free Probability Estimate is the estimated probability that a patient will not have an event prior to the specified time point. % Event-Free Probability Estimates, percentiles and associated CIs are obtained from the Kaplan Meier survival estimates for all cohort groups; Greenwood formula is used for CIs of KM estimates.
N : Total number of patients included in the analysis. NE = not estimable NR = not reached

Source: PT-Table 14.2-2.1

Table 12: Overall survival in Ph+ cohorts and in Ph- group (Efficacy set – STI571I2301) and in historical control group

	Cohort 1+2 N=19 n (%)	Cohort 3+4 N=23 n (%)	Cohort 5 N=50 n (%)	All Ph - N=65 n (%)	Historical control* N=120 n (%)
Patients with event (%)	9 (47.4)	5 (21.7)	8 (16.0)	29 (44.6)	76 (63.3)
Patients censored (%)	10 (52.6)	18 (78.3)	42 (84.0)	36 (55.4)	44 (36.7)
% Survival Probability estimates (95% CI)**					
12 Months	94.7 (68.1,99.2)	100 (100,100)	93.9 (82.3,98.0)	87.7 (76.9,93.6)	81.7 (73.5,87.5)
24 Months	78.9 (53.2,91.5)	90.0 (65.6,97.4)	85.7 (72.2,92.9)	72.1 (59.4,81.4)	57.5 (48.2,65.8)
36 Months	55.4 (30.0,74.8)	80.0 (55.1,92.0)	83.6 (69.8,91.4)	59.5 (46.5,70.4)	49.1 (39.9,57.7)
48 Months	49.2 (24.8,69.8)	74.7 (49.4,88.6)	83.6 (69.8,91.4)	57.8 (44.8,68.8)	44.8 (35.8,53.5)
Comparison with cohort 5					
p-value (Log-Rank Test)	0.0091	0.5949			<0.0001
Hazard Ratio (95% CI)	0.30 (0.12,0.78)	0.74 (0.24,2.26)		0.34 (0.16,0.76)	0.23 (0.11,0.49)

* The results for historical control and the analysis comparing cohort 5 with historical control were provided by COG.

**% Survival probability estimate is the estimated probability that a patient will not die prior to the specified time point. % Survival probability estimates and associated CIs are obtained from the Kaplan Meier survival estimates for all groups; Greenwood formula is used for CIs of KM estimates.

OS calculation start date: date of diagnosis. End date: date of death due to any cause) / date of last contact (if no event occurred).

HR of < 1.0 indicates less risk of cohort 5 compared to the group presented in the respective column (where the HR is located).

Source: [STI571I2301-Appendix 16.5-Table 14.2-1.2]

Ancillary analyses

1. Event free survival was analysed for cohort 5 and the historical control population considering the baseline characteristics of age at study start, gender, WBC at diagnosis, and CNS involvement (standard factors to assess risk of relapse in this population) and the results are summarised in Table 13. All EFS results are presented with hazard ratios (HR) and confidence intervals (CI) comparing cohort 5 with historical control using the Kaplan Meier method

Table 13: **Kaplan-Meier analysis of EFS in cohort 5 and historical control patients by baseline characteristics (Efficacy set – STI571I2301)**

	Cohort 5 N=50		Historical control N=120	
Age subgroup	**<10 years N=26**	**≥ 10 years N=24**	**<10 years N=65**	**≥ 10 years N=55**
% Event-Free Probability Estimates (95% CI)*				
48 Months	72.8 (48.7,87.0)	66.7 (44.3,81.7)	38.4 (26.7,50.0)	23.6 (13.5,35.4)
Hazard Ratios (95% CI)				
≥10 years in C5 vs. hist. control		0.30 (0.14,0.63)		
<10 years in C5 vs. hist. control	0.26 (0.11,0.62)			
Gender subgroup	**Male N=30**	**Female N=20**	**Male N=75**	**Female N=45**
% Event-Free Probability Estimates (95% CI)*				
48 Months	68.8 (46.6,83.3)	70.0 (45.1,85.3)	25.3 (16.1,35.5)	42.2 (27.8,56.0)
Hazard Ratios (95% CI)				
Male in C5 vs. hist. control	0.22 (0.10,0.46)			
Female in C5 vs. hist. control		0.42 (0.17,1.02)		
WBC at baseline	**<50,000/µL N=33**	**≥ 50,000/µL N=17**	**<50,000/µL N=70**	**≥ 50,000/µL N=50**
% Event-Free Probability Estimates (95% CI)*				
48 Months	81.8 (63.9,91.4)	38.8 (13.0,64.5)	42.7 (31.0,53.9)	16 (7.5,27.4)
Hazard Ratios (95% CI)				
≥ 50,000/uL in C5 vs. hist. control		0.33 (0.15,0.70)		
<50,000/uL in C5 vs. hist. control	0.24 (0.10,0.57)			
CNS involvement at baseline	**CNS=No N=47**	**CNS=Yes N=3**	**CNS=No N=113**	**CNS=Yes N=5**
% Event-Free Probability Estimates (95% CI)*				
36 Months	76.1.6 (61,86)	NE	36.3 (28,45)	NE
Hazard Ratios (95% CI)				
CNS disease in C5 vs. hist. control		NE		
No CNS disease in C5 vs. hist. control	0.29 (0.16,0.53)			

* % Event-Free Probability Estimate is the estimated probability that a patient will not have an event prior to the specified time point. % Event-Free Probability Estimates are obtained from the Kaplan Meier survival estimates for all groups; Greenwood formula is used for CIs of KM estimates.

N: Total number of patients included in the analysis. EFS calculation start date: date of diagnosis. End date: date of first event (relapse, secondary malignancy or death) / date of last contact (if no event occurred).

NE (not estimable):

Source: [STI571I2301-Appendix 16.5–Table 14.2-1.4], [STI571I2301-Appendix 16.5–Table 14.2-1.5], [STI571I2301-Appendix 16.5–Table 14.2-1.6] and [STI571I2301-Appendix 16.5–Table 14.2-1.7]

2. A multivariate Cox proportional regression analysis for EFS comparing cohort 5 with historical control was performed using baseline characteristics of age, gender and WBC as covariates which could have potentially influenced the EFS results.
   The exclusion of IFs from the historical control group contributed to a conservative approach for comparisons because IFs have a higher risk of events. MRD status was not available for the historical control group, therefore, it was not considered in the analysis. Since few patients in either group had CNS involvement, this factor was not considered in the analysis. Therefore, despite being considered important parameters for risk assessment, IF status, MRD status, and CNS involvement could not be included in the multivariate Cox regression analysis for EFS between the historical control group and cohort 5.
   When adjusting for all factors to account for any imbalances between cohort 5 and the historical control group, the hazard ratio for EFS remains in favour of cohort 5 compared with the historical control (HR=0.28, log-rank p<0.0001)

Table 14: **Univariate and Multivariate Cox proportional hazards model (Efficacy set – STI571I2301)**

		Univariate results unadjusted		Multivariate results adjusted	
Groups	**Events/N**	**p-value**	**Hazard ratio (95% C.I.)**	**p-value**	**Hazard ratio (95% C.I.)**
Cohort 5	14/50				
Historical control	91/120	<0.0001	0.283 (0.160, 0.499)	<0.0001	0.280 (0.158, 0.495)
Age group (<10 vs. ≥10 years)				0.09	0.712 (0.483, 1.049)
Sex (female vs. male)				0.17	0.754 (0.503, 1.129)
WBC (<50,000/uL vs. ≥50,000/uL)				<0.0001	0.416 (0.283, 0.613)

Source: [STI571I2301- Appendix 16.5-Table 14.2-1.8]

3. Prognostic factors for EFS in cohort 5 chemotherapy plus imatinib only
   In addition, the following parameters were assessed as prognostic factors for EFS: sex (female / male), race (white / other, age group (< 10 years / ≥ 10 years), MRD status at study entry (≤ 0.01% / >0.01%) and WBC (< 50,000/µL / ≥ 50,000/µL). CNS status could not be used as a prognostic factor for these analyses due to the low number of patients with CNS2 and CNS3 status at study entry. All of the above parameters were examined for their effect on EFS (univariate). Only those parameters who showed a significant effect of $p \leq 0.1$ were to be entered into a multivariate model and keeping only those in the final multivariate model which showed a significant effect on EFS with $p \leq 0.05$ using a step-wise selection procedure.
   As a result, only the WBC at study entry was independently prognostic, showing a significant effect in the univariate case with a hazard ratio of 14.28 with p=0.0142 by the Wald-test. Since none of the other parameters were significant for entering into the multivariate model, the multivariate model was left only with WBC count as a prognostic factor resulting in a lower risk of EFS events for patients in the group WBC < 50,000/µL at study start.

4. Prognostic factors for Event-Free Survival
   In addition, the following parameters were assessed as prognostic factors for EFS: sex (female / male), race (white / other, age group (< 10 years / ≥ 10 years), MRD status at study entry (≤ 0.01% / > 0.01%) and WBC (< 50,000/µL / ≥ 50,000/µL). CNS status could not be used as a prognostic factor for these analyses due to the low number of patients with CNS2 and CNS3 status at study entry. Only the WBC at study entry was prognostic, showing a hazard ratio of 14.28 with a p-value of 0.0142 by the Wald-test

5. Effect of HSCT on EFS and OS
   The estimated EFS at 4 years following per protocol HSCT was lower than the EFS in cohort 5 with an estimated rate of 65.3% vs. 73.7%, respectively; the log-rank test yielded a HR=0.62 and a p-value of 0.374. A similar result was observed when comparing the estimated EFS at 4 years following off protocol HSCT with an estimated EFS rate of 50.5%; this difference showed a HR=0.38 and a p-value of 0.0732

Table 15: **Effect of HSCT on EFS and OS (Efficacy set – STI571I2301)**

	HSCT Per protocol N=21	HSCT Off protocol N=13	HSCT all (on and off) N=34	Cohort 5 (excluding HSCT) N=30
EFS events n (%)	7 (33.3)	6 (46.2)	13 (38.2)	7 (23.3)
% Event-Free Probability Estimates (95% CI)[+]				
48 Months EFS	65.3 (40.7,81.8)	50.5 (20.6,74.4)	59.8 (40.9,74.4)	73.7 (52.3,86.7)
Comparison versus cohort 5				
p-value (Log-Rank Test)	0.3744	0.0732	0.1524	
Hazard Ratio (95% CI)	0.62 (0.22,1.78)	0.38 (0.13,1.14)	0.52 (0.21,1.30)	
Overall Survival: events n (%)	5 (23.8)	5 (38.5)	10 (29.4)	3 (10.0)
% Event-Free Probability Estimates (95% CI)[+]				
48 Months OS	75.4 (50.6,89.0)	59.2(27.9,80.7)	69.3 (50.4,82.2)	89.5 (70.9,96.5)
Comparison vs. cohort 5				
p-value (log rank test	0.1958	0.0195	0.0559	
Hazard ratio (95%)	0.40 (0.10,1.68)	0.21 (0.05,0.89)	0.30 (0.08,1.11)	

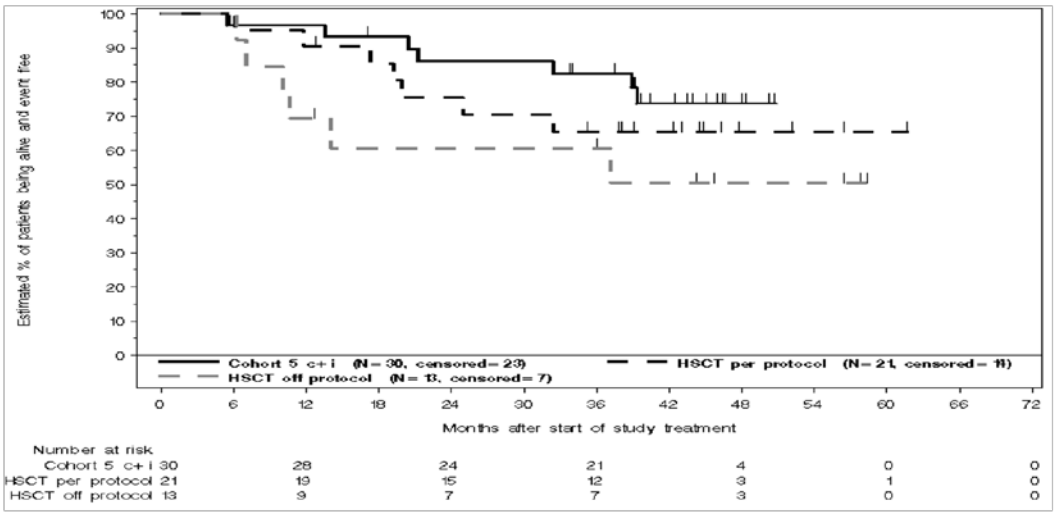
[+]% Event-Free Probability Estimate is the estimated probability that a patient will not have an event prior to the specified time point. % Event-Free Probability Estimates are obtained from the Kaplan Meier survival estimates for all groups; Greenwood formula is used for CIs of KM estimates.

All p-values and hazard ratios are referring to comparisons of cohort 5 with the groups in the respective column headings. A hazard ratio of <1.0 indicates less risk in cohort 5 compared to the respective HSCT group.

N : Total number of patients included in the analysis;

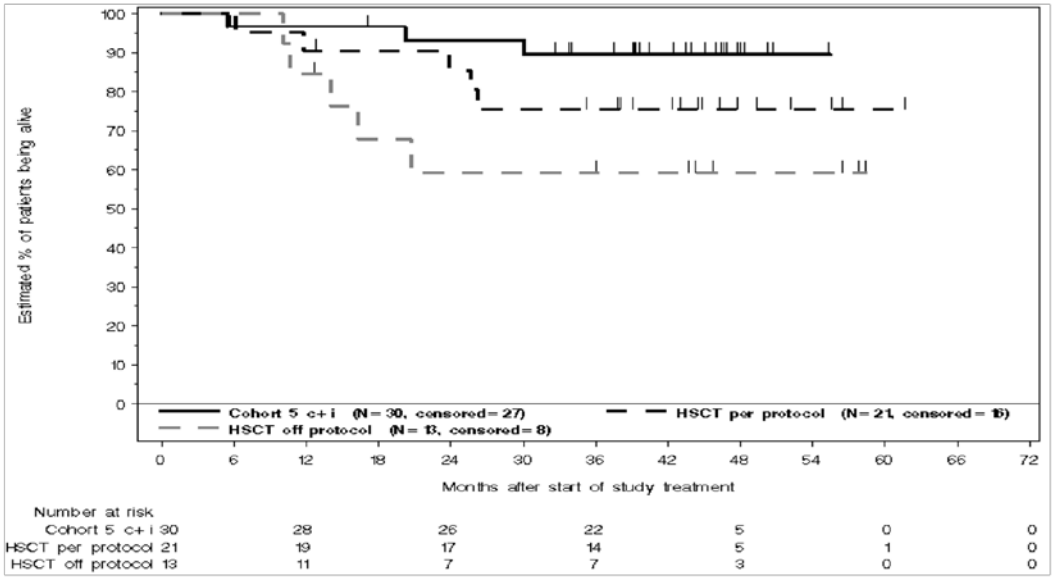
Source: [STI571I2301-Table 14.2-1.4] and [STI571I2301-Table 14.2-2.4]

Figure 07: **Kaplan-Meier curve of EFS comparing cohort 5 chemotherapy + imatinib and HSCT (Efficacy set - STI571I2301)**



Source: [STI571I2301-Figure 14.2-1.5] and [STI571I2301-Table 14.2-1.4]

Figure 08: **Kaplan-Meier curve of OS (months) comparing cohort 5 chemotherapy + imatinib vs. HSCT (Efficacy set -STI571I2301)**



Source: [STI571I2301-Figure 14.2-2.4] and [STI571I2301-Table 14.2-2.4]

6. EFS with HSCT versus chemotherapy + imatinib adjusting for baseline characteristics using Cox regression analysis

   The purpose of this analysis was to evaluate any baseline risk factors which might have biased the EFS result for the comparison of treatment options: HSCT (per protocol HSCT or off protocol HSCT) vs. cohort 5 chemotherapy + imatinib. EFS was evaluated by multivariate Cox proportional hazards analysis by entering HSCT status (yes/no) as a time dependent covariate into the model in addition to age (<10 years / ≥10 years), sex, race, MRD status (≤0.01% / >0.01%) and WBC count at study entry (< 50,000/µL / ≥ 50,000/µL). Event time was calculated both from date of diagnosis in and from date of study entry using HSCT as not time-dependent in.

   Due to missing values in some baseline factors (e.g. MRD at baseline), data from only 56 patients were kept for the Cox regression model. When the comparison of HSCT vs. cohort 5 chemotherapy + imatinib was adjusted for all baseline factors, the result was not different.

7. EFS of cohort 5 by induction failure status

   The comparison by log-rank test was statistically significant (p=0.054) but this result has to be seen in the light that some patients underwent HSCT and therefore may have contributed to the treatment effect. Only six patients in cohort 5 were classified as induction failures; 3 of them did not show an EFS event at the time of analyses. The estimated EFS rates at 36 months were 81.4% in patients who did not fail the induction treatment and 44.4% in patients who failed the induction treatment.

8. EFS by MRD

   The impact of MRD at ≤ 0.01% vs. > 0.01% at end induction on estimated EFS rate for cohort 5 was: (88.2% vs. 76.9%) at 3 years and (88.2% vs. 64.0%) at 4 years

   Overall results of all cohorts showed that there was a trend over time of an increasing percentage of patients having a non-measurable MRD of ≤ 0.01%: 29.9% of patients at study entry; 66.7% patients at end of Consolidation 1; and 71.9% at end of Consolidation 2

   For cohort 5: 10 out of 44 patients (22.7%) had > 1% MRD at study entry, only 2 out of 36 patients (5.6%) still had > 1% MRD at the end of Consolidation 1. The remaining 31 patients had ≤ 1% MRD (and none had > 1% MRD) at end of Consolidation 2.

9. EFS by NCI risk

EFS in cohort 5 revealed a significant difference between standard and high-risk (NCI) group. No event was recorded in the 13 patients of the standard risk group of cohort 5 resulting in estimated EFS at 3 years of 100% and a non estimable hazard ratio.

Table 14.2-1.8 (Page 1 of 1)
Event-free survival (months): Overall summary for cohort 5 by NCI risk group
Efficacy set

	Standard risk N=13	High risk N=37
Patients with event (%)	0 (0.0)	14 (37.8)
Patients censored (%)	13 (100)	23 (62.2)
Percentiles (95% CI)		
25 %	not reached	21.2 (10.7,39.3)
Median	not reached	not reached
75 %	not reached	not reached
% Event-Free Probability Estimates (95% CI) +		
12 Months	100.0 (100.0,100.0)	86.2 (69.9,94.0)
24 Months	100.0 (100.0,100.0)	74.9 (57.2,86.1)
36 Months	100.0 (100.0,100.0)	69.1 (51.1,81.6)
48 Months	100.0 (100.0,100.0)	57.7 (38.6,72.7)
60 Months		
Comparison vs. High risk		
P-value (Log-Rank Test)	0.0096	
Hazard Ratio (95% CI)	NE	

Sensitivity analyses

1. EFS by cohort group, from diagnosis (treating induction failure as an event)

Table 14.2-1.40 (Page 1 of 1)
Event-free survival (months): Overall summary by cohort group treating IF as events (from start of diagnosis)
Efficacy set

	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50
Patients with event (%)	15 (78.9)	11 (47.8)	17 (34.0)
Patients censored (%)	4 (21.1)	12 (52.2)	33 (66.0)
Percentiles (95% CI)			
25 %	9.8 (1.1,18.4)	22.8 (1.1,45.3)	33.3 (6.6, NE)
Median	20.5 (9.8,41.3)	66.1 (22.8,66.1)	not reached
75 %	46.8 (20.5, NE)	66.1 (NE , NE)	not reached
% Event-Free Probability Estimates (95% CI) +			
12 Months	63.2 (37.9,80.4)	87.0 (64.8,95.6)	84.0 (70.5,91.6)
24 Months	42.1 (20.4,62.5)	71.6 (47.1,86.2)	75.8 (61.3,85.4)
36 Months	31.6 (12.9,52.2)	61.4 (37.2,78.6)	71.7 (56.9,82.1)
48 Months	21.1 (6.6,41.0)	55.8 (31.9,74.3)	64.2 (48.6,76.1)
60 Months	21.1 (6.6,41.0)	50.2 (26.9,69.7)	
Comparison vs. Cohort 5			
P-value (Log-Rank Test)	0.0015	0.6844	
Hazard Ratio (95% CI)	0.34 (0.17,0.68)	0.85 (0.38,1.91)	

2. EFS of cohort 5 from diagnosis
   The Kaplan-Meier analysis of EFS in cohort 5 revealed identical estimated EFS rates at 4 years in both analyses: when using either date of diagnosis or date of study entry for EFS calculation; with 4-year EFS being 69.6%

Updated efficacy data:

COG conducted analyses with 5 year follow-up and a manuscript with these data is being prepared. COG confirmed their 5 year analyses contain only efficacy data and there is no update on safety. Upon request, COG provided the 5 year Kaplan-Meier estimates comparing EFS in patients receiving imatinib and chemotherapy with patients receiving related or unrelated bone marrow transplant.

Figure 09 compares patients in cohort 5 without HSCT with patients in all cohorts with related or unrelated HSCT. Figure 10 compares patients exclusively within cohort 5—those without HSCT and those with related or unrelated HSCT. Please note the terms related and unrelated bone marrow transplant (BMT) used by COG in the figures below, correspond to the definition of per protocol and off-protocol definitions in STI571I2301 study, respectively. Per protocol HSCT are HSCT with a HLA-matched related donor or 1 antigen mismatched and off-protocol HSCT are the rest.

Figure 09: 5 year estimated EFS for patients in cohort 5 without HSCT, patients in all cohorts with related HSCT and patients in all cohorts with unrelated HSCT.

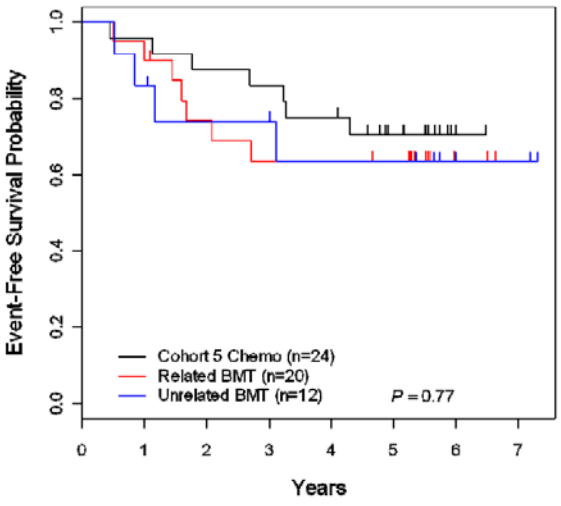
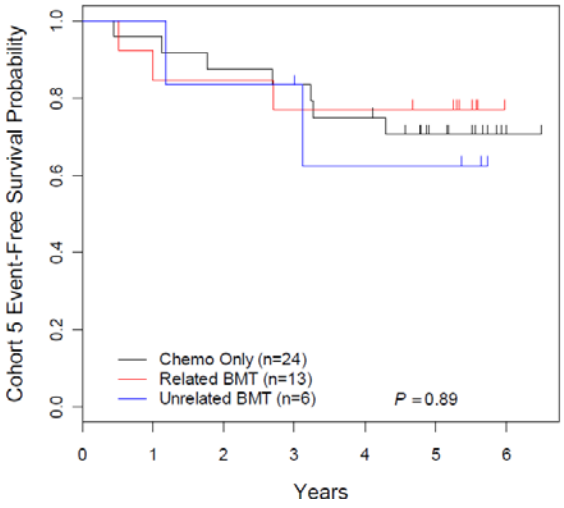


Figure 10: 5 year estimated EFS for patients in cohort 5 without HSCT, patients in cohort 5 with related HSCT and patients in cohort 5 with unrelated HSCT.



The 5 year update on efficacy shows that the probability of EFS is comparable between patients receiving only imatinib + chemotherapy vs patients receiving related HSCT vs patients receiving unrelated HSCT. With one additional year of follow-up it is confirmed that the addition of imatinib to chemotherapy results in comparable long term outcomes to those with HSCT.

Upon request, COG provided the following table describing EFS (from time of diagnosis) analyses comparing cohorts 1+2, cohorts 3+4, cohort 5, Ph negative patients and historical controls.

Table 16: EFS analyses (from time of diagnosis)

	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50	All non-Ph+ N=65	Historical control N=120
Patients with event (%)	12 (63.2)	10 (43.5)	14 (28)	31 (47.7)	91 (75.8)
Patients censored (%)	7 (36.8)	13 (56.5)	36 (72)	34 (52.3)	29 (24.2)
Percentiles (95% CI)					
25%	17.9 (5.7,24.1)	25 (7.3,54.2)	40.1 (14.7,NE)	13.8 (9.1,21.5)	8.5 (7,10)
Median	26.3 (17.9,NE)	66.1 (25,66.1)	NR	NR	18.7 (13.3,23.3)
75%	NR	NR	NR	NR	110 (39.9,NE)
% Event-Free Probability Estimates (95% CI) +					
12 Months	78.9 (53.2,91.5)	91.3 (69.5,97.8)	91.9 (79.8,96.9)	78.5 (66.4,86.6)	62.5 (53.2,70.5)
24 Months	57.9 (33.2,76.3)	76.1 (51.5,89.3)	81.6 (67.6,90)	62.8 (49.8,73.3)	40.8 (32,49.4)
36 Months	46.3 (23.2,66.7)	65.9 (41.4,82.2)	77.4 (62.9,86.8)	53.4 (40.5,64.6)	35 (26.6,43.5)
48 Months	34.7 (14.5,56)	60.4 (36,78)	69.6 (53.8,80.9)	51.6 (38.8,63)	31.6 (23.5,40)
Comparison vs. Cohort 5					
P-value (Log-Rank Test)	0.0100	0.5230		0.0262	< 0.0001
Hazard Ratio (95% CI)	0.37 (0.17,0.81)	0.75 (0.31,1.8)		0.5 (0.26,0.93)	0.28 (0.16,0.5)

Supportive study(ies)

Study STI571AIT07

This study was designed and conducted by 10 participating national paediatric leukaemia study groups in Europe (EsPhALL). Study STI571AIT07 was initially designed as an open-label, randomised study to determine whether the addition of imatinib to standard chemotherapy extended DFS in paediatric patients with Ph+ ALL.

Patients who achieved complete remission (CR) following frontline induction therapy were defined as Good risk and were randomised to receive imatinib + chemotherapy or chemotherapy alone. Patients who did not achieve CR following frontline induction therapy were defined as Poor risk, were not randomised, and all of these patients received imatinib + chemotherapy. However, after the publication of interim results from Study STI571I2301 by Schultz et al (2009) which showed the benefit of adding imatinib to chemotherapy to paediatric patients of all risk with Ph+ ALL, the participating groups no longer considered it acceptable to randomise patients into a chemotherapy only arm. Therefore the protocol was amended so that all patients would receive imatinib regardless of risk category. As a result of the amendment, the study enrolled an insufficient sample size to properly test for the primary efficacy analysis. Additional factors confounding efficacy results included the following: the impact of the therapeutic effect of HSCT since a high percentage (85.2%) of patients were transplanted within the study; and 12/44 (27%) patients randomised to receive no imatinib switched arms to receive imatinib prior to the amendment, thus diluting treatment effects.

Consequently, data from study [STI571AIT07] are included to provide additional safety data and are considered to be supportive only.

Table 17: Summary of Study STI571AIT07

	Details
Study	An open-label, randomized phase II/III-study in pediatric patients with Ph+/BCR-ABL+ ALL stratified by risk status (Good risk and Poor risk) with the objective to compare the safety and efficacy in the Good risk group of patients randomized to imatinib combined with chemotherapy vs. those receiving chemotherapy without adding imatinib. All patients in the Poor risk group received chemotherapy with imatinib without prior randomization. First patient randomized/enrolled: Jan-2004, last patient randomized/enrolled: Dec-2009. Randomization terminated: Dec-09 Data cut-off for final analysis Dec 2010
Design and number of patients	Randomized, open label, phase II/III study N=178 patients with Ph+/BCR-ABL+ ALL were eligible and enrolled; Good risk: 108 patients; Poor risk: 70 patients. Among the Good risk patients, 18 patients in the Good risk group were not randomized, hence: N=90 Ph+ ALL patients were randomized in Good risk: N=44[1] patients in the "No imatinib" arm (chemotherapy without imatinib) and, N=46 patients in the "+ imatinib" arm (imatinib combined with chemotherapy) N=70 Ph+ ALL Poor risk patients were treated with imatinib combined with chemotherapy
Dose and treatment duration	**Imatinib dose**: 300 mg/m^2/day Median duration of exposure to chemotherapy + imatinib up to consolidation 3 in Good risk imatinib arm was 121 days
No. of patients in the Efficacy/Safety Set	**Good risk patients:** Full analysis set (FAS) (as randomized): Plus imatinib=46 and No imatinib=44 Administered set/safety set (treatment actually administered at least once): Plus imatinib=58 and No imatinib=31 Per protocol (excluding patients who were not treated as per randomization): Plus imatinib=46 and No imatinib=31 **Poor risk patients:** Full analysis set (FAS): Plus Imatinib=70
Primary Endpoint	Disease free survival (DFS), events defined as relapse, secondary malignancy, or death in complete continuous remission (CCR) from the time of randomization in Ph+ ALL pediatric patients in the Good risk group (primary group) treated with or without imatinib in combination with intensive chemotherapy. Patients had the option to undergo HSCT when conditions were fulfilled.
Secondary Endpoints	• Event free survival[2] (EFS), events defined as resistance, relapse, secondary malignancy, and death in CCR, in the Poor risk group, from study entry including patients who received HSCT (as in DFS) • Overall survival (OS), events defined as death from any cause in Good risk patients (from randomization with or without imatinib) and Poor risk patients, from study entry; including the option of HSCT • Comparison of the safety profile in patients receiving imatinib with intensive chemotherapy vs. patients receiving intensive chemotherapy alone • The role of the molecular response [3]as a surrogate for DFS • Minimal residual disease (MRD)[3] rate over time [at five time points: end of frontline induction therapy, end of induction, and after consolidation blocks in both groups (Good risk and Poor risk)].
Additional analyses	• DFS and EFS: not censoring HSCT (FAS), • DFS and EFS (Administered set) • DFS and OS: Kaplan Meier summaries for Age group, WBC, Gender and MRD

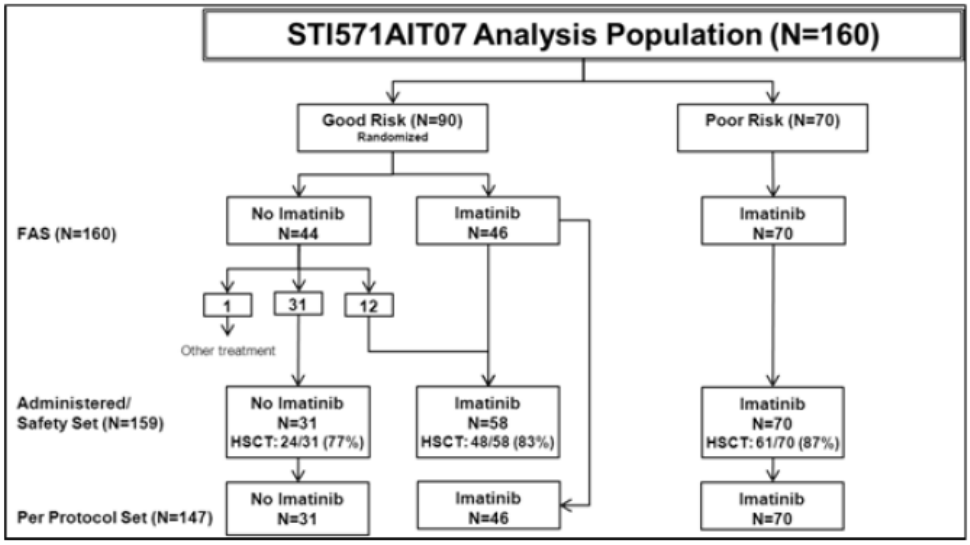
[1] Twelve patients were randomized to No imatinib and received imatinib as they either switched from assigned treatment (n=7) or deviated during treatment course (n=5). One additional patient was randomized to No imatinib but received 'other' treatment.

[2] DFS and EFS are defined differently because Poor risk patients were not randomized and were analyzed from study entry and EFS included all DFS events plus resistance.

[3] Molecular response (MR) and minimal residual disease (MRD) were assessed by quantitative RT-PCR of mononuclear bone marrow and peripheral blood cells. A molecular response is defined by a percentage of ≤ 0.01%.

Source: [ST1571AIT07] [Synopses of Individual Studies], [Tabular Listing of All Clinical Studies]

Figure 11: **Patient population in Study STI571AIT07**



Source: [ST1571AIT07–Table 14.1-1.2], [ST1571AIT07–Table 14.1-1.3], [ST1571AIT07–Table 14.1-1.4]

Patients with a confirmed diagnosis of Ph+ ALL were enrolled into the study after receiving initial induction chemotherapy according to national group protocols (Phase IA). Patients were stratified as Poor risk (i.e. poor prognosis) or Good risk (i.e. good prognosis), as defined below:

• Poor risk group: patients who were prednisone-poor responders, i.e. blast cell count ≥ 1000/μl in peripheral blood after 7 days of prednisone given in combination with intrathecal (IT) methotrexate (MTX), or having a M3 bone marrow (BM) at day 15 or M2/M3 (see definitions below) BM at day 21 or lack of a complete remission (CR) after the induction course.

• Good risk group: patients who were prednisone-good responders, i.e. blast cell count <1000/μl in peripheral blood after 7 days of prednisone given in combination with IT MTX, or having M1/M2 (see definitions below) BM at day 15 or M1 BM at day 21 and achieved CR after the induction course.

M1, M2, M3 are defined as follows:

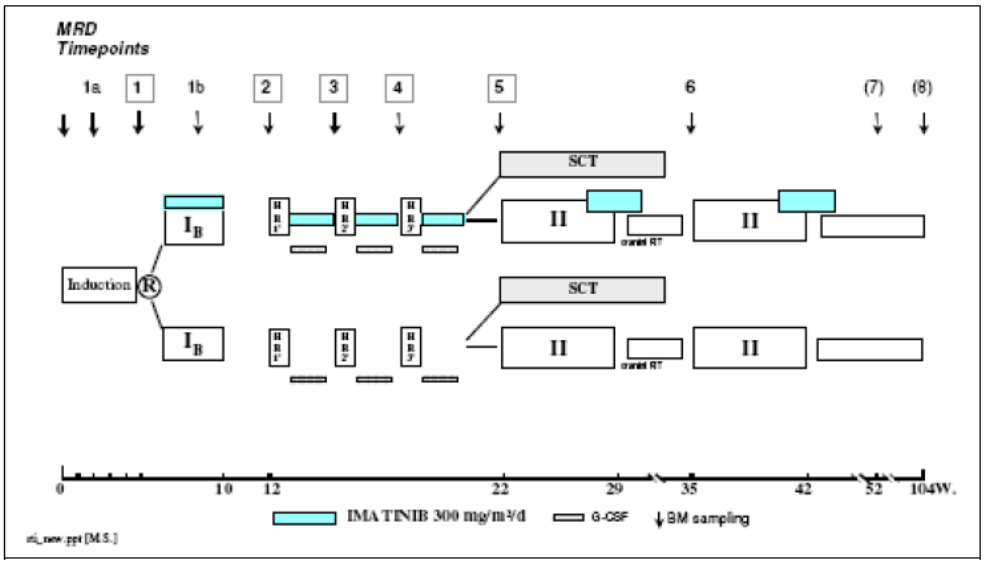
• M1: <5% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.

• M2: 5-25% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.

• M3: >25% blasts in a BM aspirate.

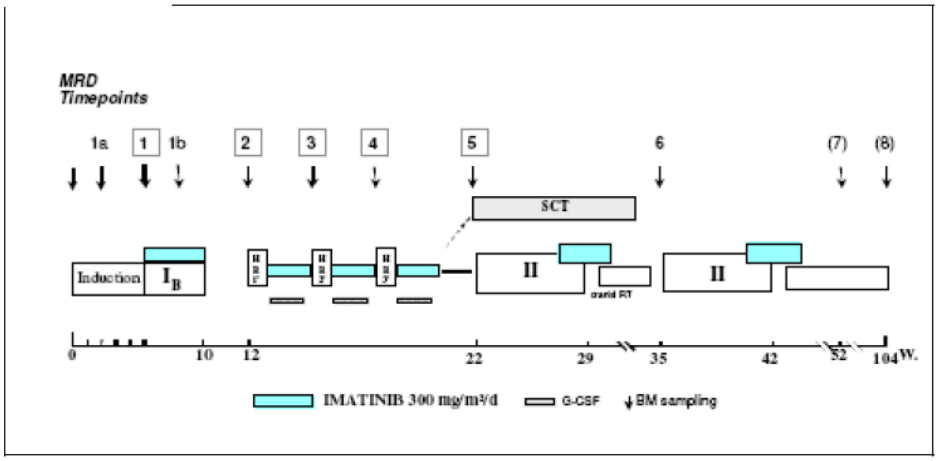
All Poor risk patients received imatinib in combination with intensive chemotherapy. Good risk patients were randomised to receive either imatinib in combination with intensive chemotherapy or intensive chemotherapy alone. After induction therapy, all patients continued with three consecutive blocks of Consolidation therapy (high risk consolidation blocks HR1, HR2, and HR3), for a total of 20 days of chemotherapy per treatment block. After consolidation therapy, patients who received HSCT did not continue with imatinib therapy regardless of group. After consolidation therapy, patients who did not undergo HSCT and who were considered suitable to receive further chemotherapy continued with 'Protocol II' which consisted of two reinduction phases (Phase IIA and Phase IIB). Phase IIA started 14 days after completion of consolidation therapy, and Phase IIB started 36 days after completion of consolidation therapy. After reinduction therapy, patients received maintenance antimetabolite-based low intensity chemotherapy and cranial irradiation therapy. After cranial irradiation, the reinduction phases (Phase IIA and Phase IIB) were repeated. Continuation therapy started 2 weeks after completion of delayed intensification (Protocol II), after which the maximum duration of chemotherapy was 24 months. Figure 12 and Figure 13 present the overall study design and treatment blocks for Good and Poor risk groups, respectively.

Figure 12: **Treatment of Good risk Ph+ ALL with or without imatinib**



Induction: Good risk patients received frontline induction therapy (~4 weeks) from a protocol of a national pediatric leukemia study group followed by R (randomization) to imatinib + chemotherapy or chemotherapy alone prior to the second part of induction (IB). Patients continued onto consolidation blocks (HR1, HR2, HR3) (20 days chemotherapy alone or plus 14 days of imatinib) and received granulocyte colony stimulating factor (G-CSF) between consolidation blocks (starting from the 5th day after completion of the block, until the WBC count was >20.000 µl). Post consolidation patients were screened for stem cell transplant (SCT). Patients who underwent SCT did not continue imatinib regardless of treatment group. Patients who did not undergo SCT post consolidation continued to receive two courses of Protocol II (reinduction therapy: IIa and IIb (chemotherapy alone or plus imatinib) separated by cranial radiation therapy (RT) followed by continuation / completion therapy. Bone marrow (BM) sampling was conducted at various timepoints (as shown with an arrow) as well as MRD assessments (boxes 1-5). Source: [ST1571AIT07–Appendix 16.1.1-Figure 3]

Figure 13: **Treatment of Poor risk Ph+ ALL with imatinib**



Induction: Poor risk patients received frontline induction therapy (~4weeks) from a protocol of a national pediatric leukemia study group. Patients then continued to the second part of induction (IB) and received chemotherapy plus imatinib. Patients continued onto consolidation blocks (HR1, HR2, HR3) (20 days chemotherapy plus 14 days of imatinib) and received granulocyte colony stimulating factor (G-CSF) between consolidation blocks (starting from the 5th day after completion of the block, until the WBC count was >20.000 µl). Post consolidation patients were screened for stem cell transplant (SCT). Patients who underwent SCT did not continue imatinib. Patients who did not undergo SCT post consolidation continued to receive two courses of Protocol II (reinduction therapy: IIa and IIb (chemotherapy plus imatinib) separated by cranial radiation therapy (RT) followed by continuation / completion therapy. Bone marrow (BM) sampling was conducted at various timepoints (as shown with an arrow) as well as MRD assessments (boxes 1-5).

Source: [ST1571AIT07–Appendix 16.1.1–Figure 4]

In December 2009, positive data reported from study STI571I2301 resulted in an amendment to the protocol terminating randomisation in the Good risk group. Results included in the STI571ATI07 were

provided to Novartis by EsPhALL and are derived from all patients enrolled prior to the amendment in December 2009.

Results

Table 18: DFS (Good Risk)/ EFS (Poor Risk) Kaplan-Meier summary over time (overall)- censoring HSCT at date of HSCT (FAS)

	DFS Good risk		EFS Poor risk
	No imatinib	Plus imatinib	Plus imatinib
	N=44	N=46	N=69**
	n (%)	n (%)	n (%)
Events/N (%)	6/44 (13.6)	4/46 (8.7)	9/69 (13)
Censored/N (%)	38/44 (86.4)	42/46 (91.3)	60/69 (87)
Percentiles (95% CI) +			
25%	21.0 (NE)	24.9 (15.5,30.7)	7.9 (7,9.6)
Median	30.9 (NE)	30.7 (NE)	9.6 (NE)
75%	NR	NR	23.3 (NE)
% Disease/Event-Free Probability Estimates (95% CI) +			
12 Months	95.4 (82.8,98.8)	97.4 (83.2,99.6)	45.6 (12.9,73.9)
24 Months	65.4 (30.4,86)	81.2 (30.7,96.4)	NE
36 Months	49.1 (14.3,77.1)	NE	NE
48 Months	49.1 (14.3,77.1)	NE	NE
Comparison Good Risk-no Imatinib vs. Good Risk-plus Imatinib (Log-Rank test)			
Hazard ratio (95% CI)	0.978 (0.27,3.547)		
P-value	0.9733		

Note: All Poor risk analyses are based on EFS events (from treatment start date and including resistance as an event) and all Good risk analyses are based on DFS events (from randomization date). Greenwood formula is used for CIs of KM estimates. HR < 1 is indicating a lower risk in Good risk plus imatinib.

p-value * Indicates statistical significance (2-sided) at 0.05 level

Estimated rates based on less than 4 patients are not presented.

N: Total number of patients included in the analysis; NE: not estimable; NR: not reached

** Date of HSCT was not available for one Poor risk patient, hence this patient was excluded.

Source : Post-text Table 14.2-1.2

Table 19: DFS (Good Risk)/EFS (Poor Risk) Kaplan-Meier summary over time (overall)-not censoring HSCT (FAS)

	DFS Good risk		EFS Poor risk
	No imatinib	Plus imatinib	Plus imatinib
	N=44	N=46	N=70
	n (%)	n (%)	n (%)
Events/N (%)	16/44 (36.4)	12/46 (26.1)	31/70 (44.3)
Censored/N (%)	28/44 (63.6)	34/46 (73.9)	39/70 (55.7)
Percentiles (95% CI) +			
25%	15.5 (8.3,35.2)	30.7 (NE)	11.6 (8.7,15.9)
Median	NR	73.1 (NE)	71.1 (NE)
75%	NR	NR	NR
% Disease-free/ Event-Free Probability Estimates (95% CI) +			
12 Months	84.1 (69.5,92.1)	93.2 (80.5,97.8)	71.0 (58.7,80.2)
24 Months	67.6 (51.5,79.4)	78.9 (63.2,88.4)	53.5 (40.4,65.0)
36 Months	61.7 (45.0,74.7)	72.9 (56.1,84.1)	53.5 (40.4,65.0)
48 Months	61.7 (45.0,74.7)	72.9 (56.1,84.1)	53.5 (40.4,65.0)
Comparison Good Risk-no Imatinib vs. Good Risk-plus Imatinib (Log-Rank test)			
Hazard ratio (95% CI)	0.635 (0.295,1.369)		
P-value	0.2424		

Note: All Poor risk analyses are based on EFS events (from treatment start date and including resistance as an event) and all Good risk analyses are based on DFS events (from randomization date). Greenwood formula is used for CIs of KM estimates. HR < 1 is indicating a lower risk in Good risk plus imatinib.

p-value * Indicates statistical significance (2-sided) at 0.05 level

Estimated rates based on less than 4 patients are not presented.

N: Total number of patients included in the analysis; NE: not estimable; NR: not reached

Source: Post-text Table 14.2-1.7

2.4.2. Discussion on clinical efficacy

The justification for a non-randomised study design in the VHR ALL subpopulation investigated was based on the following characteristics of the patient population: 1) overall poor prognosis (5-year EFS < 45%); 2) lack of a generally accepted standard of care; 3) limited population of patients for enrollment within an acceptable timeframe; and 4) presence of historical control data for comparison of efficacy and safety.

The main doubt would not be the regimen administered but if the addition of imatinib to other chemotherapy regimens could provide similar outcomes. There are several paediatric chemotherapy regimens used for Ph+ ALL; the one used by COG in Study STI571I2301 is considered a standard regimen as included in NCCN guidelines.

Efficacy data and additional analyses

The primary endpoint of the main study has been clearly positive, EFS for cohort 5 (69.6%) was more than twice historical controls (31.6%). Estimated OS rate at 48 months was 83.6% in cohort 5 compared to 44.8% in the historical control group. In addition, several sensitivity analyses and subset of patients have supported the main results, which highlights the robustness of the outcomes.

Risk factors (age, cytogenetics, immunophenotype, and response to induction therapy) were not evenly distributed among the study cohorts and this might have contributed to an unknown extent on the most favourable results seen in cohort 5.

The historical controls used in this study allow to compare and put into perspective the results of this trial.

The control group consisted in a data set of patients from several protocols for B-precursor ALL between January 1986 and November 1999. The introduction of imatinib in combination with high intensive backbone chemotherapy has given an impressive result in terms of EFS and OS at 48 months. This result appears to be independent of HSCT role in the study, since the results in the population excluding HSCT patients were similar to the whole population (HSCT vs Chemo+Glivec alone).

The results appear better than other treatments (excluding HSCT) assessed so far in Ph+ ALL children.

There are uncertainties on the impact of Glivec on transplantation and there is a need to generate additional data by a non-randomised single arm clinical trial or alternatively a registry. This requirement has been addressed by the MAH proposing a registry collecting data on interventions and outcomes in paediatric Ph+ALL patients treated with chemotherapy + imatinib ± HSCT. The CHMP reviewed the concept sheet submitted by the MAH and requested input from the PDCO (see appendix 01).

The CHMP finally agreed to the concept sheet of a European observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ ALL patients treated with chemotherapy + imatinib ± HSCT (as reflected in the RMP). Approximately 100 male or female paediatric patients with a documented diagnosis of newly diagnosed Ph+ ALL (within 6 months of diagnosis) treated or on treatment with chemotherapy + imatinib ± HSCT, would be recruited in this registry. For each patient enrolled in the registry, information will be collected according to the standard practice of the site with a minimum of once yearly update. Long term safety and efficacy data will be collected such that the follow-up for efficacy and safety will be at least 5 years.

2.4.3. Conclusion on clinical efficacy

In comparison to historical controls, the introduction of imatinib in combination with high intensive backbone chemotherapy showed clinically meaningful results in terms of EFS and OS at 48 months.
In order to address the uncertainties related to the impact of Glivec on HSCT, the CHMP considers the following measure necessary:

To conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ Acute Lymphoblastic Leukaemia (ALL) patients treated with chemotherapy + imatinib ± HSCT.

Due date for submission of final results: 31/12/2020.

2.5. Clinical safety

2.5.1. Introduction

Studies STI571I2301 and STI571AIT07 provide data in support of the assessment of safety in Ph+ ALL paediatric patients. Both studies were conducted in full compliance with Good Clinical Practice and were closely monitored by the cooperative groups, COG and EsPhALL, respectively.
The two studies (STI571I2301 and STI571AIT07) present substantial differences in terms of study design, dose and duration of imatinib, as well as differences in chemotherapy treatment. Therefore, the data from the two studies are presented separately. In both studies, the safety set was defined as the set of patients who received at least one dose of study drug. The safety population comprised 93 Ph+ patients (92 analysed by Novartis) in Study [STI571I2301] and 159 Ph+ patients (128 imatinib and 31 no imatinib) in Study [STI571AIT07]. All analyses of study STI571AIT07 were performed by the EsPhALL trial data centre in Italy. No data from this study was transferred to Novartis. Therefore, the exposure data could not be pooled with the STI571I 2301 study.

Patient exposure

Study STI571I2301

For Ph+ ALL patients, duration of imatinib exposure was calculated as the sum of the time from start to end of imatinib treatment per block. Imatinib-free treatment blocks were not included.
Of the 92 Ph+ ALL patients included in the study, 34 underwent HSCT, 21 patients on study and 13 following withdrawal from the study. The exposure in patients who did not undergo HSCT is described in table 20.

Table 20: **Overall exposure to imatinib/chemotherapy (Safety set excluding HSCT patients – STI571I2301)**

	Ph+ patients (imatinib exposure[1] in days)				Ph- patients (chemotherapy only exposure)
	Cohort 1+2 N=14	Cohort 3+4 N=14	Cohort 5 N=30	Overall Ph+ N=58	N=42
N	12	14	30	56	42
Mean (SD)	267.3 (184.61)	324.9 (181.40)	586.2 (273.55)	452.5 (274.64)	634.4 (365.14)
Minimum	12	58	62	12	1
Median	275.5	323.0	708.0	465.0	783.0
Maximum	498	577	867	867	1093
<1 year	7 (58.3)	8 (57.1)	7 (23.3)	22 (39.3)	13 (31.0)
1 - <2 years	5 (41.7)	6 (42.9)	10 (33.3)	21 (37.5)	8 (19.1)
2 - <3 years	0	0	13 (43.3)	13 (23.2)	21 (50.0)
3 years or more	0	0	0	0	0

[1]Exposure is the sum of the times from start to the end of the imatinib within each treatment block. Imatinib-free treatment blocks are not included.

Source: [STI571I2301-Appendix 16.5-Table 14.3-1.1]

Among the Ph+ ALL patients receiving per protocol HSCT the overall median imatinib exposure prior to HSCT was 42 days (range, 21 to 77 days) and the median exposure to imatinib following HSCT was 169 days (range, 14 to 192 days). Among the Ph+ patients the overall median imatinib exposure prior to patients receiving off protocol HSCT was 53 days (range, 28 to 165 days)

Study STI571I2301 permitted the imatinib dose to be reduced from 340 mg/m2/day to 230 mg/m2/day for patients who could not tolerate the higher dose. However, imatinib dose and dose modifications were not systematically entered in the dose administration record and therefore are not presented. Only overall treatment of imatinib, including start and stop dates, were captured in the CRF. Longer imatinib treatment did not correspond to higher number of patients with dose delays, as illustrated by the fact that the highest percentage of patients with dose delays were in cohorts 3 and 4, instead of in cohort 5.

Table 21: **Delayed start of next treatment block (Safety set – STI571I2301)**

	Cohort 1 N=7 n (%)	Cohort 2 N=12 n (%)	Cohort 3 N=11 n (%)	Cohort 4 N=12 n (%)	Cohort 5 N=50 n (%)	Overall N=92 n (%)
Total number of patients with delays	2 (28.6)	6 (50.0)	9 (81.8)	9 (75.0)	34 (68.0)	60 (65.2)
Patients with 1 delay >14 days	2 (28.6)	4 (33.3)	4 (36.4)	5 (41.7)	14 (28.0)	29 (31.5)
Patients with 2 delays >14 days	0	1 (8.3)	2 (18.2)	2 (16.7)	9 (18.0)	14 (15.2)
Patients with 3 delays >14 days	0	1 (8.3)	0	1 (8.3)	7 (14.0)	9 (9.8)
Patients with >3 delays >14 days	0	0	3 (27.3)	1 (8.3)	4 (8.0)	8 (8.7)

Source: [STI571I2301-Table 14.3-1.11]

Study STI571AIT07

The overall treatment exposure is described in Table 22.

Table 22: Overall treatment exposure* (Safety set –STI571AIT07)

	Good risk No Imatinib (i.e. chemotherapy alone) N=31	Good risk Plus Imatinib N=58	Poor risk Plus Imatinib N=70	All Plus Imatinib N=128
Treatment exposure (days)				
N (%)	27 (87.1)	53 (91.4)	61 (87.1)	114 (89.1)
Mean (SD)	114.3 (15.6)	123.2 (17.3)	121.5 (13.7)	122.3 (15.4)
Min	90	86	81	81
Q1	99	112	115	113
Median	112	121	120	120
Q3	127	132	131	132
Max	145	169	152	169
Expected exposure**	102	102	102	102

Treatment exposure is calculated (in days) from start date of Phase IB (i.e. first treatment phase following randomization including chemotherapy and add-on imatinib for a planned 28 days) to end date of Consolidation 3, for patients who actually entered each phase.
* Start and end dates of treatment could refer to chemotherapy treatment and not only to imatinib
** Expected exposure is calculated by adding up all days when imatinib was planned to be given up to the end of Consolidation 3.
Actual imatinib treatment dates (start/end dates) per block were not captured in the CRFs, hence no information on dose intensity and on exact imatinib treatment duration could be provided.
Source: [STI571AIT07-Table 14.3-2.4]

The protocol permitted modification of dose and dose-delay for the management of toxicity. Unexpected non-haematological grade 3- 4 toxicities, grade 3-4 neutropenia or thrombocytopenia with clinically significant bleeding or infection required that treatment be withheld for a period of time. Following a dose-interruption, treatment with imatinib was restarted at a reduced dose (240 mg/m2 daily) once the event resolved to grade 2 or lower.

Table 23: Treatment delays or dose modifications from start of study to Consolidation 3 (Safety set – STI571AIT07)

	Good risk No Imatinib N=31 n (%)	Good risk Plus Imatinib N=58 n (%)	Poor risk Plus Imatinib N=70 n (%)	All Plus Imatinib N=128 n (%)
Schedule modifications				
One week delay or more	6 (19.4)	25 (43.1)	25 (35.7)	50 (39.1)
Less than one week delay	14 (45.2)	13 (22.4)	20 (28.6)	33 (25.8)
Anticipation*	1 (3.2)	1 (1.7)	2 (2.9)	3 (2.3)
No modification	8 (25.8)	17 (29.3)	19 (27.1)	36 (28.1)
Not known	2 (6.5)	2 (3.4)	4 (5.7)	6 (4.7)
Modification of treatment**				
Dose decrease ≥ 10%	13 (41.9)	26 (44.8)	40 (57.1)	66 (51.6)
Dose increase ≥ 10%	4 (12.9)	3 (5.2)	3 (4.3)	6 (4.7)
No modification	11 (35.5)	20 (34.5)	19 (27.1)	39 (30.5)
Not known	3 (9.7)	9 (15.5)	8 (11.4)	17 (13.3)

Modification of treatment refers to treatment from Phase IB (i.e. the first treatment phase after randomization including chemotherapy and add on imatinib for a planned 28 days) up to Consolidation 3.
Patients with multiple modifications during treatment (either in schedule or in dosing) are counted once in each modification category.
* Anticipation: was defined as treatment which was initiated earlier than scheduled in the protocol
** Modification of either imatinib or the chemotherapy regimen.
Source: [STI571AIT07-Table 14.3-2.2]

Adverse events

Study STI571I2301

The following were identified by COG as "targeted toxicities:"

- Coagulation [partial thromboplastin time (PTT)]

- Coagulation [prothrombin time (PT)]
- Haemorrhage [Haemorrhage/ bleeding with Grade 3 or 4 thrombocytopenia]
- Haemorrhage [Haemorrhage/ bleeding without Grade 3 or 4 thrombocytopenia]
- Haemorrhage [CNS haemorrhage/ bleeding]
- Hepatic [aspartate aminotransferase/ glutamic oxaloacetic transaminase (AST/ SGOT)]
- Hepatic [SGPT (ALT)]
- Blood Bilirubin

It was required that non-targeted AEs be reported by the investigators if they were grade 3 or higher and recorded in the COG database. However, in practice, there were cases of AEs less than grade 3 that were reported. AEs that met the criteria for expedited reporting were expedited via the AdEERs reporting guidelines.

The incidence of non-targeted AEs of at least grade 3 by system organ class (SOC) and preferred term in Ph+ patients treated with chemotherapy + imatinib as well as Ph- patients who received chemotherapy alone is summarised in Table 24.

Table 24: **Frequent (at least 5 patients in any group) non-targeted adverse events (grade 3, 4, 5) regardless of causality by system organ class and preferred term in Ph+ and Ph- patients (Safety set –STI571I2301)**

System Organ Class Preferred Term	Cohort 1+2 N=19 n (%)	Cohort 3+4 N=23 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	All Ph- N=65 n (%)
Investigations	13 (68.4)	14 (60.9)	38 (76.0)	65 (70.7)	40 (61.5)
Neutrophil Count	12 (63.2)	11 (47.8)	37 (74.0)	60 (65.2)	37 (56.9)
White Blood Cell Count	12 (63.2)	13 (56.5)	34 (68.0)	59 (64.1)	33 (50.8)
Platelet Count	11 (57.9)	10 (43.5)	36 (72.0)	57 (62.0)	36 (55.4)
Hemoglobin	7 (36.8)	12 (52.2)	32 (64.0)	51 (55.4)	31 (47.7)
Surgical and Medical procedures	10 (52.6)	13 (56.5)	27 (54.0)	50 (54.3)	31 (47.7)
Packed Red Blood Cell Transfusion	10 (52.6)	11 (47.8)	27 (54.0)	48 (52.2)	29 (44.6)
Platelet Transfusion	9 (47.4)	12 (52.2)	25 (50.0)	46 (50.0)	28 (43.1)
Infections and Infestations	10 (52.6)	10 (43.5)	29 (58.0)	49 (53.3)	32 (49.2)
Neutropenic Infection	9 (47.4)	8 (34.8)	26 (52.0)	43 (46.7)	24 (36.9)
Infection	4 (21.1)	2 (8.7)	13 (26.0)	19 (20.7)	18 (27.7)
Device Related Infection	4 (21.1)	2 (8.7)	10 (20.0)	16 (17.4)	7 (10.8)
Blood and Lymphatic System Disorders	11 (57.9)	6 (26.1)	23 (46)	40 (43.5)	26 (40.0)
Febrile Neutropenia	10 (52.6)	6 (26.1)	19 (38.0)	35 (38.0)	20 (30.8)
Lymphopenia	2 (10.5)	2 (8.7)	10 (20.0)	14 (15.2)	11 (16.9)
Gastrointestinal Disorders	7 (36.8)	8 (34.8)	21 (42.0)	36 (39.1)	17 (26.2)
Pharyngitis	3 (15.8)	2 (8.7)	10 (20.0)	15 (16.3)	7 (10.8)
Vomiting	2 (10.5)	1 (4.3)	9 (18.0)	12 (13.0)	2 (3.1)
Nausea	0	2 (8.7)	7 (14.0)	9 (9.8)	5 (7.7)
Diarrhoea	1 (5.3)	1 (4.3)	6 (12.0)	8 (8.7)	3 (4.6)
Abdominal Pain	2 (10.5)	0	6 (12.0)	8 (8.7)	2 (3.1)
Metabolism and Nutrition Disorders	6 (31.6)	6 (26.1)	23 (46.0)	35 (38.0)	29 (44.6)
Hypokalaemia	5 (26.3)	5 (21.7)	21 (42.0)	31 (33.7)	16 (24.6)
Decreased appetite	1 (5.3)	2 (8.7)	7 (14.0)	10 (10.9)	3 (4.6)
Hyponatraemia	2 (10.5)	1 (4.3)	6 (12.0)	9 (9.8)	4 (6.2)
Hypophosphataemia	1 (5.3)	4 (17.4)	4 (8.0)	9 (9.8)	1 (1.5)
Hyperglycaemia	2 (10.5)	1 (4.3)	4 (8.0)	7 (7.6)	11 (16.9)
Hypocalcaemia	0	2 (8.7)	4 (8.0)	6 (6.5)	6 (9.2)
Dehydration	0	1 (4.3)	5 (10.0)	6 (6.5)	4 (6.2)
Vascular Disorders	1 (5.3)	8 (34.8)	10 (20v)	19 (20.7)	6 (9.2)
Hypotension	1 (5.3)	5 (21.7)	4 (8.0)	10 (10.9)	5 (7.7)
Hypertension	0	1 (4.3)	5 (10.0)	6 (6.5)	2 (3.1)
Respiratory thoracic and Mediastinal Disorders	3 (15.8)	5 (21.7)	10 (20.0)	18 (19.6)	6 (9.2)
Hypoxia	0	1 (4.3)	7 (14.0)	8 (8.7)	2 (3.1)
Epistaxis	2 (10.5)	2 (8.7)	2 (4.0)	6 (6.5)	2 (3.1)
Pneumonitis	1 (5.3)	2 (8.7)	4 (8.0)	7 (7.6)	1 (1.5)
General Disorders and Administration Site Conditions	2 (10.5)	3 (13.0)	7 (14.0)	12 (13.0)	4 (6.2)
Pain	2 (10.5)	2 (8.7)	5 (10.0)	9 (9.8)	4 (6.2)
Musculoskeletal and Connective Tissue Disorders	1 (5.3)	5 (21.7)	3 (6.0)	9 (9.8)	1 (1.5)
Myalgia	0	3 (13.0)	2 (4.0)	5 (5.4)	0

Terms are presented as in COG CRF; A patient with multiple AES within one non-targeted term is only counted once for that AE.
AEs for patients having HSCT were only included up to consolidation 2.
Source: [STI571I2301-Appendix 16.5-Table 14.3-1.4]

Targeted toxicities of ≥ grade 3 for patients who received chemotherapy + imatinib as well as Ph- patients who did not receive imatinib are summarised in Table 25.

Table 25: **Targeted toxicities (grade 3, 4 or 5) by preferred term in Ph+ and Ph- patients (Safety set – STI571I2301)**

	Cohort 1+2 N=19 n (%)	Cohort 3+4 N=23 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	All Ph- N=65 n (%)
Patients with targeted toxicities	10 (52.6)	12 (52.2)	33 (66.0)	55 (59.8)	41 (63.1)
Alanine aminotransferase increased	10 (52.6)	12 (52.2)	27 (54.0)	49 (53.3)	37 (56.9)
Aspartate aminotransferase increased	8 (42.1)	5 (21.7)	17 (34.0)	30 (32.6)	13 (20.0)
Hemorrhage	1 (5.3)	4 (17.4)	5 (10.0)	10 (10.9)	9 (13.8)
Partial thromboplastin time prolonged	0	2 (8.7)	7 (14.0)	9 (9.8)	5 (7.7)
Blood bilirubin	2 (10.5)	3 (13.0)	4 (8.0)	9 (9.8)	3 (4.6)
Prothrombin time prolonged	0	0	2 (4.0)	2 (2.2)	0

Note: Targeted toxicity terms are presented according to COG CRF; A patient with multiple AEs within one targeted toxicity is counted once for that toxicity.
AE reporting for HSCT patients are only included up to the end of consolidation 2.
Source: [STI571I2301-Appendix 16.5-Table 14.3-1.2]

The impact on hepatic toxicities of the reduction of the imatinib treatment duration to 14 days per block (amendment 5B) is described in Table 24.

Table 26: **Hepatic toxicities in maintenance cycle 5 pre- and post-Amendment 5B (Safety set – STI571I2301)**

	During the course of Maintenance cycle 5		
Hepatic toxicities Preferred terms	**Pre-amendment 5B N=12 n (%)**	**Post-amendment 5B N=27 n (%)**	**Overall (during maintenance 5) N=39 n (%)**
Patients with targeted toxicities	12 (100)	26 (96.3)	38 (97.4)
Alanine aminotransferase increased	11 (91.7)	25 (92.6)	36 (92.3)
Grade 1	2 (16.7)	13 (48.1)	15 (38.5)
Grade 2	2 (16.7)	3 (11.1)	5 (12.8)
Grade 3	6 (50.0)	8 (29.6)	14 (35.9)
Grade 4	1 (8.3)	1 (3.7)	2 (5.1)
Aspartate aminotransferase increased	9 (75.0)	18 (66.7)	27 (69.2)
Grade 1	1 (8.3)	9 (33.3)	10 (25.6)
Grade 2	5 (41.7)	4 (14.8)	9 (23.1)
Grade 3	2 (16.7)	4 (14.8)	6 (15.4)
Grade 4	1 (8.3)	1 (3.7)	2 (5.1)
Blood bilirubin increased	6 (50.0)	10 (37.0)	16 (41.0)
Grade 1	2 (16.7)	6 (22.2)	8 (20.5)
Grade 2	1 (8.3)	3 (11.1)	4 (10.3)
Grade 3	3 (25.0)	1 (3.7)	4 (10.3)
Grade 4	0	0	0

Pre-amendment 5B: until 20-Aug-2005; post-amendment 5B as of 21-Aug-2005
Percentages are based on the number of patients treated in the respective maintenance cycle.
Source: [STI571I2301-Table 14.3.1-4.1]

In Table 25 the number of Ph+ ALL patients with grade 3, 4 or 5 AEs is summarised by cohort and treatment block, with the shaded cells corresponding to imatinib integrated with chemotherapy.

Table 27: Adverse events (grade 3, 4, 5) by treatment block in Ph+ patients treated with chemotherapy + imatinib (Safety set – STI571I2301)

	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	Cohort 4 n (%)	Cohort 5 n (%)
Consolidation 1	n=7	n=12	n=11	n=12	n=50
Number of patients with AE	4 (57.1)	7 (58.3)	5 (45.5)	7 (58.3)	34 (68.0)
Consolidation 2	n=6	n=12	n=11	n=12	n=50
Number of patients with AE	2 (33.3)	9 (75.0)	6 (54.5)	8 (66.7)	38 (76.0)
Reinduction 1	n=3	n=7	n=8	n=6	n=30
Number of patients with AE	2 (66.7)	6 (85.7)	4 (50.0)	4 (66.7)	23 (76.7)
Intensification 1	n=3	n=7	n=8	n=5	n=29
Number of patients with AE	2 (66.7)	5 (71.4)	7 (87.5)	4 (80.0)	23 (79.3)
Reinduction 2	n=3	n=7	n=8	n=5	n=27
Number of patients with AE	1 (33.3)	5 (71.4)	5 (62.5)	2 (40.0)	17 (63.0)
Intensification 2	n=3	n=7	n=7	n=5	n=25
Number of patients with AE	2 (66.7)	7 (100)	5 (71.4)	4 (80.0)	23 (92.0)
Maintenance cycles 1 – 4	n=2	n=7	n=7	n=4	n=25
Number of patients with AE	2 (100)	6 (85.7)	5 (71.4)	4 (100)	23 (92.0)
Maintenance cycles 5 – 12	n=2	n=7	n=6	n=3	n=21
Number of patients with AE	2 (100)	5 (71.4)	5 (83.3)	3 (100)	19 (90.5)

Shaded cells = + imatinib; Unshaded cells = no imatinib. For patients undergoing HSCT, adverse events only up to the end of Consolidation 2 are included. Percentages are based on the number of patients treated in the respective cohort.

Source [STI571I2301-Table 14.3.1-2.1],

Table 26 presents frequent AEs, grade 3, 4, 5, suspected to be related to imatinib, as assessed by the investigator (shaded fields indicate imatinib administration in the respective treatment block).

Table 28: Frequent (at least 5 patients in any group) adverse events (grade 3, 4, 5) suspected to be related to imatinib by preferred term and treatment block (Safety set – STI571I2301)

	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	Cohort 4 n (%)	Cohort 5 n (%)	Overall n (%)
Consolidation 1	n=7	n=12	n=11	n=12	n=50	n=92
Number of patients with AE	0	0	4 (36.4)	5 (41.7)	21 (42.0)	30 (32.6)
White blood cell count decreased			2 (18.2)	3 (25.0)	11 (22.0)	16 (17.4)
Neutrophil count decreased			2 (18.2)	3 (25.0)	10 (20.0)	15 (16.3)
Alanine aminotransferase increased			0	1 (8.3)	7 (14.0)	8 (8.7)
Platelet count decreased			1 (9.1)	1 (8.3)	6 (12.0)	8 (8.7)
Hemoglobin decreased			3 (27.3)	1 (8.3)	5 (10.0)	9 (9.8)
Consolidation 2	n=6	n=12	n=11	n=12	n=50	n=91
Number of patients with AE	0	8 (66.7)	5 (45.5)	7 (58.3)	25 (50.0)	45 (49.5)
Platelet count decreased		7 (58.3)	4 (36.4)	2 (16.7)	19 (38.0)	32 (35.2)
White blood cell count decreased		7 (58.3)	3 (27.3)	4 (33.3)	18 (36.0)	32 (35.2)
Neutrophil count decreased		7 (58.3)	4 (36.4)	5 (41.7)	16 (32.0)	32 (35.2)
Hemoglobin decreased		4 (33.3)	3 (27.3)	4 (33.3)	12 (24.0)	23 (25.3)
Alanine aminotransferase increased		1 (8.3)	1 (9.1)	1 (8.3)	6 (12.0)	9 (9.9)
Reinduction 1	n=3	n=7	n=8	n=6	n=30	n=54
Number of patients with AE	0	6 (85.7)	3 (37.5)	2 (33.3)	16 (53.3)	27 (50.0)
Platelet count decreased		2 (28.6)	1 (12.5)	1 (16.7)	11 (36.7)	15 (27.8)
White blood cell count decreased		3 (42.9)	2 (25.0)	1 (16.7)	10 (33.3)	16 (29.6)
Neutrophil count decreased		2 (28.6)	2 (25.0)	1 (16.7)	10 (33.3)	15 (27.8)
Hemoglobin decreased		2 (28.6)	2 (25.0)	0	10 (33.3)	14 (25.9)
Febrile neutropenia		1 (14.3)	0	0	4 (13.3)	5 (9.3)
Intensification 1	n=3	n=7	n=8	n=5	n=29	n=52
Number of patients with AE	1 (33.3)	0	2 (25.0)	2 (40.0)	19 (65.5)	24 (46.2)
Neutrophil count decreased	1 (33.3)		1 (12.5)	2 (40.0)	11 (37.9)	15 (28.8)
Hemoglobin decreased	0		1 (12.5)	1 (20.0)	11 (37.9)	13 (25.0)
Platelet count decreased	1 (33.3)		1 (12.5)	2 (40.0)	10 (34.5)	14 (26.9)
White blood cell count decreased	1 (33.3)		1 (12.5)	2 (40.0)	9 (31.0)	13 (25.0)
Alanine aminotransferase increased	0		2 (25.0)	1 (20.0)	5 (17.2)	8 (15.4)

	Cohort 1 n (%)	Cohort 2 n (%)	Cohort 3 n (%)	Cohort 4 n (%)	Cohort 5 n (%)	Overall n (%)
Reinduction 2	n=3	n=7	n=8	n=5	n=27	n=50
Number of patients with AE	0	4 (57.1)	3 (37.5)	2 (40.0)	12 (44.4)	21 (42.0)
Platelet count decreased		1 (14.3)	2 (25.0)	0	9 (33.3)	12 (24.0)
Neutrophil count decreased		3 (42.9)	3 (37.5)	1 (20.0)	8 (29.6)	15 (30.0)
White blood cell count decreased		3 (42.9)	3 (37.5)	1 (20.0)	8 (29.6)	15 (30.0)
Hemoglobin decreased		0	1 (12.5)	0	6 (22.2)	7 (14.0)
Neutropenic infection		0	1 (12.5)	1 (20.0)	3 (11.1)	5 (10.0)
Intensification 2	n=3	n=7	n=7	n=5	n=25	n=47
Number of patients with AE	0	0	0	1 (20.0)	18 (72.0)	19 (40.4)
Hemoglobin decreased				0	10 (40.0)	10 (21.3)
Neutrophil count decreased				0	10 (40.0)	10 (21.3)
Platelet count decreased				0	10 (40.0)	10 (21.3)
Alanine aminotransferase increased				0	8 (32.0)	8 (17.0)
White blood cell count decreased				0	8 (32.0)	8 (17.0)
Maintenance 1 – 4	n=2	n=7	n=7	n=4	n=25	n=45
Number of patients with AE	2 (100)	6 (85.7)	4 (57.1)	2 (50.0)	18 (72.0)	32 (71.1)
Neutrophil count decreased	1 (50.0)	4 (57.1)	4 (57.1)	0	12 (48.0)	21 (46.7)
Platelet count decreased	1 (50.0)	3 (42.9)	2 (28.6)	0	10 (40.0)	16 (35.6)
Hemoglobin decreased	1 (50.0)	1 (14.3)	2 (28.6)	0	10 (40.0)	14 (31.1)
White blood cell count decreased	1 (50.0)	2 (28.6)	3 (42.9)	0	9 (36.0)	15 (33.3)
Febrile neutropenia	2 (100)	3 (42.9)	1 (14.3)	0	5 (20.0)	11 (24.4)
Neutropenic infection	1 (50.0)	0	2 (28.6)	1 (25.0)	5 (20.0)	9 (20.0)
Alanine aminotransferase increased	0	2 (28.6)	0	0	4 (16.0)	6 (13.3)
Maintenance 5 – 12	n=2	n=7	n=6	n=3	n=21	n=39
Number of patients with AE	2 (100)	5 (71.4)	5 (83.3)	3 (100)	17 (81.0)	32 (82.1)
Neutrophil count decreased	1 (50.0)	4 (57.1)	4 (66.7)	1 (33.3)	14 (66.7)	24 (61.5)
White blood cell count decreased	1 (50.0)	3 (42.9)	4 (66.7)	1 (33.3)	11 (52.4)	20 (51.3)
Alanine aminotransferase increased	2 (100)	5 (71.4)	3 (50.0)	2 (66.7)	8 (38.1)	20 (51.3)
Aspartate aminotransferase increased	2 (100)	3 (42.9)	1 (16.7)	2 (66.7)	5 (23.8)	13 (33.3)
Lymphopenia	0	0	1 (16.7)	1 (33.3)	5 (23.8)	7 (17.9)
Platelet count decreased	0	0	2 (33.3)	0	4 (19.0)	6 (15.4)
Febrile neutropenia	0	1 (14.3)	2 (33.3)	0	3 (14.3)	6 (15.4)
Hemoglobin decreased	0	1 (14.3)	1 (16.7)	0	3 (14.3)	5 (12.8)

Shaded cells = plus imatinib; Un-shaded cells = no imatinib (except "Overall" column)

For patients undergoing HSCT, only AEs up to the end of Consolidation 2 are included.
For 2 patients in cohort 3 in Intensification 1, AEs were recorded as being suspected to be related to imatinib, even though these patients did not receive imatinib at that time.
Surgical and medical procedures (packed red blood cell and platelet transfusions) are not included as they are an intervention.

Source: [STI571I2301-Table 14.3.1-2.5]

Study STI571AIT07

Most patients experienced at least one AE during the study. The AEs reported were consistent with the established safety profile of imatinib. The most frequently reported AEs across the treatment arms were decreased WBC count, haemoglobin, platelet count, and granulocyte count as well as infections (Table 29).

Table 29: Adverse events regardless of study drug relationship by preferred term (Safety set – STI571AIT07)

	Good risk		Poor risk	All imatinib
	No imatinib	Plus imatinib	Plus imatinib	
	N=31	N=58	N=70	N=128
Preferred term	n (%)	n (%)	n (%)	n (%)
WBC Count [a]	28 (90.3)	57 (98.3)	65 (92.9)	122 (95.3)
Hemoglobin [a]	28 (90.3)	55 (94.8)	65 (92.9)	120 (93.8)
Platelet Count [a]	28 (90.3)	56 (96.6)	63 (90.0)	119 (93.0)
Granulocyte Count [a]	26 (83.9)	54 (93.1)	62 (88.6)	116 (90.6)
Infection	26 (83.9)	54 (93.1)	61 (87.1)	115 (89.8)
Pyrexia	25 (80.6)	50 (86.2)	61 (87.1)	111 (86.7)
Nausea	20 (64.5)	42 (72.4)	58 (82.9)	100 (78.1)
Hepatic Enzyme [b]	22 (71.0)	47 (81.0)	49 (70.0)	96 (75.0)
Vomiting	21 (67.7)	43 (74.1)	53 (75.7)	96 (75.0)
Stomatitis	22 (71.0)	42 (72.4)	52 (74.3)	94 (73.4)
Abdominal pain	19 (61.3)	41 (70.7)	48 (68.6)	89 (69.5)
Diarrhoea	16 (51.6)	29 (50.0)	38 (54.3)	67 (52.3)
Blood Bilirubin [b]	18 (58.1)	24 (41.4)	35 (50.0)	59 (46.1)
Depression	11 (35.5)	25 (43.1)	34 (48.6)	59 (46.1)
Skin Disorder	13 (41.9)	20 (34.5)	28 (40)	48 (37.5)
Activated PTT [b]	10 (32.3)	22 (37.9)	23 (32.9)	45 (35.2)
Blood Glucose [b]	11 (35.5)	16 (27.6)	25 (35.7)	41 (32.0)
Antithrombin III [a]	5 (16.1)	17 (29.3)	18 (25.7)	35 (27.3)
Myalgia	4 (12.9)	11 (19.0)	22 (31.4)	33 (25.8)
Blood Fibrinogen	6 (19.4)	12 (20.7)	17 (24.3)	29 (22.7)
Creatinine [b]	11 (35.5)	13 (22.4)	14 (20)	27 (21.1)
Weight [b]	12 (38.7)	12 (20.7)	13 (18.6)	25 (19.5)
Myopathy Toxic	8 (25.8)	15 (25.9)	10 (14.3)	25 (19.5)
Gastritis	4 (12.9)	13 (22.4)	9 (12.9)	22 (17.2)
Neurotoxicity	3 (9.7)	7 (12.1)	13 (18.6)	20 (15.6)
Oedema	7 (22.6)	6 (10.3)	13 (18.6)	19 (14.8)
Hematuria	4 (12.9)	6 (10.3)	7 (10)	13 (10.2)
Proteinuria	1 (3.2)	7 (12.1)	6 (8.6)	13 (10.2)
Euphoric Mood	1 (3.2)	8 (13.8)	3 (4.3)	11 (8.6)
Melena	2 (6.5)	2 (3.4)	8 (11.4)	10 (7.8)
Arrhythmia	2 (6.5)	4 (6.9)	4 (5.7)	8 (6.3)
Left Ventricular Dysfunction	2 (6.5)	2 (3.4)	4 (5.7)	6 (4.7)
Cardiac Failure	1 (3.2)	2 (3.4)	3 (4.3)	5 (3.9)
Gastric Ulcer	0	1 (1.7)	2 (2.9)	3 (2.3)
Thrombosis	1 (3.2)	1 (1.7)	1 (1.4)	2 (1.6)
Osteonecrosis	0	0	1 (1.4)	1 (0.8)

[a] Decrease in laboratory parameter

[b] Increase in laboratory parameter

The table includes treatment phases up to HR3 Block (Consolidation 3).

Toxicity CRFs indicated pre-specified AEs by grade (range 0 to 4, including lab ranges) based on the NCI-CTC scale version 2.0 modified for pediatric oncology patients [STI571AIT07- Appendix 16.1.2].

Source: [STI571AIT07 Table 12-4], [STI571AIT07-Table 14.3-1.2]

Serious adverse event / deaths / other significant events

Deaths

Study STI571I2301

Four deaths occurred on therapy or within 30 days of the last day of treatment. Of these, two patients received chemotherapy + imatinib. For both patients, Grade 5 AEs were reported and infection was the major cause of death, as determined by the investigator. Both infection events were reported as suspected to be related to study medication by investigator. However, neither of these deaths was reported as suspected to be related to study medication (neither imatinib nor chemotherapy).

The other 2 patient deaths on therapy were in the Ph- control group and did not receive imatinib.

Table 30: Deaths (Safety set – STI571I2301)

	Cohort 1+2 N=19 n (%)	Cohort 3+4 N=23 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	All Ph- N=65 n (%)
Deaths	9 (47.4)	5 (21.7)	8 (16.0)	22 (23.9)	29 (44.6)
Deaths on therapy (within 30 days of the last dose of treatment)	0	1 (4.3)	1 (2.0)	2 (2.2)	2 (3.1)

Source: [STI571I2301-Appendix 16.5- Table 14.3-1.6]

As expected for the nature of the underlying disease, the most common primary cause of death was malignant disease progression, followed by infection and multi-organ failure. The proportion of patients who died due to malignant disease progression was 3 times higher in Ph- patients (27.7%) receiving chemotherapy alone compared to Ph+ ALL patients (8.7%) receiving chemotherapy + imatinib (Table 31).

Table 31: Primary cause of death (Safety set – STI571I2301)

	Cohort 1-4 N=42 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	All Ph- N=65 n (%)
Deaths	14 (33.4)	8 (16.0)	22 (23.9)	29 (44.6)
Primary cause of death				
Disease related (progressive/persistent disease)	7 (16.7)	1 (2.0)	8 (8.7)	18 (27.7)
Infection	4 (9.5)	3 (6.0)	7 (7.6)	3 (4.6)
Multi-Organ Failure	0	4 (8.0)	4 (4.3)	4 (6.2)
Hemorrhage	1 (2.4)	0	1 (1.1)	1 (1.5)
Other reason	1 (2.4)	0	1 (1.1)	1 (1.5)
Unknown	1 (2.4)	0	1 (1.1)	1 (1.5)
ARDS	0	0	0	1 (1.5)

Note: This table includes all deaths in this study

Source: [STI571I2301 Appendix 16.5-Table 14.3-1.7]

Overall 34 patients received HSCT during the study; of these patients, 10 (29.4%) had died at the time of the analysis

Study STI571AIT07

Deaths and causes of death are summarised by Risk group and treatment in Table 30.

Table 32: Deaths and cause of death by Risk and treatment group (Safety Set – STI571AIT07)

	Good risk		Poor risk	All Patients
	No imatinib	Plus imatinib	Plus imatinib	Plus imatinib
	N=31	N=58	N=70	N=128
	n (%)	n (%)	n (%)	n (%)
Deaths	**8 (25.8)**	**9 (15.5)**	**24 (34.3)**	**33 (25.8)**
Deaths after HSCT				
Yes	7 (87.5)	7 (77.8)	19 (79.2)	26 (78.8)
Reason for Death				
Progressive ALL	4 (50)	5 (55.6)	12 (50)	17 (51.5)
HSCT	1 (12.5)	1 (11.1)	2 (8.3)	3 (9.1)
Sepsis	0	1 (11.1)	3 (12.5)	4 (12.1)
Pneumonia	0	1 (11.1)	1 (4.2)	2 (6.1)
Other infection	0	0	3 (12.5)	3 (9.1)
Other	3 (37.5)	1 (11.1)	3 (12.5)	4 (12.1)
Not known	0	0	0	0
Death occurred				
During 1st CR	3 (37.5)	3 (33.3)	8 (33.3)	11 (33.3)
In subsequent CR	0	1 (11.1)	3 (12.5)	4 (12.1)
During progression of ALL	4 (50)	5 (55.6)	12 (50)	17 (51.5)
Other	1 (12.5)	0	1 (4.2)	1 (3)

Source : [STI571AIT07-Table 14.3-1.1]

Serious adverse events

Study STI571I2301

Table 33 describes AEs that were reported in the AdEERS database.

Table 33: AdEERS by cohort (Safety Set – STI571I2301)

	Cohort 1+2	Cohort 3+4	Cohort 5	All Ph+
	N=19	N=23	N=50	N=92
	n (%)	n (%)	n (%)	n (%)
AEs reported in AdEERS system	6 (31.6)	7 (30.4)	23 (46.0)	36 (39.1)

[STI571I2301-Listing 14.3.2-1.2] lists AdEERs including relationship to imatinib for Ph+ ALL patients by cohort.
Source: [STI571I2301-Table 14.3.1-8.1]

The number of patients with AEs reported in the AdEERS database by SOC is described in Table 34.

Table 34: **AdEERS by system organ class in cohort 5 excluding HSCT vs. all cohorts per protocol HSCT (Safety Set – STI571I2301)**

	Cohort 5 excluding HSCT N=30 n (%)	All cohorts per protocol HSCT * N=21 n (%)
Number of patients with AdEERS	15 (50.0)	7 (33.3)
Investigations	8 (26.7)	2 (9.5)
Gastrointestinal disorders	4 (13.3)	1 (4.8)
Infections and infestations	4 (13.3)	0
Vascular disorders	4 (13.3)	1 (4.8)
Metabolism and nutrition disorders	3 (10.0)	1 (4.8)
Nervous system disorders	3 (10.0)	0
Cardiac disorders	1 (3.3)	1 (4.8)
Musculoskeletal and connective tissue disorders	1 (3.3)	1 (4.8)
Psychiatric disorders	1 (3.3)	0
Respiratory, thoracic and mediastinal disorders	1 (3.3)	2 (9.5)
Skin and subcutaneous tissue disorders	1 (3.3)	1 (4.8)
Renal and urinary disorders	0	2 (9.5)

* Patients meeting specific criteria were eligible for HSCT on study after Consolidation block 2. At any time during the protocol therapy, patients had an option to be removed from protocol treatment to obtain off protocol HSCT (that did not meet per protocol HSCT criteria). At 16 to 24 weeks after per protocol HSCT, treatment with imatinib was resumed initially at a lower dose of 230 mg/m^2/day and increased to 340 mg/m^2/day, when no toxicities (≥ grade 3) were observed after 4 weeks of post-HSCT imatinib, for a total duration of 6 months.

Per protocol HSCT patients received imatinib + chemotherapy +/- radiation prior to transplantation and imatinib + graft versus host disease (GVHD) prophylaxis post HSCT.

AdEERs reported for patients receiving HSCT are included up to and also after the date of HSCT.

Source: [STI571I2301-Table 14.3.1-5.3], [STI571I2301-Appendix 16.1.1]

SAEs in Study STI571AIT07

Table 35 describes serious adverse events reported in study STI571AIT07.

Table 35: Serious adverse events regardless of study drug relationship by system organ class and preferred term (Safety set –STI571AIT07)

	Good risk		Poor risk	All Patients
	No imatinib	Plus imatinib	Plus imatinib	Plus imatinib
Primary system organ class	**N=31**	**N=58**	**N=70**	**N=128**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary SOC	10 (32.3)	16 (27.6)	24 (34.3)	50 (39.1)[c]
Infections and Infestations	5 (16.1)	7 (12.1)	14 (20.0)	21 (16.4)
Fungal Infection	1 (3.2)	1 (1.7)	4 (5.7)	5 (3.9)
Localised Infection	2 (6.4)	1 (1.7)	2 (2.9)	3 (2.3)
Infection	3 (9.7)	5 (8.6)	9 (12.9)	14 (10.9)
Other	3 (9.7)	7 (12.1)	8 (11.4)	15 (11.7)
Other [a]	3 (9.7)	7 (12.1)	8 (11.4)	15 (11.7)
Nervous System Disorders	1 (3.2)	1 (1.7)	3 (4.3)	4 (3.1)
Convulsion	1 (3.2)	1 (1.7)	1 (1.4)	2 (1.6)
Paraesthesia	0	0	1 (1.4)	1 (0.8)
Cerebral Haemorrhage	0	0	1 (1.4)	1 (0.8)
Cardiac Disorders	0	0	2 (2.9)	2 (1.6)
Cardiac Failure	0	0	2 (2.9)	2 (1.6)
Hepatobiliary Disorders	1 (3.2)	1 (1.7)	1 (1.4)	2 (1.6)
Hepatic Failure	1 (3.2)	1 (1.7)	1 (1.4)	2 (1.6)
Gastrointestinal Disorders	1 (3.2)	1 (1.7)	0	1 (0.8)
Pancreatitis	0	1 (1.7)	0	1 (0.8)
Gastrointestinal Haemorrhage	1 (3.2)	0	0	0
Psychiatric Disorders	0	1 (1.7)	0	1 (0.8)
Psychotic Disorders	0	1 (1.7)	0	1 (0.8)
Immune System Disorders	1 (3.2)	1 (1.7)	0	1 (0.8)
Anaphylactic Shock	1 (3.2)	1 (1.7)	0	1 (0.8)
Musculoskeletal and Connective Tissue Disorders	1 (3.2)	1 (1.7)	0	1 (0.8)
Osteonecrosis	1 (3.2)	1 (1.7)	0	1 (0.8)
Renal and Urinary Disorders	1 (3.2)	1 (1.7)	0	1 (0.8)
Renal Impairment	1 (3.2)	1 (1.7)	0	1 (0.8)

[a] 18 patients had 'other' SAEs per investigator; including 9 cases of allergic reaction to asparaginase.
The table includes all treatment phases and HSCT.
Source: [STI571AIT07-Table 14.3-1.20], [STI571AIT07-Table 12-10]

Laboratory findings

In both studies, laboratory reference values were not entered during the study in the CRF on a continuous scale and no normal ranges were available from these studies.

In addition, ANC and platelet decrease below a minimum threshold level (<750/µL for ANC counts and <75000/µL for platelet counts) were marked in the CRF and the date of recovery was noted.

Other laboratory evaluations such as ALT, AST, bilirubin increased, PTT prolonged, haemorrhage, PT prolonged, were captured as pre-specified targeted toxicities.

Laboratory data were not available from the Ph- ALL population.

In study [STI571AIT07], laboratory abnormalities for pre-specified assessments were collected on the CRF toxicity form according to investigator assignment using NCI-CTC grade (version 2, adopted for the use of paediatric oncology patients). Information was collected on the following laboratory parameters: haematological, renal, and pancreatic/liver and coagulation toxicities.

Haematology Results-Study STI571I2301

As expected for the treatment regimen, most Ph+ ALL patients had a drop in ANC <750/µL at some time, regardless of imatinib administration. The percentages of patients with a decrease in ANC <750/µL in Consolidation 1 were 85.7% (cohort 1), 58.3% (cohort 2), 54.5% (cohort 3), 72.7% (cohort 4) and 82.0% (cohort 5). Most patients recovered from this degree of neutropenia with the exception of one patient in cohort 1 and one patient in cohort 5. The median time to recovery (ANC ≥ 750/µL) in Consolidation 1 ranged from 5 to 8 days for all cohorts. Across all treatment blocks, the time to recovery was similar in cohort 5 compared to all cohorts combined, ranging from 3 days to 35

days. In general, during earlier treatment courses recovery occurred within 7 days and in later courses, in particular during Maintenance courses, the time to recovery to ≥ 750/µL was 8 to 14 days or longer.

There is no apparent difference in the incidence of ANC <750/µL nor in the time to recovery related to the incorporation of imatinib into each treatment course.

The number of patients with platelets <75000/µL at anytime varied in all cohorts by treatment lock, being highest in Consolidation 2 and Intensifications 1 and 2 and lowest in Maintenance 5 to 12. The overall median time to recovery ranged from 5.5 to 17 days, and was similar in cohort 5 (5.5 days to 20.5 days).

In general, there was no difference between treatment blocks, with the exception of a longer time to recovery to >75000/µL in Reinduction 2 for patients treated with imatinib and a longer time to recovery for patients not treated with imatinib in Intensification 2.

Haematology Results–Study STI571AIT07

With respect to haematology, decreased white blood count, haemoglobin and platelet count was observed in over 90% of the patients in both groups without and with imatinib. There were no significant differences observed across the treatment groups

Safety in special populations

Study STI571I2301 included 15 patients aged <4 years including 3 patients aged 1 to 2 years old. To better assess the safety profile in the younger paediatric population, a safety analysis of <4 vs. ≥ 4 years old was considered appropriate.

Deaths, AdEERs, and other significant AEs are summarised by age group in Table 34.

Table 36: Deaths, AdEERs and other significant AEs by age group (Safety set – STI571I2301)

	<4 years all cohorts N=15		≥ 4 years all cohorts N=77	
	Cohort 1-4 N=4 n (%)	Cohort 5 N=11 n (%)	Cohort 1-4 N=38 n (%)	Cohort 5 N=39 n (%)
Deaths	3 (75.0)	0	11 (28.9)	8 (20.5)
Deaths during therapy [1]	1 (25.0)	0	0	1 (2.6)
Patients with grade 3 or 4 AEs	4 (100)	9 (81.8)	33 (86.8)	38 (97.4)
Patients with AEs reported as AdEERS	1 (25.0)	3 (27.3)	12 (31.6)	20 (51.3)
Patients who discontinued due to toxicity [2]	0	0	2 (5.3)	2 (5.1)

[1] During therapy includes the period 30 days following last dose (last course end date).

[2] Based on the primary reason for discontinuation from study treatment.

Source: [STI571I2301-Listing 14.3.2-1.4], [STI571I2301-Listing 14.3.2-1.1], [STI571I2301-Listing 14.3.2-1.2], [STI571I2301-Listing 14.1-1.1]

The most frequent AEs in all age groups were related to investigations (laboratory abnormalities). Patients who had HSCT also reported frequently with surgical and medical procedures regardless of the age and with infections and infestations (age <12 years) and gastrointestinal disorders (age 12 to <18 years).

The number of patients ≥ 18 years of age was too low to present meaningful results. In patients < 12 years of age in cohort 5, the most frequent AEs were haematological (decreased neutrophil count, decreased platelet count, decreased haemoglobin, WBC decreased, packed red blood cell (RBC) transfusion) or related to investigations (ALT increased, hypokalaemia) and infections (neutropenic infection, febrile neutropenia).

No clinically relevant differences were observed concerning the frequencies of AEs in different age groups; however, the number of patients included in the respective age groups was relatively low. The AEs reported were consistent with the known safety profile of imatinib.

In Study STI571AIT07 the incidence of AEs was similar in the <4 years and ≥ 4 years age groups.

Safety related to drug-drug interactions and other interactions

No new information has been generated in support of this indication. Results of drug-drug interaction studies have been detailed in prior applications and are described in the approved prescribing information.

Discontinuation due to adverse events

Study STI571I2301

Overall the percentage of discontinuations due to AEs was low when imatinib was added to the chemotherapy regimen. Four patients (4.3%) in the Ph+ group (two patients in cohorts 3 plus 4 and 2 patients in cohort 5) and one patient in the Ph- group were discontinued prematurely from the study due to toxicity.

- One patient in cohort 3 discontinued study treatment due to pancreatitis (causality assessed as due to PEG L-Asparaginase).

- One patients in cohort 4 discontinued study treatment due to hepatic toxicity (ALT increased, AST increased) following per protocol HSCT. At the time of the grade 3 transaminase elevation this patient was receiving the study medication (imatinib) during the HSCT followup phase. Imatinib was permanently discontinued due to hepatic toxicity approximately 2 weeks after having restarted following HSCT therapy. The patient was taken off all protocol therapy approximately 3 months after imatinib was permanently discontinued. The investigator suspected a possible relationship between the event (alanine aminotransferase increased) and the study medication (imatinib). The investigator suspected an unlikely relationship between the events (liver disorder, gamma glutamyltransferase increased, aspartate aminotransferase increased, and dyspnea) and the study medication (imatinib).

- One patient in cohort 5, who had previously experienced severe conjunctivitis due to cytarabine, discontinued the study treatment due to palmar plantar erythrodysesthesia, a skin disorder consisting of blisters on the right shin and left foot that occurred after HSCT.

- One patient in cohort 5 experienced life threatening constitutional symptoms (general symptom) and was noted with (cerebral) ventriculomegaly and transependymal edema on MRI suggesting hydrocephalus and was assessed as unlikely due to imatinib by the investigator.

Table 37: Overall Patient Disposition (Safety Set – STI571I2301)

	Cohort 1+2 N=19 n (%)	Cohort 3+4 N=23 n (%)	Cohort 5 N=50 n (%)	All Ph+ N=92 n (%)	All Ph- N=65 n (%)
Number enrolled	19 (100)	23 (100)	50 (100)	92 (100)	65 (100)
from frontline studies	3 (15.8)	16 (69.6)	38 (76.0)	57 (62.0)	49 (75.4)
from a similar induction therapy	16 (84.2)	7 (30.4)	12 (24.0)	35 (38.0)	16 (24.6)
Induction failures	3 (15.8)	1 (4.3)	6 (12.0)	10 (10.9)	22 (33.8)
Non-induction failures	16 (84.2)	22 (95.7)	44 (88.0)	82 (89.1)	43 (66.2)
HSCT	5 (26.3)	9 (39.1)	20 (40.0)	34 (37.0)	23 (35.4)
Non-HSCT	14 (73.7)	14 (60.9)	30 (60.0)	58 (63.0)	42 (64.6)
Completed protocol treatment *	8 (42.1)	10 (43.5)	27 (54.0)	45 (48.9)	32 (49.2)
Discontinued protocol treatment	11 (57.9)	13 (56.5)	23 (46.0)	47 (51.1)	33 (50.8)
No follow-up	0	2 (8.7)	3 (6.0)	5 (5.4)	1 (1.5)
Follow-up ongoing	6 (31.6)	13 (56.5)	38 (76.0)	57 (62.0)	34 (52.3)
Follow-up discontinued	13 (68.4)	8 (34.8)	9 (18.0)	30 (32.6)	30 (46.2)
Reasons for follow-up discontinuation **					
Death	7 (36.8)	4 (17.4)	6 (12.0)	17 (18.5)	27 (41.5)
Entry on to another study	3 (15.8)	2 (8.7)	0	5 (5.4)	2 (3.1)
Lost to follow-up	2 (10.5)	1 (4.3)	2 (4.0)	5 (5.4)	1 (1.5)
Withdrawal of consent	1 (5.3)	1 (4.3)	1 (2.0)	3 (3.3)	0

* Completed protocol treatment means completion of therapy up to Maintenance 12.

** Percentages are calculated from the total N per column (cohort).

Source: [STI571I2301-Appendix 16.5-Table 14.1-1.1]

Study STI571AIT07

Of the 128 patients treated with imatinib, only one patient discontinued the study due to toxicity. Toxicity was assessed by the investigator as probably related to asparaginase, and not causally related to imatinib.

Table 38: Patient disposition and primary reasons for discontinuation (FAS – STI571AIT07)

	Good risk		Poor risk	All patients
	No imatinib N=44 n (%)[b]	Plus imatinib N=46 n (%)[b]	Plus imatinib N=70 n (%)	Plus imatinib N=116 n (%)
Completed study treatment	29 (32.2)	34 (37.8)	39 (55.7)	73 (62.9)
Discontinued study treatment	15 (16.7)	12 (13.3)	31 (44.3)	43 (37.1)
Reasons for discontinuation				
Toxicity [a]	0	1	0	1
Relapse at any site	11	9	23	32
Death in CCR	4	2	8	10

[a] Patient=0900040165; biopsy indicated a drug reaction probably secondary to asparaginase and not related to imatinib

[b] Percentage is based on total number of patients in the Good risk group (N=90).

No patients were lost to follow-up.

Source: [STI571AIT07-Table 14.1-1.2], [STI571AIT07-Section 14.3.3.]

Post marketing experience

A worldwide literature search was performed to capture any investigator reports on safety aspects which are not included in the study reports (Ovid date of search: 1948 to Nov 2011; Embase date of search: 1996 to 22 Dec 2011). The results of this literature search did not provide any evidence of unexpected or unknown events that would be attributable to treatment with imatinib, thus supporting the established safety and tolerability profile of imatinib.

The post-marketing safety of imatinib is monitored on an ongoing basis. In the post-marketing setting, with approximately 776114 patient-years of post-marketing exposure, no safety concerns have emerged that were not previously known for imatinib with the submission of these paediatric Ph+ ALL

studies. The safety profile of imatinib remains consistent with the information provided in the Core Data Sheet.

2.5.2. Discussion on clinical safety

The safety database comprised 93 Ph+ subjects from the pivotal study STI571I2301 and 159 Ph+ patients (128 imatinib) from the supportive study STI571AIT07. Of them, 58 children from the main trial (subset excluding HSCT patients) were treated with high intensive chemotherapy + imatinib, being 30 patients the target population since this is the subjects in the cohort 5.

The exposure to imatinib in the cohort 5 has been more than 2 years, though the optimal duration with imatinib treatment is unclear.

The percentage of patients with AEs was higher in the group treated with imatinib than in the chemotherapy as only treatment. This seems logical and expectable. As relevant AEs in a higher percent observed in the cohort 5, neutrophil and platelet count, haemoglobin, neutropenic infection, pharyngitis, vomiting, nausea, diarrhoea, abdominal pain, electrolytes, hypertension and hypoxia, are the more notorious, whereas myelosuppression and hepatotoxicity were the most remarkable safety concerns in the subgroup of targeted toxicities. On the whole, the safety profile of the combination of high intensive chemotherapy + imatinib, does not seem to add any safety concern on the widely known safety profile of imatinib.

Regarding the deaths and SAEs, more patients died in the Ph- group (group treated with chemotherapy only) than in the imatinib arm (24% vs 44.5%, respectively), which is reassuring. This result has been supported by the STI571AIT07 study, in where the highest percentage of deaths was found in the no imatinib arm. Nevertheless, speaking about SAEs, the cohort 5 has 50 % of SAEs (excluding the subset of patients with BMT), which is by far, the highest percent of SAEs among cohorts. A direct comparison with Ph- subset is lacking.

In the laboratory findings the results highlight the AEs described above: neutropenia, platelet changes and liver enzymes.

Finally, the discontinuation and the post marketing experience do not lead to any safety concerns.

2.5.3. Conclusions on clinical safety

Overall, the sample size of the safety database is limited and data on the long-term use of imatinib in this new population are lacking. The safety findings from these two studies are pointing out that adding imatinib increases the toxicity of the backbone chemotherapy; there were more AEs and SAEs though less deaths.

No new safety concerns for imatinib have been identified.

In order to address the limitations related to the limited size of the safety database, the CHMP considers the following measure necessary:

To conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ Acute Lymphoblastic Leukaemia (ALL) patients treated with chemotherapy + imatinib ± HSCT.

Due date for submission of final results: 31/12/2020

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan version number “5 updated with paediatric Ph+ ALL clinical study data” within this variation procedure.

The EU-summary of the RMP version 7 with paediatric Ph+ ALL is as follows:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Important identified risks		
Myelosuppression	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: **SPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.3 Preclinical safety data
Edema and Fluid Retention	Routine pharmacovigilance activities	This item is adequately communicated through current labeling: **SPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.
CNS and GI Hemorrhages	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: **SPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.
Gastrointestinal Obstruction, Perforation or Ulceration	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: **SPC Section:** 4.8 Undesirable effects.
Hepatotoxicity	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: **SPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties 5.3 Preclinical safety data.
Skin Rashes and Severe Cutaneous Reactions	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Hypothyroidism	Routine pharmaco-vigilance activities	This item is appropriately communicated through current labeling: SPC section 4.4 Special Warning and Precautions for Use
Hypophosphatemia	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Cardiac Failure	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activity**	This item is appropriately communicated through current labeling: **SPC Sections:** 4.4 Special warnings and precautions for use 4.8 Undesirable effects.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	Subclinical LVD monitored by 2-D echocardiography in the nilotinib registration study with imatinib as an active comparator (Study AMN107A2303). 12-month and 24-month CSRs have been completed.	
Acute Renal Failure	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: **SPC Sections:** 4.2 Posology and method of administration, Renal insufficiency 4.4 Special warnings and precautions for use 4.8 Undesirable effects. 5.2 Pharmacokinetic properties, Organ function impairment
Severe Respiratory Adverse Reactions	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Rhabdomyolysis and Myopathy	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Ovarian Hemorrhage and Hemorrhagic Ovarian Cyst	Routine pharmacovigilance activities	This item is appropriately communicated through current labeling: Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Tumour lysis syndrome	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Growth retardation in children	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activity** To obtain long term follow data to assess the effects of treatment, on growth, sexual characteristic acquisition and fertility for paediatric patients exposed to TKI inhibitors in the Novartis supported CML registry study CSTI571A2405.	This item is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects.
Important potential risks		

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Second Malignancies in Survivors	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activities** Extended data collection up to 11 years in designated registration study (STI571A0106). Regular annual review of age-adjusted standardised incidence ratios from registration studies.	This item is appropriately communicated through current labeling: SPC Section 5.3 Preclinical safety data
Disseminated Intravascular Coagulation	Routine pharmacovigilance activities	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.
Hypoglycemia	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.
Suicidality	Routine pharmacovigilance activities	No risk minimisation activities are proposed. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.
Tolerability during Pregnancy and Pregnancy Outcomes	Routine pharmacovigilance activities including cumulative analysis in PSUR. **Additional activity** Pregnancy registry for imatinib and nilotinib (CSTI571A2403).	This item is appropriately communicated through current labeling: **SPC Sections:** 4.6 Pregnancy and lactation and 5.3 Preclinical safety data.
Important identified interactions		
Strong CYP3A4 Inhibitors	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Strong CYP3A4 Inducers	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Drugs eliminated by	Routine pharmacovigilance	This item is appropriately communicated through current

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
CYP3A4	activities including cumulative analysis in PSUR.	labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Important potential interactions		
Drugs Eliminated by CYP2C9, CYP2C19 and CYP2D6	Routine pharmacovigilance activities including cumulative analysis in PSUR.	This item is appropriately communicated through current labeling: SPC Section 4.5 Interaction with other medicinal products and other forms of interaction.
Acetaminophen/ paracetamol	Routine pharmacovigilance activities including cumulative analysis in PSUR.	No risk minimisation activities are proposed. This item was removed from the CDS labeling 24-Sep-2010. There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities uncover additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.
Important missing information		
Paediatric patients: Long term follow up	Routine pharmacovigilance activities **Additional activities** To obtain long-term follow-up data to assess the effects of treatment, on growth, sexual characteristic acquisition, fertility, hematologic and biochemical laboratory changes and second malignancies as well as pharmacokinetic data in the paediatric population. These measures will be assessed in the CSTI571A2405 study (a registry FUM in CML patients). Proposed previous action related to paediatric patient pharmacokinetic data that has been updated based on PDCO discussion and PIP modification was agreed to provide in addition to physiology-based pharmacokinetic model submitted with this Ph+ ALL paediatric submission. An additional update of the PK modeling that is provided with this Ph+ ALL	Growth retardation in children is appropriately communicated through current labeling: SPC Section 4.4 Special warnings and precautions for use Relevant preferred terms are reported as AEs in SPC Section 4.8 Undesirable effects. Second malignancy is appropriately communicated through current labeling: SPC Section 5.3 Preclinical safety data There is a lack of conclusive data indicating causal relationship at this time. Should the PV activities identify additional data, the risk will be communicated through the labeling and additional risk minimisation activities may be proposed if necessary.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
	paediatric submission will follow for patients as young as six months of age, if and when such additional information is obtained from a study to be planned in paediatric PAH patients.	
Paediatric patients below 2 years of age	Routine pharmacovigilance activities.	This item is appropriately communicated through current labeling: SPC Sections 4.2 Posology and method of administration. Children
Renal impairment	Routine pharmacovigilance activities.	This item is appropriately communicated through current labeling: **SPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties.
Hepatic impairment	Routine pharmacovigilance activities.	This item is appropriately communicated through current labeling: **SPC Sections:** 4.2 Posology and method of administration 4.4 Special warnings and precautions for use 4.8 Undesirable effects 5.1 Pharmacodynamic properties 5.2 Pharmacokinetic properties.
Elderly patients	Routine pharmacovigilance activities.	This item is appropriately communicated through current labeling: SPC Section 4.2 Posology and method of administration.

2.7. Update of the Product information

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

In addition, sections 5.3 and 6.6 of the SmPC have been updated in order to include information with regard to the environmental risk.

Changes were also made to the PI to bring it in line with the current QRD template, which were reviewed and accepted by the CHMP. Furthermore, minor editorial changes have been introduced.

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

2.8. Significance of paediatric studies

The CHMP is of the opinion that studies 1 (COG AALL0031) and 2 (EsPhALL), which are contained in the agreed Paediatric Investigation Plan, which is completed, and have been initiated before 26 January 2007 and completed after 26 January 2007, are considered as significant. Study 1 was a well-founded dose-finding cohort study that is significant because it is considered as the pivotal efficacy study for the paediatric use assessed in this procedure. Study 2 was initially conducted as a comparative efficacy study, continuing as a prospective safety study, and the study is significant because it informs the safe use of the medicinal product in the paediatric population, in conjunction with multi-agent chemotherapy.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Four-year EFS in cohort 5 was 69.6%, more than twice that of historical controls with 31.6% (HR=0.28 CI 95% 0.16-0.49). The beneficial effects of imatinib were also reflected in the OS results (estimated OS rate at 48 months was 83.6% in cohort 5 compared to 44.8% in the historical control group; HR=0.23).
Analyses comparing EFS and OS for cohort 1+2 vs cohort 5 showed better results for cohort 5 for both endpoints (p=0.0101 and p=0.0091, respectively). For the comparison of cohort 3+4 vs cohort 5, there was a trend in favour of cohort 5 with longer EFS and OS in the continuous dose cohort. An update after 5 years shows a clear benefit for imatinib.

Uncertainty in the knowledge about the beneficial effects

HSCT is still recommended in the eradication of Ph+ ALL and patients in Complete Remission are firm candidates, if possible, to receive a HSCT. There is uncertainty in Ph+ ALL paediatric patients whether the addition of imatinib to a standard regimen has any effect on the efficacy and/or safety of subsequent HSCT. In order to address this uncertainty, the MAH will conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ ALL patients treated with chemotherapy + imatinib ± HSCT.

Risks

Unfavourable effects

The percentage of patients with AEs was higher in the group treated with imatinib than in the chemotherapy as only treatment. This seems logical and expectable. As relevant AEs in a higher percent observed in the cohort 5, neutrophil and platelet count, haemoglobin, neutropenic infection, pharyngitis, vomiting, nausea, diarrhoea, abdominal pain, electrolytes, hypertension and hypoxia, are the more relevant, whereas myelosuppression and hepatotoxicity were the most remarkable safety concerns in the subgroup of targeted toxicities.
Regarding the deaths and SAEs, more patients died in the Ph- group (group treated with chemotherapy only) than in the imatinib arm (24% vs 44.5%, respectively), which is reassuring. This result has been supported by the STI571AIT07 study, in where the highest percentage of deaths was found in the no imatinib arm. Nevertheless, speaking about SAEs, the cohort 5 has 50 % of SAEs

(excluding the subset of patients with BMT), which is by far, the highest percent of SAEs among cohorts.
In the laboratory findings the results highlight the AEs above described, neutropenia, platelet changes and liver enzymes.
Finally, the discontinuation and the post marketing experience do not lead to any safety concerns.

Uncertainty in the knowledge about the unfavourable effects

The safety profile in children seems to be comparable to adults, though the limited sample size preclude drawing firm conclusions. In spite of this uncertainty, the profile of AEs and their frequency are reassuringly similar to adults, without any new safety concern.

The high percentage of SAEs in cohort 5, which is the main set of data supporting this application, raises concerns in relation to the addition of Glivec to chemotherapy regimen. However, the benefit for the patients in terms of EFS and OS clearly outweighs the risks.

Finally, the long term exposure to Glivec might be partially covered by data from others paediatric indications.

In order to address the limitations related to the limited size of the safety database, the MAH will conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ ALL patients treated with chemotherapy + imatinib ± HSCT.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The outcomes in terms of EFS and OS from the COG study are pointing out a promising result in this high risk population. These results appear to be difficult to obtain with the currently used chemotherapy regimen. Certainly, the relevance of the results is high and as a consequence, several guidelines around the world already include the use of Glivec in the treatment of Ph+ ALL paediatric patients.

The safety findings from the two studies supporting this application point out an increased toxicity of the backbone chemotherapy.

Benefit-risk balance

The introduction of imatinib in combination with high intensive backbone chemotherapy gives clinically meaningful results in terms of EFS and OS at 48 months. These results appear to be independent of HSCT role in the study, since the outcome in the population excluding HSCT patients were pretty similar to the whole population (HSCT vs Chemo+Glivec alone). The benefits showed by Glivec in the treatment of Ph+ ALL in children, outweigh the toxicity associated with chemotherapy+imatinib.

Discussion on the Benefit-Risk Balance

In summary, relevant results have been shown when adding imatinib to standard chemotherapy regimen in the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL). From a safety point of view there are no major concerns given that imatinib is a well-known medicinal product, also used in children in other indications.

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4. Recommendations

Final Outcome

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

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

Extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ALL) integrated with chemotherapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC.

The Package Leaflet was updated in accordance.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.

The requested variation proposed amendments to the SmPC, Annex II, and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk management plan (RMP)**

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

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
To conduct an observational registry collecting efficacy and safety data in newly diagnosed paediatric Ph+ Acute Lymphoblastic Leukaemia (ALL) patients treated with chemotherapy + imatinib ± HSCT. Submission of final study report.	31/12/2020

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0028/2012 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0028/2012 have been completed after the entry into force of that Regulation.