Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for imatinib mesylate

Proprietary Product Name: Glivec

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

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TGA Health Safety Regulation

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities. Text in this extract has been amended from the original text to correct errors contained in the original CER.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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List of abbreviations

Abbreviation	Meaning
ALL	Acute lymphoblastic leukaemia
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATP	Adult treatment panel
AUC	Area under the concentration-time curve
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
CHD	Coronary Heart Disease
CI	Confidence interval
CK	Creatine phosphokinase
Cmax	Maximum concentration
CML	Chronic myelogenous leukaemia
CNS	Central nervous system
COG	Central oncology group
CRF	Case Report Form
CSR	Clinical study report
CV	Coefficient of variation
DDI	Drug drug interaction
DFS	Disease free survival

Abbreviation	Meaning
EFS	Event free survival
FDC	Fixed dose combination
FMI	Final marketing image
GMR	Geometric mean ratio
HR	Heart rate
HSCT	Haemopoetic stem cell transplant
IV	Intravenous
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein cholesterol
LS mean	Least-squares mean
NDA	New drug application
PBPK	Physiological based pharmacokinetics
PD	Pharmacodynamic(s)
Ph	Philadelphia
PK	Pharmacokinetic(s)
PopPK	Populations pharmacokinetics
QD	once daily
RBC	Red blood (cell) count
SD	Standard deviation
SEM	Standard error of the mean
SOC	System Organ Class
SPC	Summary of product characteristics
SS	Steady state
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol.

1. Introduction

This is a submission to amend the currently approved indication for Philadelphia chromosome positive acute lymphoblastic leukaemia (PH+ALL) to *"Imatinib, integrated with chemotherapy, is indicated for the treatment of newly diagnosed paediatric patients with Philadelphia chromosome positive acute lymphoblastic leukaemia"*.

Imatinib is a small molecule protein tyrosine kinase inhibitor. It inhibits the activity of several tyrosine kinases i.e.: c-Kit, the receptor for stem cell factor coded by the c-Kit proto-oncogene, the platelet derived growth factor receptors alpha and beta (PDGFR alpha and PDGFR beta), the ABL family of non-receptor tyrosine kinases consisting of ABL1 and ABL2, the discoidin domain receptors DDR1 and DDR2 which are receptors for collagen, and c-Fms the receptor for macrophage stimulating factor.

Imatinib was first registered on 13 August 2001 and has been approved in Australia for the treatment of a number of solid tumour and haematological conditions where tyrosine kinases play a role in the disease. This includes acute lymphoblastic leukaemia (ALL) the most common disease in the paediatric population. Imatinib was approved for the treatment of adult patients with Philadelphia positive ALL on 10 May 2007.

The proposed additional indication is to include paediatric patients thereby the indication to read for treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy.

Imatinib is presently marketed as hard gelatine capsules containing 50mg or 100mg of imatinib and a film coated tablet containing 100mg or 400mg of imatinib.

Proposed dosage and administration: For the treatment of PH positive ALL in children should be based on body surface area (mg per meter squared (/m^2). A dose of 340mg/m^2 daily is recommended for children with Philadelphia positive ALL not to exceed a total dose of 600mg per day. Treatment can be given as a once daily dose.

Imatinib has been given orphan drug designation for Ph positive ALL from May 2006.

2. Clinical rationale

Imatinib is currently approved in over 110 countries for the treatment of both haematological or malignancies in solid tumours. Imatinib is already approved in a paediatric indication namely Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in blast crisis, accelerated phase or chronic phase after failure of Interferon – alpha therapy. The recommended dose is 340mg/m^2 daily. Imatinib is also currently approved in the European Union (EU) for the treatment of adult patients with newly diagnosed Philadelphia positive acute lymphoblastic leukaemia (ALL) integrated with chemotherapy at a recommend dose of 600mg per day. Imatinib is also approved in the EU and the US for the treatment of adult patients with relapsed or refractory Ph positive ALL.

Accordingly, the current pivotal study ST1571I2301 (to be known as 2301) is presented as a pivotal study supporting efficacy and safety in the treatment of newly diagnosed ALL very high risk paediatric patients. Also presented as a supportive study, study A1T07 was undertaken with newly diagnosed Philadelphia positive ALL patients who were both good and poor risk. However because of problems with randomisation and patient accrual the study has been determined as appropriate for assessment for safety only in the present submission.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Module 5 includes a pooled population PK analysis from four studies involving patients with Philadelphia positive CML, Philadelphia positive ALL and other haematological disorders as indicated in Table 1. Also provided is a physiologically based PK (PBPK) model involving paediatric patients from the ages of 1 to 18 years.

Table 1: Summary of clinical and PK studies and PBPK analyses included in the submission

Study No.	Objectives	Patient population	Total daily dose
Studies included in the previous submission in pediatric patients			
CSTI571A0103	Tolerability, efficacy, and PK	Ph+ CML or ALL	260, 340, 440, 570 mg/m^2
CSTI571A2108	Response rate, disease-free survival, safety and PK	Ph+ CML chronic phase	340 mg/m^2
Studies included in this submission in pediatric Ph+ALL patients			
CSTI571A0103	Tolerability, efficacy and PK	Ph+ CML or ALL	260, 340, 440, 570 mg/m^2
CSTI57103001	Safety, tolerability, and PK	Ph+CML or ALL	175 to 260 mg/m^2
CSTI571A2108	Response rate, disease-free survival, safety and PK	Ph+CML	340 mg/m^2
CSTI571A2110	PK and safety	Ph+ALL, Ph+CML	260 to 340 mg/m^2 daily dosing

The pivotal study for evaluation of efficacy and safety was study 2301 in newly diagnosed ALL very high risk patients. Also provided is a supportive study A1T07 which again was in newly diagnosed Philadelphia positive ALL patients of both good and poor risk. As will be discussed within this submission the data provided in relation to efficacy for the supportive study is extremely limited and therefore not considered to be satisfactory for evaluation. The safety data is considered pertinent.

Module 1 contains the relevant application letter and forms, draft Australian PI and European summary of product characteristics.

Module 2 also contains relevant clinical over views, summary of clinical pharmacology, clinical efficacy, clinical safety and literature references.

3.2. Paediatric data

All the data presented in this submission are in relation to paediatric patients. This includes all pharmacological analyses together with the data from the pivotal study 2301 and various supportive studies.

3.3. Good clinical practice

All aspects of good clinical practice have been observed in the pivotal study and supportive studies.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The clinical pharmacology of imatinib has previously been extensively described in the imatinib original application for newly diagnosed CML in adult and paediatric patients and patients with gastrointestinal stromal tumours. This evaluation provides an overview of the studies which support the clinical pharmacology summary of imatinib in the paediatric Philadelphia (Ph) positive ALL indication, as indicated in Table 2.

Table 2: Summary of clinical studies included in the previous submission and this submission

Study No.	Objectives	Patient population	Total daily dose
Studies included in the previous submission in pediatric patients			
CSTI571A0103	Tolerability, efficacy, and PK	Ph+ CML or ALL	260, 340, 440, 570 mg/m^2
CSTI571A2108	Response rate, disease-free survival, safety and PK	Ph+ CML chronic phase	340 mg/m^2
Studies included in this submission in pediatric Ph+ALL patients			
CSTI571A0103	Tolerability, efficacy and PK	Ph+ CML or ALL	260, 340, 440, 570 mg/m^2
CSTI57103001	Safety, tolerability, and PK	Ph+CML or ALL	175 to 260 mg/m^2
CSTI571A2108	Response rate, disease-free survival, safety and PK	Ph+CML	340 mg/m^2
CSTI571A2110	PK and safety	Ph+ALL, Ph+CML	260 to 340 mg/m^2 daily dosing

This paediatric PK data in the submission comprises two modelling study reports namely the pooled population pharmacokinetic modelling report update (IP PBPK) and the study report A2110. The pooled population pharmacokinetic analysis was conducted in paediatric patients aged 2 to 18 years with haematological disorders including CML, PH positive ALL or other indicated haematological disorders in four clinical studies A0103, 3001, 2108 and A2110. Since the 100 and 400mg tablet formulations were bioequivalent with the 100mg hard gelatine capsule there was no reason not to pool this PK data from the above studies.

The PBPK modelling report did not use any clinical data and was based on a physiological simulation. The PBPK model assessed the effect of the developmental pharmacology on systemic exposure to imatinib in paediatric patients. The objectives of the PBPK modelling report were:

- to predict paediatric PK using the PBPK approach based on the imatinib clearance in adult population then compare the results to the experimentally observed values
- to predict Imatinib plasma concentration – time profiles in plasma and tissue in paediatric subjects and to assess the effect of paediatric growth process using the PBPK model developed and
- to evaluate factors influencing the Imatinib exposure in paediatric patients with particular attention to children in the age range of 1 to 2 years.

4.2. Pooled population pharmacokinetic modelling report:

A population PK analysis was undertaken from four clinical studies A2110, A2108, 3001 and 0103. The study designs for these four trials are given in Table 3. Objectives of the analysis were to:

- characterise the pharmacokinetic profile of imatinib in paediatric patients

- confirm pharmacokinetics in children from 2 years of age on and
- establish adequate dosing schedule schemes for paediatric patients by model – based simulation using the final Pop PK model.

Table 3: Study designs and pharmacokinetic sampling times for studies contributing to the PopPK analysis (N=67)

Study identifier	Type of study	Study population	Dosage regimen	Primary endpoint(s)	Nominal PK sampling schedule	Sample size
CSTI571A0103	Dose escalation study, 2 courses of 28 days each	Ph+ CML or ALL, age 2 to 22 years	Four dose cohorts: 260, 340, 440, 570 mg/m^2 Orally once daily (BID if dose ≥ 800mg/day)	MTD, DLT, pharmacokinetics in children	During course 1: day 1: 0 (predose), 0.5, 1, 1.5, 2, 4, 8, 24h (for BID dosing 1,2,3,4,10,12,13,16,24h) day 8: as day 1, including a 48h sample (patient must not take drug on day 9)	25
CSTI57103001	Phase I, non-randomized open label	Ph+ CML or Ph+ ALL pediatric patients, age 2 to 18 years	Orally once daily: 175 mg/m^2 to 260 mg/m^2	Safety, tolerability, and pharmacokinetics of imatinib in children	Day 1: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24 hours. Day 8: 0.5, 1, 1.5, 2,3, 4, 8, 24, 32, 48 hours (a 24 hour treatment free period after 24 hour sampling).	6
CSTI571A2108	Non-randomized open-label	Ph+ Chronic Phase CML, age 3-20 years	340 mg/m^2 oral once daily	Determine efficacy, disease-free survival, toxicity, and pharmacokinetics in children	Only during course 1, day 1: 1-3 hr; 6-9 hr; 24 hr	33
CSTI571A2110	Non-randomized open-label	Ph+ ALL or CML, age 1 to less than 4 years	Orally once daily daily dose ranging from 260 mg/m^2 to 340 mg/m^2 in original protocol , equivalent to 400mg/day and 600mg/day in adults. Amended protocol permits doses down to 60/mg/m^2 with physician discretion and Novartis approval.	PK parameters in pediatric patients aged from 1 to less than 4 years	2 PK profiles per patient: (1) day 1; (2) any day between day 2 and day 21 at the following time: 0 (pre-dose); 1-2 hr; 2-4 hr; 6-24 hr	3
Source: [population pharmacokinetics of imatinib in pediatric patients with CML or Ph+ ALL or other glivec indicated hematological disorders-pooled analysis modeing report update, 2011]						

Data from subjects between 2 and 18 years of age were pooled from the four studies and plasma concentrations were measured for imatinib and the major pharmacologically active metabolite CPG74588. Non-linear mixed effects models for the Pop PK imatinib and the metabolite were developed using Nonmem version V1 level 2 with 1 interaction. The final model was used to assess clearance across body surface area, body weight and age. The clearance relationship with body weight from the final model was compared to the previously reported adult model. The final model was then used to simulate PK parameters and related PK exposure measures including AUC, Cmax, Cmin for the proposed paediatric dose of 260 and 340mg/m^{2}as well as for various alternative dosing schemes including those designed to match the AUC for children with adults as indicated in Table 4.

Table 4: Dosing strategies evaluated by simulation in terms of their impact on AUC, Cmax, and Cmin

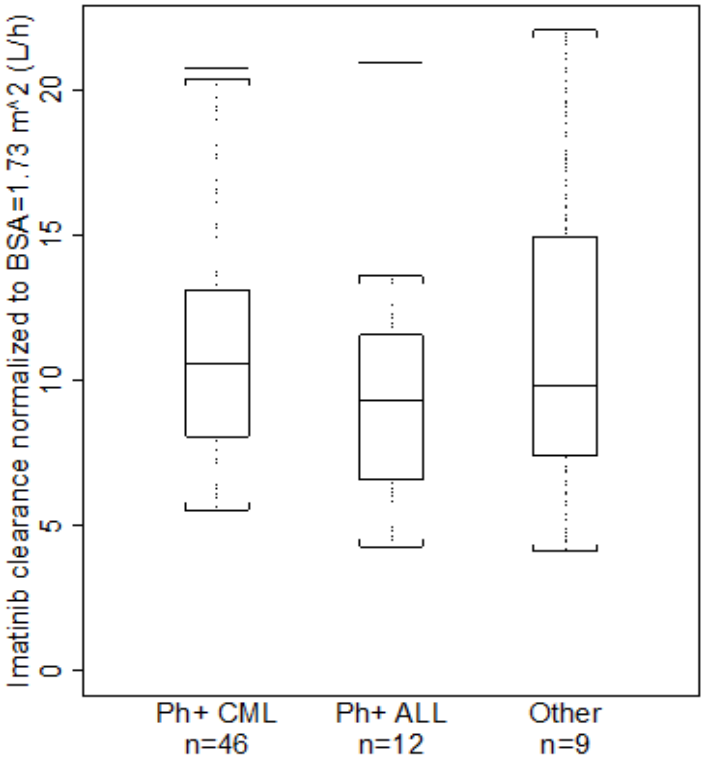
Name of dosing strategy	Dosing algorithm
Fix400	Fixed dose of 400 mg qd regardless of BSA
Fix600	Fixed dose of 600 mg qd regardless of BSA
BSA260	Dose of 260 mg/m^2 BSA, rounded to the nearest multiple of 50mg
BSA340	Dose of 340 mg/m^2 BSA, rounded to the nearest multiple of 50mg
tBSA260	Like BSA260, but not to exceed 400 mg qd
tBSA340	Like BSA3400, but not to exceed 600 mg qd
ModelAUC40	Model-based dose to match a target AUC of 40 mg/L*h
ModelAUC60	Model-based dose to match a target AUC of 60 mg/L*h

The results of the analysis revealed the Pop PK imatinib were characterised by a one compartmental 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 log normal distributions and the residual error by a combined error model. Analysis revealed that CL/F and V/F increased with body surface area. After correcting for the body surface area (BSA) effect the following covariates were not found to have clinically significant effects on the exposure of imatinib: age, gender, race, white blood count, haemoglobin, body weight, body mass index (BMI) and disease type. The clearance for a subject whose BSA was equal to 1.73/m^{2}was 9.06 litres per hour which corresponds with estimates from previous work in the adult population.

There was no statistically significant difference in imatinib clearance among disease types as indicated in Figure 1 Patients with Ph positive ALL were estimated to have an imatinib clearance of 9.7% (SE 15.9%) less than that for Ph positive CML.

Figure 1: Imatinib clearance normalized to BSA=1.73m^2 by disease type (N=67)



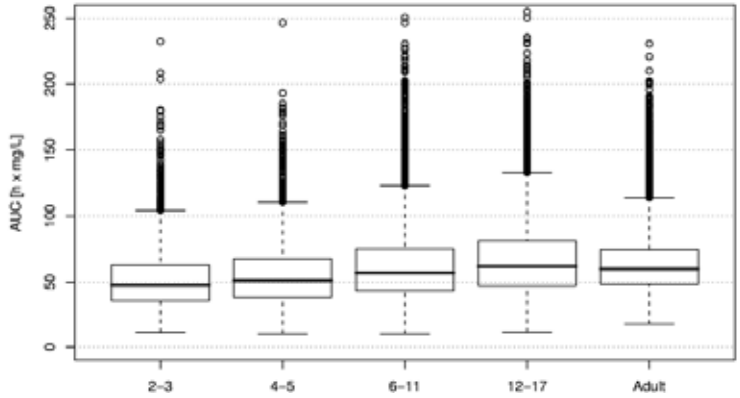
Comparison of the relationship between clearance and body weight in the final model with a previously developed adult model shows that the models are consistent with each other for body weights of 60 kilograms and higher. Refitting the final model without subjects younger than 4 years led to similar parameter estimates. Prediction of concentration–time profiles for the excluded subjects show that the observed concentrations were generally within the predicted 90 percent variability band. Pop PK model was used to assess AUC for 1 year old children. The uncertainty was greater for 1 year olds than 2 year olds. Slightly lower exposure was observed for 1 year olds as compared to 2 years and above.

The pop PK of CGP74588 was characterised by a two compartment model parameterised in terms of apparent clearance (CML/F), apparent volumes of the central compartment (VCM/F) and peripheral compartment (VPM/F) and the apparent intercompartmental clearance (QM/F). The fraction of imatinib and metabolised to CGP74588 in parent- metabolite modelling was fixed to 0.13 or 13 percent. The final pop PK model for the metabolite includes BSA as a covariate with clearances and volumes increased with BSA.

The exposure of 18 year old subjects (dosing scheme of 340mg/m^2 and not to exceed 600mg) was simulated using the adult model, as indicated in Figure 2. The exposure of children in

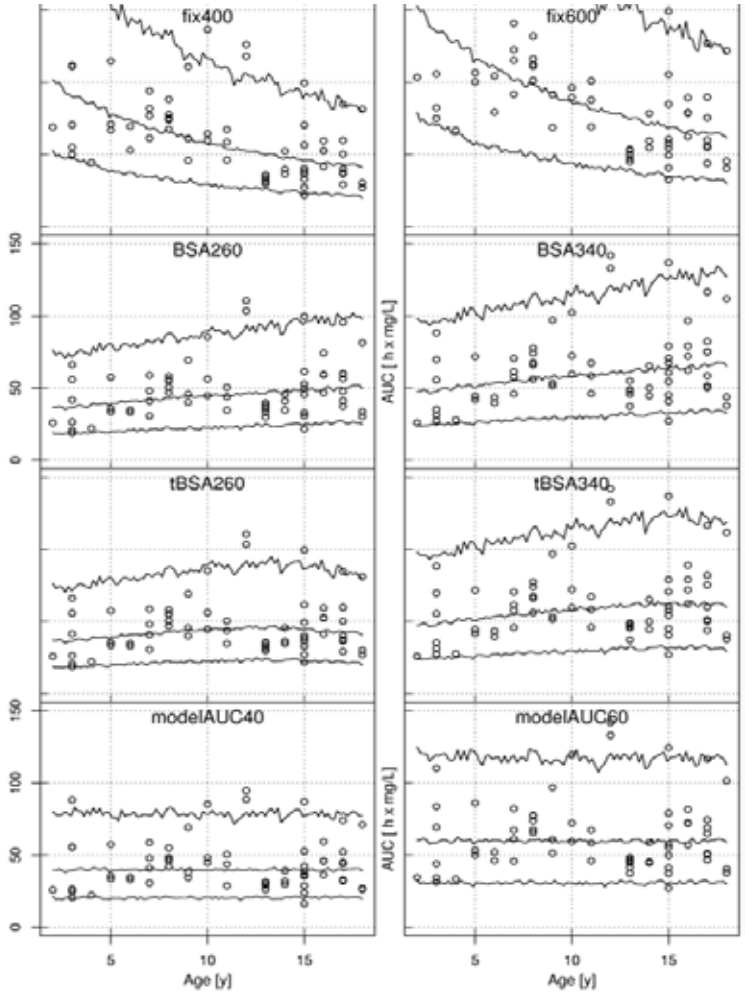
different age groups for 340mg/m^2 corresponds closely to the exposure of adults simulated using the same model.

Figure2: 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 the dose of 260mg/m^2 not to exceed 400mg or 340mg/m^2 not to exceed 600mg lead to relatively constant exposures for AUC, Cmax and Cmin across the range of observed body surface area and ages. The AUC is achieved by these doses are similar to adult AUC as indicated in Figure 3.

Figure 3: AUC versus age in the different dosing strategies



Comment:

Clearance of imatinib was found to increase with increasing BSA supporting a BSA based dosing scheme for imatinib in paediatric patients. The various cohorts analysed did not have clinically significant effects after correcting for BSA effects. This model corresponds well with the observed data when compared to an adult model and shows that the final model is able to successfully extrapolate to younger children between the ages of 2 and 4 years as well as adults. It is therefore reasonable to conclude that the current dosing schemes of 260mg/m^2 or 340mg/m^2, not to exceed 400mg or 600mg, respectively, are applicable for patients aged 1 year or older.

4.3. Physiology–based PK (PBPK) modeling

The objectives of this modeling were:

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

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

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 a phase 3 trial in the adult population was used as reference for paediatric scaling. Two separate approaches were employed:

- the steady state (SS-model) approach scaling only clearance to steady state AUC and
- the dynamic (DYN-model) PK simulation to assess the imatinib concentration – time profile within dosing intervals.

The effects of body size and blood perfusion on the PK profiles were evaluated in addition to maturation and clearance. The model evaluations were conducted by comparing the predicted steady state AUC and predicted imatinib concentration-time profile with non-compartmental AUC computed by the trapezoidal rule and observed data from the pooled clinical studies respectively.

The results determined that the SS model simulations showed that the majority of actual steady state AUC values (95% or 29 of 31) normalized for 340mg/m2 in paediatric patients fell within 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 agreement for most paediatric patients except for younger patients under the age of 2 years for which the exposure appeared to be over-predicted. The predicted deviation from adult was higher for their first dose then at steady state (day 28). The largest deviation was observed for Cmax. The predicted age effect on AUC and Cmin were less than that on Cmax. The differences in predictions of children and adults seemed to be the mixed results of changing distribution volume and blood circulating turnover, in addition to clearance maturation with age. Even 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 of 1 year of age.

Comment:

The projection of paediatric exposure to imatinib using a PBPK model was generally in good agreement with the actual measured PK exposure values in a limited number of paediatric patients ranging from age 2 to 18 years. Incorporation of the PK parameters and maturation processes within the model gave reasonable description of imatinib PK in paediatrics from 2 to 18 years. The exposure for a 1 year subject is likely to be over predicted using the PBPK model based on some bias seen in predictions for age 2 and 3 years. No major exposure – related safety concerns would be expected in dosing if dosed according to BSA.

4.4. Study A2110:

The primary objective of this study was to characterise the PK of imatinib in paediatric patients aged 1 to less than 4 years via a properly integrated physiologically based PK (PBPK) or population PK approaches. The primary end points were CL/F, V/F, Tmax, PBPK parameters, Cmax and AUC.

Due to insufficient patient enrolment (three out of ten patients) and scarcity of PK data, limited PK data was available and a non-compartmental analysis was not conducted.

This was a non-randomised open label study in which patients diagnosed with CML or PH positive ALL between the ages of 1 to 4 years were treated with imatinib administered as a daily dose ranging from 260mg/m^2 to 340mg/m^2. The maximum planned duration of treatment in this study was 21 days during which two sets of PK profiles were collected from each patient.

Only three patients were ultimately involved in this study which limited assessment of data. The PK results did show that there were no major differences in imatinib exposure between the two different visits. The PK profiles for imatinib and CGP74588 showed a large inter-patient variability. However the dose normalized Cmax and Cmin values were similar to adult patients. The observed Cmin for the three patients were consistent with those simulated at a corresponding dose from the final population PK model. Previous results had shown in adult patients imatinib is highly bound to plasma protein ranging from 94 to 97% over clinical relevant concentration ranges. The current study showed that imatinib is highly bound to plasma protein in paediatric patients. The degree of plasma protein binding was comparable to that observed in adult patients.

Comment:

The Cmin values from this study in the three paediatric patients were consistent with simulated values from the population PK model.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No new pharmacodynamic data in relation to paediatric patients was undertaken or determined in this evaluation.

6. Dosage selection for the pivotal studies

No specific dose finding data was performed in the Ph positive ALL setting. The choice of once daily dosing with imatinib 340mg/m^2 for the pivotal study was based on the results of a COG paediatric phase 1 study in PH positive leukaemia which included 14 chronic phase CML patients, seven AML patients and 10 ALL patients. Among the 10 ALL patients 7 achieved an M1

marrow response and one achieved an M2 marrow response with the recommended dose. Pharmacokinetic analyses showed that the doses of 260mg and 340mg/m^2 had exposures similar to those observed in adults treated daily at 400mg and 600mg. The study also showed that daily oral imatinib was well tolerated in children at doses ranging from 260 to 570mg/m^2. An intermediate dose of 340mg/m^2 was therefore adopted for the pivotal study [ST1571I2301].

It was also noted that from the population PK modelling the model based simulation of various dosing schemes confirmed that the exposure of imatinib in paediatric patients receiving 260mg/m^2 not exceeding 400mg once daily or 340mg/m^2 once daily not exceeding 600mg once daily are comparable to those in adult patients receiving 400mg or 600mg once daily respectively.

It is also appropriate to note that there are two dosage forms of imatinib available, namely hard gelatine capsules and film coated tablets. For paediatric patients who are unable to swallow capsules they may be opened and the contents should be dissolved either in water or apple juice. *In vitro* data has demonstrated dispersed imatinib remains stable in water or apple juice.

7. Clinical efficacy

7.1. Studies providing efficacy data

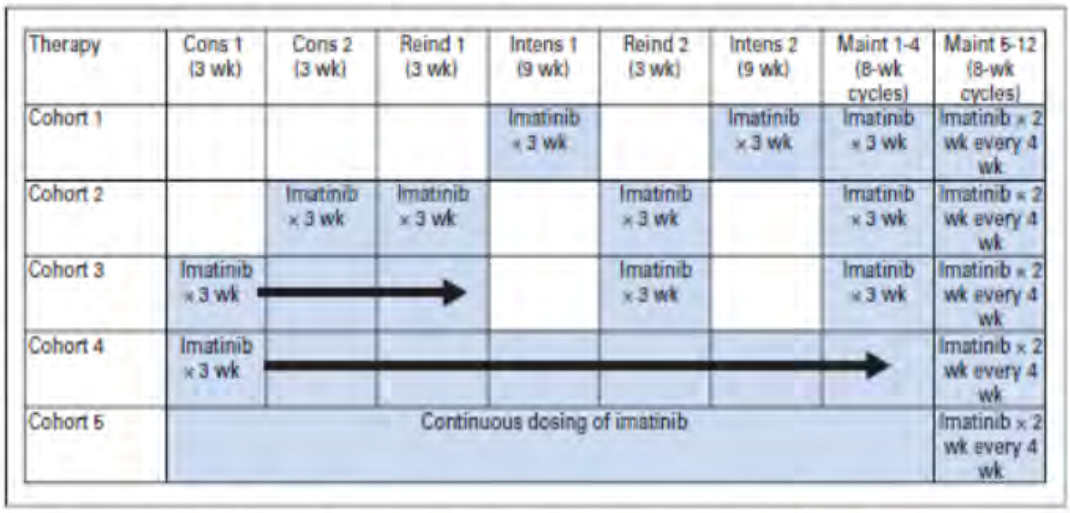
This submission is based on efficacy and safety data from the pivotal phase 3 study 2301. It is appropriate to note that a further study AIT07 (a phase 2/ phase 3 trial) which was a multi-centre study initially designed as an open label randomised study to determine whether the addition of imatinib to standard chemotherapy extended disease free survival (DFS) in paediatric patients with Philadelphia positive ALL. However after the publication of the results from study 2301 demonstrating a significant benefit of adding imatinib to chemotherapy for paediatric patients of all risk for Philadelphia positive ALL, the participating groups considered it unacceptable to randomise patients into chemotherapy only arms. The protocol was therefore amended so that patients received imatinib regardless of risk category. This meant the sample size is inadequate to properly test for the primary efficacy analysis. Accordingly sponsors have not included this study in the efficacy evaluation. This evaluator will include the efficacy data available although accepts the fact that it represents very limited value in terms of determining the role of imatinib in the treatment of paediatric patients with Ph positive ALL.

7.2. Pivotal efficacy study STI571I2301

7.2.1. Methods

The pivotal study 2301 was sponsored, designed and conducted by the cooperative group COG. The primary objective of this study was to determine the feasibility of patient equivalent toxicity of an intensified chemotherapy regimen and incorporating novel agents for the treatment of children and young adults with very high risk ALL including Ph positive ALL. The study consisted of five cohorts each receiving the same intensive chemotherapy regimen back bone post-induction therapy that varied in the integration of imatinib treatment by increasing exposure in five sequential cohorts and is indicated in Table 5.

Table 5: Integration of imatinib into successive blocks of therapy (STI571I2301)



Cons: Consolidation Block; Reind: Reinduction Block; Intens: Intensification Block; Maint: Maintenance Block. All shaded boxes indicate imatinib was administered during that cycle of therapy. Cohort 1: n=7; Cohort 2: n=12; Cohort 3: n=11; Cohort 4: n=12; Cohort 5: n=50. Patients were assigned to the 5 cohorts sequentially adding imatinib to chemotherapy cautiously and leaving more imatinib – free treatment courses in the first 3 cohorts. A new cohort was started only when preceding cohorts did not show substantial safety issues as defined in the protocol

Positive interim results showed acceptable tolerability and superior efficacy for patients in cohort 5 which led to an amendment increasing the sample size in the group of Ph positive ALL patients receiving continuous imatinib treatment. A subsequent interim analysis demonstrated that earlier administration and higher cumulative doses of Imatinib were associated with improved 1 year event free survival (EFS) in all cohorts with the best results being observed in patients treated with continuous dosing in cohort 5 (95.3%, n = 50) which was higher than the historical controls of 65.7% (n = 56). At a later date COG performed another analysis at the cut off date of 31 October 2008 with a primary end point of 3 years EFS in Ph positive ALL patients. This demonstrated three year EFS results for cohort 5 at 80% with observed EFS rate more than twice that of historical controls at 35% (n = 120).

Accordingly a statistical analysis plan in December 2009 performed additional analyses in cohort 5 with a cut off date of 5 September 2009 with a primary end point of EFS and this was assessed in the context of data from historical controls.

EFS is defined as relapse at any site, secondary malignancy, and death from any cause after study entry.

7.2.2. Endpoints

The pivotal study 2301 was a multi-centre phase 3 open label sequential cohort non-randomised study which involved paediatric and young adult patients of less than 22 years with very high risk ALL defined as five year event free survival of less than 45% the large majority of whom had the Ph positive subtypes. A summary of study end points is indicated in Table 6.

Table 6: Summary of endpoints for Study STI571I2301

Primary endpoint	Event-free survival (EFS), with events defined as relapse at any site, secondary malignancy, or death from any cause in Ph+ patients enrolled in cohort 5, including patients who received HSCT*. EFS includes the period from study entry until any event occurs.
Secondary endpoints	• Overall survival (OS) in Ph+ patients, with event defined as death from any cause, from study entry, including patients who received HSCT*.

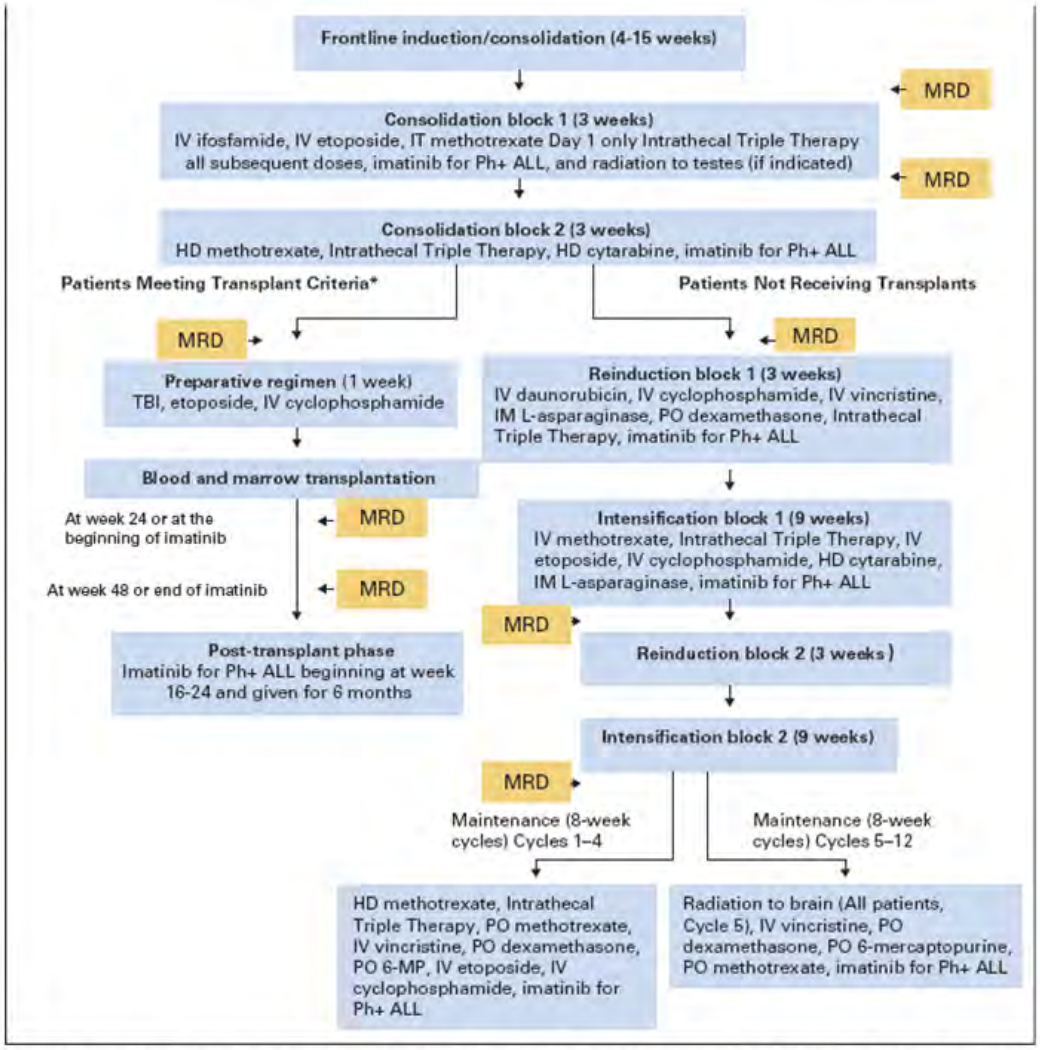
Additional analyses	• Exposure-response of imatinib per cohort, and for combined cohorts, for EFS and OS.
	• Comparison of EFS and OS in cohort 5 (excluding patients who received HSCT) with:
	  • all patients undergoing HSCT in all cohorts
	  • per-protocol HSCT
	  • off-protocol HSCT
	  • all of the above analyses excluding induction failure (IF)
	• Safety and tolerability of adding imatinib to intensive chemotherapy in cohort 5 (including HSCT).
	• Comparison of safety profile in patients receiving intensive chemotherapy + imatinib vs. patients undergoing per protocol HSCT
	• Exploratory (Cox regression) analysis of EFS adjusted for baseline characteristics, Minimal Residual Disease (MRD) status and Central Nervous System (CNS) status.
	• Comparison of OS by date of diagnosis and date of study entry for the Ph+, Ph- and historical control populations.
	• EFS and OS in cohort 5 by age, WBC, gender, race, MRD and NCI risk.
	• Comparison of safety of Ph+ with Ph- patient groups

* Patients who received "per protocol" HSCT were assessed for EFS during the preparatory treatment and during the post-HSCT phase. Patients who received "off protocol" HSCT went off protocol at the time of HSCT and were assessed for EFS during follow-up.

7.2.3. Study design

The study design is indicated in Figure 4:

Figure 4: Study design STI571I2301



*Human leukocyte antigen (HLA)-matched sibling or relative or 1 antigen mismatched sibling or relative (excluding HLA-DR mismatched)

At enrollment, patients had completed 4 to 6 weeks of 3 or 4 drug induction therapy consistent with a front-line pediatric cooperative group regimen. MRD: minimal residual disease; IV: intravenous; IT: intrathecal; HD: high dose; TBI: total body irradiation; IM: intramuscular; PO: oral.

7.2.4. Patient characteristics and treatments

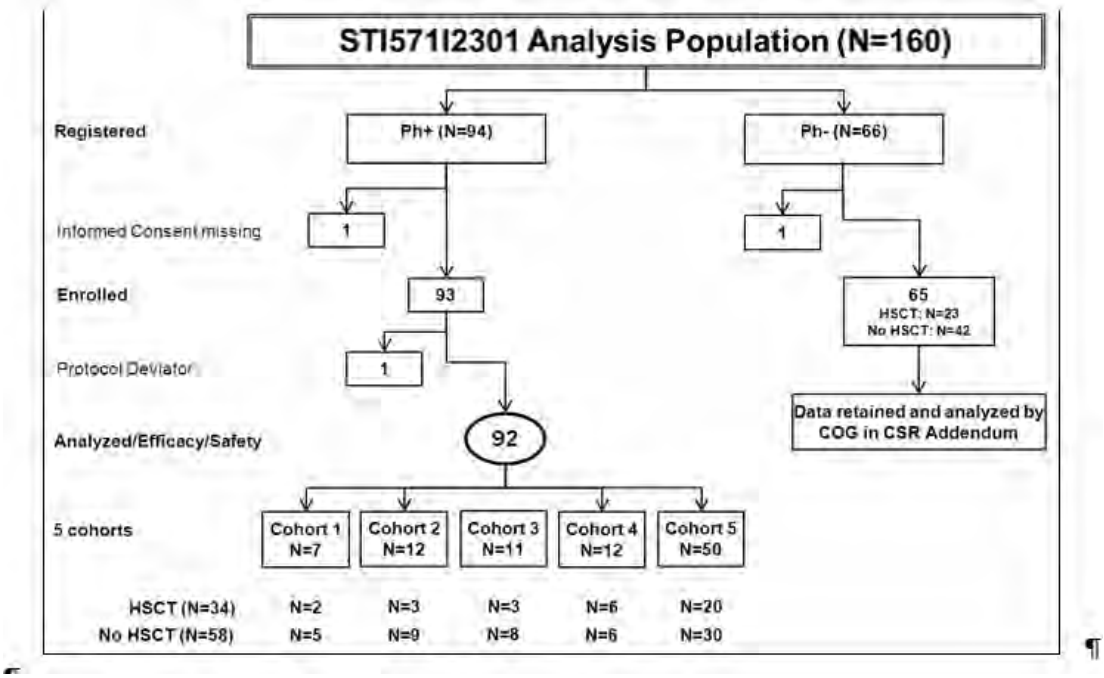
All patients in this study received an initial intensive chemotherapy regimen. The Ph positive patients received imatinib integrated with intensive chemotherapy in successive blocks of increasing imatinib exposure depending on the cohort as indicated in Table 5. In cohorts 1 to 4 imatinib was given at 340mg/m^2 in three week blocks while in cohort 5 imatinib was given at 340mg/m^2 per day continuously except during maintenance blocks 5 through 12 which consisted of two week imatinib blocks every four weeks.

It is noted that patients with HLA matched related donors or one antigen mismatch were rated donors eligible for stem cell transplant after consolidation block 2. At 16 to 24 weeks after per-protocol HSCT treatment with imatinib was resumed initially at a lower dose of 230mg/m^2 per day increased to 340mg/m^2 per day when no toxicity of at least grade 3 were observed after four weeks of post-HSCT imatinib.

7.2.5. Analysis populations

Breakdown of the population analysis for the 160 patients initially entered on to trial is indicated in Figure 5:

Figure 5: Patient Population in Study STI571I2301



The historical control data set for the analyses presented in this submission included 120 Ph ALL patients previously enrolled in five clinical trials performed by the COG.

Reviewing the results of the pivotal study patients and sequential cohorts with increasing duration of imatinib had intermittent chemotherapy cohort 1 through to cohort 5. Analyses are presented by cohort or combined cohort groups compared to cohort 5 which included patients who received imatinib for the longest duration. Both efficacy and safety analyses included the same number of patients and no patients were excluded. Twenty of the 50 patients in the main analysis group of cohort 5 underwent HSCT. Thirty patients were treated only with chemotherapy plus imatinib. Six patients in cohort 5 failed induction treatment as indicated in Table 7:

Table 7: Analysis set and subgroups (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 (%)
Patients analyzed/Enrolled set	7 (100)	12 (100)	11 (100)	12 (100)	50 (100)	92 (100)
Efficacy set	7 (100)	12 (100)	11 (100)	12 (100)	50 (100)	92 (100)
Safety set	7 (100)	12 (100)	11 (100)	12 (100)	50 (100)	92 (100)
Subgroup by HSCT status						
Chemotherapy (no HSCT)	5 (71.4)	9 (75.0)	8 (72.7)	6 (50.0)	30 (60.0)	58 (63.0)
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)
Subgroup by induction failure*						
No induction failure	6 (85.7)	10 (83.3)	11 (100)	11 (91.7)	44 (88.0)	82 (89.1)
M3 induction failure	1 (14.3)	1 (8.3)	0	1 (8.3)	6 (12.0)	9 (9.8)
M2/M2 induction failure**	0	1 (8.3)	0	0	0	1 (1.1)

*Induction failures were defined prior to study entry as: patients with a bone marrow status of M3 (>25% blasts) at the end of standard induction therapy and patients with a bone marrow 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.

**Patient 733885 failed extended induction; had a BM status M2 at end induction then continued to have M2 at end of extended induction therapy. Hence this patient is known as M2/M2 induction failure.

7.2.6. Patient disposition

A total of 160 paediatric patients were enrolled in this study between 14 October 2002 and 20 October 2006. Ninety three were Ph positive patients and received imatinib plus chemotherapy. One patient who was considered not evaluable was excluded from analysis. Approximately half of the Ph positive patients, that is, n=45 or 48.9%, completed protocol treatment and the remaining 47 patients discontinued before completing protocol treatment. The proportion of patients who discontinued protocol was highest in cohort 1 at 71.4% and lowest in patients receiving imatinib continuously in cohort 5 at 46%. Overall the three most frequent reasons for discontinuation were patient decision 10.9%, or relapse at any site 10.9% and off protocol HSCT 9.8%. As of the cut off date 5 September 2009 follow up was ongoing for 57 patients, follow up was discontinued for 30 patients (32.6%) and 5 patients (5.4%) had no follow date available. The overall patient disposition for the various cohorts is summarized in Tables 8 and 9:

Table 8: Overall patient disposition Ph+ cohorts (Enrolled 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 (%)
Patients enrolled	7 (100)	12 (100)	11 (100)	12 (100)	50 (100)	92 (100)
Patients from frontline studies	1 (14.3)	2 (16.7)	5 (45.5)	11 (91.7)	38 (76.0)	57 (62.0)
Patients with 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)

Table 9: Patient disposition for end of protocol treatment, by cohort (Enrolled 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 (%)
Patients enrolled	7 (100)	12 (100)	11 (100)	12 (100)	50 (100)	92 (100)
Completed protocol treatment	2 (28.6)	6 (50.0)	5 (45.5)	5 (41.7)	27 (54.0)	45 (48.9)
Discontinued protocol treatment early	5 (71.4)	6 (50.0)	6 (54.5)	7 (58.3)	23 (46.0)	47 (51.1)
Reasons for discontinuations						
Decision of patient/family	1 (14.3)	1 (8.3)	1 (9.1)	1 (8.3)	6 (12.0)	10 (10.9)
Relapse at any site	2 (28.6)	2 (16.7)	2 (18.2)	0	4 (8.0)	10 (10.9)
Non-AALL0031 HSCT	0	2 (16.7)	2 (18.2)	2 (16.7)	3 (6.0)	9 (9.8)
Physician's choice	1 (14.3)	0	0	1 (8.3)	5 (10.0)	7 (7.6)
Toxicity	0	0	1 (9.1)	1 (8.3)	2 (4.0)	4 (4.3)
Death *	0	0	0	1 (8.3)	2 (4.0)	3 (3.3)
M2 or M3 at end of Consolidation 2	1 (14.3)	1 (8.3)	0	0	1 (2.0)	3 (3.3)
Lost to follow-up	0	0	0	1 (8.3)	0	1 (1.1)
Major change in protocol therapy	0	0	0	0	0	0
Secondary malignancy	0	0	0	0	0	0

* Three (3) patients died during protocol therapy: 2 patients after chemotherapy plus imatinib (Patient 741882 in cohort 4, and Patient 751476 in cohort 5) died within 30 days post-last dose of imatinib; 1 HSCT patient (Patient 752453, cohort 5) died >4 months after last dose of imatinib and >3 months after HSCT.

7.2.7. Demographic and other baseline characteristics

Demographic and baseline characteristics for the patients including the Ph positive patients, the Ph negative patients and the historical control group is indicated in Table 10.

Table 10: Demographics at baseline for Ph+ ALL cohorts, Ph-ALL group and historical control group (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 (%)	Historical control N=120 n (%)
Age-groups for risk classification						
<10 years	10 (52.6)	10 (43.5)	26 (52.0)	46 (50)	29 (44.6)	65 (54.2)
≥10 years	9 (47.4)	13 (56.5)	24 (48.0)	46 (50)	36 (55.4)	55 (45.8)
Age-groups per ICH guidelines						
<12 years	12 (63.2)	12 (52.2)	30 (60.0)	54 (58.7)	37 (56.9)	83 (69.2)
12-<18 years	7 (36.8)	9 (39.1)	16 (32.0)	32 (34.8)	27 (41.5)	34 (28.3)
18 years or more	0	2 (8.7)	4 (8.0)	6 (6.5)	1 (1.5)	3 (2.5)
Sex						
Male	15 (78.9)	14 (60.9)	30 (60.0)	59 (64.1)	36 (55.4)	75 (62.5)
Female	4 (21.1)	9 (39.1)	20 (40.0)	33 (35.9)	29 (44.6)	45 (37.5)
Race						
White	15 (78.9)	20 (87.0)	34 (68.0)	69 (75.0)	48 (73.8)	76 (63.3)
Other	4 (21.1)	3 (13.0)	16 (32.0)	23 (25.0)	17 (26.2)	44 (36.7)
Risk group						
Standard risk	6 (31.6)	4 (17.4)	13 (26.0)	23 (25.0)	18 (27.7)	35 (29.2)
High risk	13 (68.4)	19 (82.6)	37 (74.0)	69 (75.0)	47 (72.3)	85 (70.8)
WBC at diagnosis						
<50,000/uL	10 (52.6)	12 (52.2)	33 (66.0)	55 (59.8)	41 (63.1)	70 (58.3)
≥50,000/uL	9 (47.4)	11 (47.8)	17 (34.0)	37 (40.2)	24 (36.9)	50 (41.7)
Induction failure[b]						
No	16 (84.2)	22 (95.7)	44 (88.0)	82 (89.1)	43 (66.2)	120 (100)
Yes – M3	2 (10.5)	1 (4.3)	6 (12.0)	9 (9.8)	9 (13.8)	[a]
Yes – M2/M2	1 (5.3)	0	0	1 (1.1)	13 (20.0)	[a]
MRD at study entry						
≤0.01%	0	5 (21.7)	18 (36)	23 (25)	17 (26.2)	-
>0.01%	14 (73.7)	14 (60.9)	26 (52)	54 (58.7)	30 (46.2)	-
CNS involvement at study entry[c]						
No (CNS1)	18 (94.7)	23 (100)	47 (94.0)	88 (95.7)	65 (100)	113 (94.2)
Yes (CNS 2/CNS3)	1 (5.3)	0	3 (6.0)	4 (4.3)	0	5 (4.2)
Unknown	0	0	0	0	0	2 (1.7)

[a]Historical controls (of Ph+ ALL patients) did not include induction failures.

[b]Induction failures were defined prior to study entry as: patients with a bone marrow status of M3 (>25% blasts) at the end of standard induction therapy and patients with a bone marrow 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.

[c]Definition of CNS status: CNS 1 = No blasts in CSF present, CNS 2 = Blasts in CSF with <5 WBC/uL in CSF, CNS 3 = Blasts in CSF with at least 5 WBC/uL in CSF

Demographic and baseline characteristics were comparable across the cohorts. It is noted that of the Ph positive ALL patients 50% were less than 10 years of age and two patients were less than two years of age both from cohort 5. Comparisons of minimal residual disease status (MRD) at study entry showed more patients in cohort 3, 4 and 5 with MRD equal to or less than 0.01% included 25% in cohort 4 and 36% in cohort 5. It is also noted that the distribution of baseline characteristics are similar in cohort 5 to the historical control group. It is noted that the Ph negative group included a higher percentage of induction failures than the Ph positive ALL cohorts at 33.8% versus 10.9% respectively. It is also noted 34 of the Ph positive ALL patients or 37% of patients in the pivotal study underwent HSCT an unknown number had

HSCT in the historical control groups. No clinically significant differences in baseline characteristics were observed from patients who received HSCT compared to those that received chemotherapy plus imatinib only.

7.2.8. Primary efficacy endpoint - Event free survival in Study STI571I2301 and historical control group

The primary efficacy end point of the study was EFS from study entry in Ph positive ALL patients and in cohort 5 including the option of HSCT. Imatinib had its highest impact on EFS in patients with Ph positive ALL when administered early on in the course of treatment and for a longer duration, with the best results noted in cohort 5 (n=50): the 48 month EFS rate for cohort 5 was 69.6% which was more than twice that of the historical controls with 31.6% and an HR 0.28% log rank P < 0.0001 as indicated in Table 11. Fourteen patients in cohort 5 showed an EFS event with nine patients relapsing at any site and five patients who died without relapse prior to death. Of the five patients who died, four had undergone HSCT and one patient received only chemotherapy plus imatinib.

Table 11: 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)

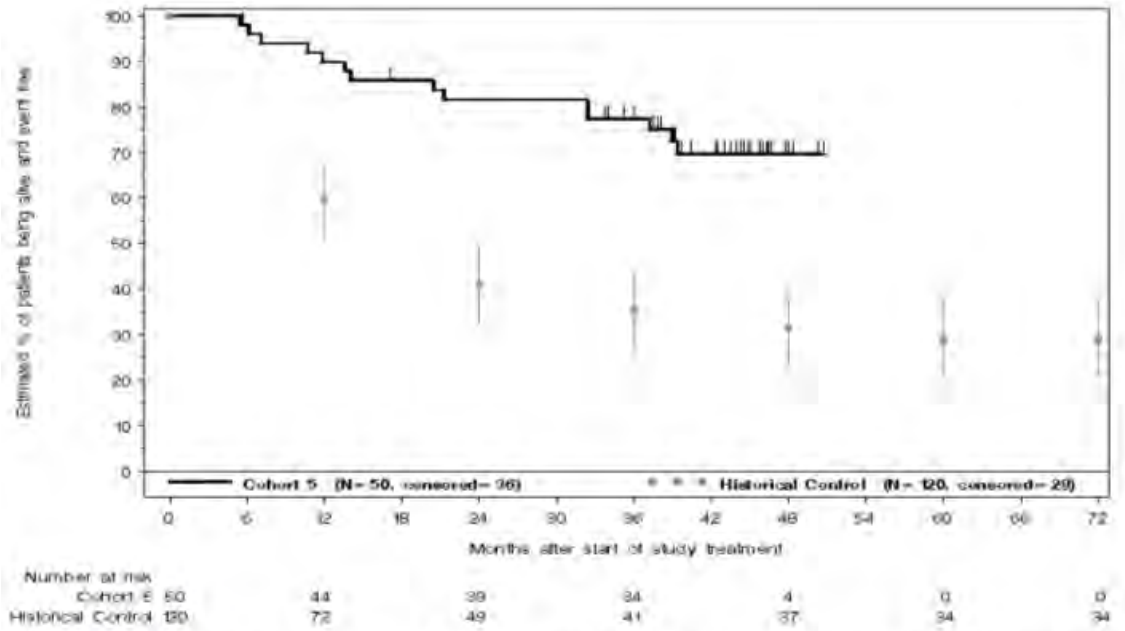
*The results for historical control and the analysis comparing cohort 5 with historical control were provided by COG [STI571I2301-Appendix 16.5 Table 14.2-1.8].

**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.

The estimated rate of EFS at 48 months was 34.7% in cohort 1+2 and was 60.4% in cohort 3+4. Comparison between cohort 5 and cohort 1+2 yielded a HR of 0.38 with a p-value of 0.0101 (log-rank). Comparison between cohort 5 and cohort 3+4 yielded a HR of 0.76 with a p-value of 0.5292 (log-rank) Figure 6 represents the Kaplan-Meier estimates of cohort 5 compared to the historical control group obtained from COG.

Figure 6: 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.

7.2.9. EFS in cohort 5 and historical control by baseline characteristics

Event free survival is analysed for cohort 5 and the historical control population considering various baseline characteristics including age at study start, gender, white blood count at diagnosis and CNS involvement and results are summarised in Table 12:

Table 12: 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)			
	Cohort 5 N=50		**Historical control N=120**	

* % 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):

For all characteristics assessed there was an advantage in terms of event free survival for the patients in cohort 5 compared to the historical controls. This was further analysed utilizing a Cox regression analysis for selected baseline characteristics including age, gender and white blood count as the others had insufficient numbers available or not available for the historical controls namely minimal residual disease status. Again advantages were noted for the cohort 5 patients compared to the historical controls with HR 0.28 log rank P < 0.0001 as indicated in Table 13:

Table 13: 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)

7.2.10. Overall survival

Comparison of overall survival for the various cohorts compared to the historical controls is summarised in Table 14. The estimated overall 48 month survival rate in cohort 5 was 83.6% compared to a rate of 44.8% for the historical controls with an HR 0.23 log rank P < 0.0001. This compared to an overall survival at 48 months of 49.2% for cohorts 1 + 2 and 74.7% for cohorts 3 + 4. Comparison between cohort 5 and cohort 1+2 yielded a HR of 0.30 (log-rank p=0.0091). Comparison between cohort 5 and cohort 3+4 yielded a HR of 0.74 (log-rank p=0.5949). This is indicated in Table 14 and Figure 7:

Table 14: Overall survival in Ph+ cohorts (Efficacy set – STI571I2301) and historical control

	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50	Historical control N=120
Events: n (%)	9 (47.4)	5 (21.7)	8 (16.0)	76 (63.3)
% Survival Probability estimates (95% CI)**				
12 Months	94.7 (68.1,99.2)	100 (100,100)	93.9 (82.3,98.0)	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)	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)	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)	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)		0.23 (0.11,0.49)

	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50	Historical control N=120
Events: n (%)	9 (47.4)	5 (21.7)	8 (16.0)	76 (63.3)

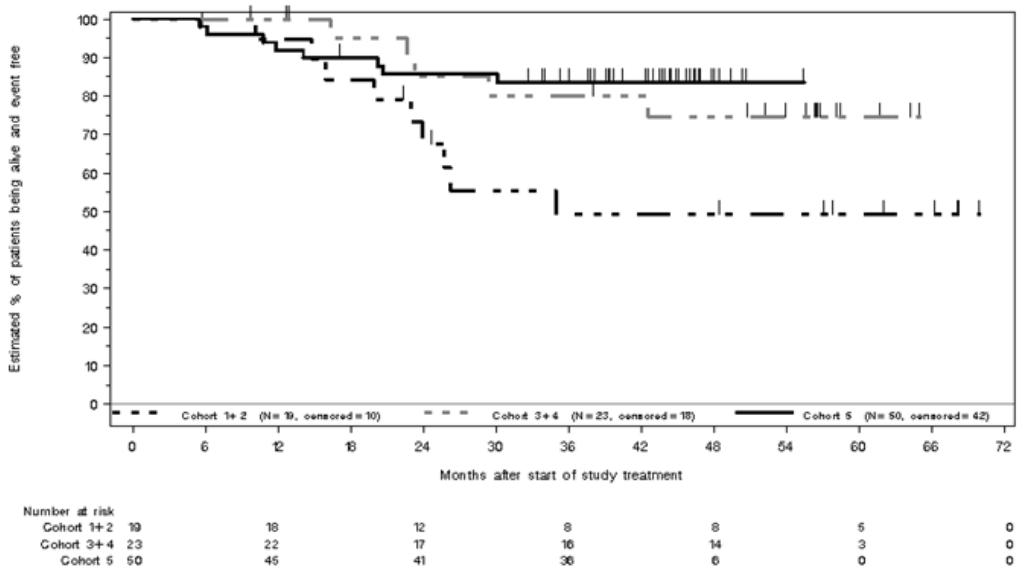
* The results for historical control and the analysis comparing cohort 5 with historical control were provided by COG.

** % 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).

Figure 7: Overall survival by cohort groups (Efficacy set – STI571I2301)



7.2.11. Effect of imatinib exposure on EFS

The effect of scheduled exposure to imatinib on event free survival using the cohort with increasing exposure from 1 to 5 was examined using the Cox proportional hazards model. This

revealed that with increasing exposure to Imatinib from cohorts 1 to 5 the respectively estimated event free survival showed a P value of 0.080. It was estimated that each level increase in cohort number reduced the risk of an event by an estimated average of 23%.

7.2.12. Effect of HSCT

Recognising the potential influence of HSCT on outcomes and involvement of this procedure in many of the patients in the study additional analysis was undertaken excluding all patients who underwent HSCT from cohort 5 and comparing this group with all patients who received per protocol HSCT (n=21) and all patients who received off protocol HSCT (n=13). The analysis of EFS is indicated in Table 15 and Figure 8. A positive trend was noted for EFS favouring per protocol HSCT over off protocol HSCT and cohort 5 chemotherapy plus imatinib over per protocol HSCT. These figures were however not statistically significant.

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

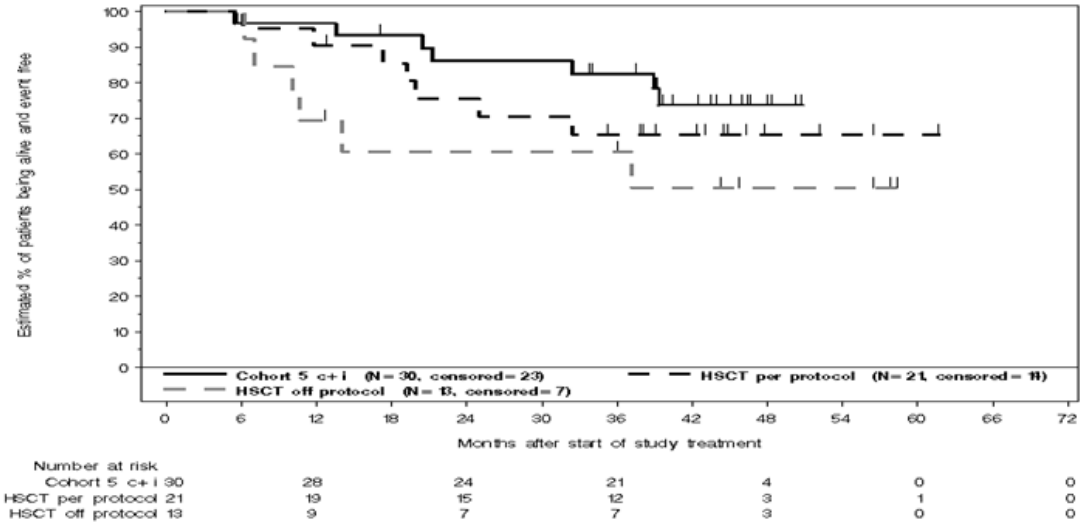
	HSCT Per protocol N=21	HSCT Off protocol N=13	HSCT all (on and off) N=34	Cohort 5 (excluding HSCT) N=30
EFS events n (%)	7 (33.3)	6 (46.2)	13 (38.2)	7 (23.3)
% Event-Free Probability Estimates (95% CI)[+]				
48 Months EFS	65.3 (40.7,81.8)	50.5 (20.6,74.4)	59.8 (40.9,74.4)	73.7 (52.3,86.7)
Comparison 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.

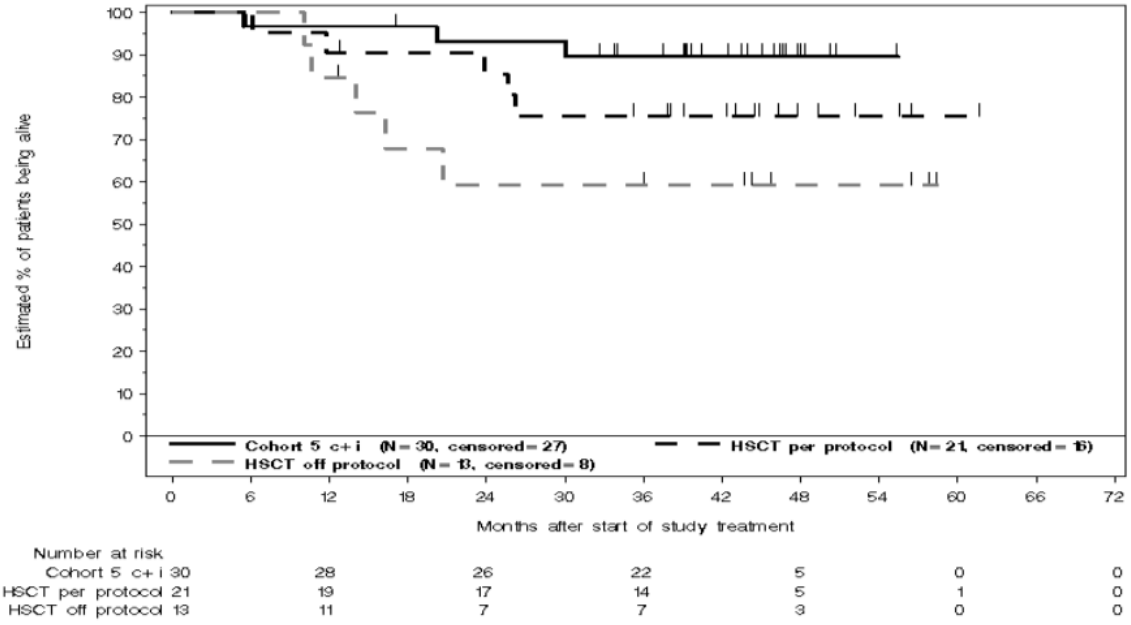
N : Total number of patients included in the analysis;

Figure 8: Kaplan-Meier curve of EFS comparing cohort 5 chemotherapy + imatinib and HSCT (Efficacy set – STI571I12301)



Overall survival for cohort 5 for patients who underwent HSCT both per protocol and off protocol is indicated in Figure 9. At 4 years the estimated overall survival rate of cohort 5 (chemotherapy plus Imatinib only, excluding HSCT n=30) was 89.5% versus 75.4% in the per protocol HSCT and 59.2% in the off protocol HSCT. Cox regression analysis adjusting for various baseline factors failed to show any differences in these data.

Figure 9: Kaplan-Meier curve of OS (months) comparing cohort 5 chemotherapy + imatinib vs. HSCT (Efficacy set – STI571I12301)



7.3. Evaluator's conclusions on pivotal efficacy study STI571I2301

This data has clearly shown that for patients in cohort 5 of the pivotal study there was a highly significant benefit for the use of imatinib plus chemotherapy compared to the historical controls in relation to both event free survival and overall survival. Sub-group analyses confirmed this data. There was also a lesser but again significant benefit between cohort 5 and cohorts 1 + 2 who only had limited exposure to imatinib. The reviewer recognises the fact that as this is a relatively uncommon disease and that an appropriately randomised study would have been very difficult to conduct. The choice of historical controls however does raise some concerns particularly in the context that these came from various COG studies involving earlier chemotherapy protocols. The chemotherapy involved in induction for patients on study 2301 was extremely intensive involving quite a large number of agents which raises the question whether the intensity of induction therapy may not have been a significant factor in determining event free survival and overall survival irrespective of the role of imatinib. This would benefit from further evaluation.

7.4. Supportive study STI571AIT07

7.4.1. Methods

A further study AIT07 was an open labelled randomised phase 2/3 study assessing safety and efficacy of imatinib with chemotherapy in paediatric patients with Philadelphia positive acute lymphoblastic leukaemia and was performed between January 2004 and November 2010 involving 10 paediatric leukaemia study groups. The primary objective of this study was to evaluate the disease free survival in the good risk group of patients treated either with or without imatinib in correlation with intensive chemotherapy including the option of HSCT. The

randomisation component involved chemotherapy plus imatinib or chemotherapy alone for the good risk patients. A total of 229 patients who were randomised were registered for the study and among the 213 eligible patients 35 were not entered onto the study. Of the 178 eligible patients 108 were good risk patients. Of these 108 patients 18 were not randomised due to clinical decision and patient refusal and only 90 patients were randomised to imatinib plus chemotherapy or chemotherapy alone.

7.4.2. Results

This study was terminated early because of recognition of the results from the pivotal study 2301 and a decision that no further randomisation was appropriate. This resulted in an insufficient sample size to properly test for the primary efficacy analysis. Nevertheless in relation to the primary end point of disease free survival, 6 out of 44 or 14% of chemotherapy alone patients and 4 out of 46 or 9% of chemotherapy plus imatinib patients had a disease free survival event. This was not statistically significantly different, with a hazard ratio of 0.978 and a log rank test of 0.9733. The estimated DFS rates at 24 months were comparable in the Good risk-no imatinib arm (65%) and Good risk-imatinib arm (81%), with very similar and wide confidence intervals of the estimated rates in both groups.

It is noted that over 80% of patients had undergone HSCT significantly influencing the results, but when disease free survival was assessed not censoring for HSCT 16 of 44 or 36% of the good risk patients receiving chemotherapy alone and 12 of 46 or 26% receiving chemotherapy plus imatinib had a DFS event., with the hazard ratio of 0.635 and P value of 0.2424. At the end of 24 months the estimated DFS rate was 68% in non-imatinib arm and 79% in the Imatinib arm.

In relation to overall survival at 48 months, in the good risk Imatinib patients it was 85% which was slightly higher than the non-imatinib patients at 73%, with a hazard ratio of 0.644.

7.5. Evaluator's conclusions on supportive study STI571AIT07

These data certainly did not provide any further evidence supporting the role of imatinib in the maintenance phase of patients having undergone intensive chemotherapy induction for Ph positive ALL. Nevertheless as determined by the sponsors and investigators the data really is difficult to interpret and thereby provides little to add to the significance of the results from the pivotal trial 2301.

8. Clinical safety

8.1. Studies providing evaluable safety data

This submission presents safety data from 220 Ph positive ALL paediatric patients treated with imatinib from two studies i.e. the pivotal study 2301 involving 92 imatinib treated patients and a supportive study AIT07 involving 128 Imatinib treated patients. As there was substantial differences in design for the two studies data regarding safety are presented separately. The safety population was defined as patients who received at least one dose of study drug. The safety population was 92 patients for study 2301 and 128 for AIT07. The study design and population for the pivotal study has been presented and for the supportive study AI07 these are indicated in Table 16 and Figures 10, 11 and 12:

Table 16: Summary of study STI571AI07

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)].

	Details
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%.

Figure 10: Patient population in Study STI571AIT07

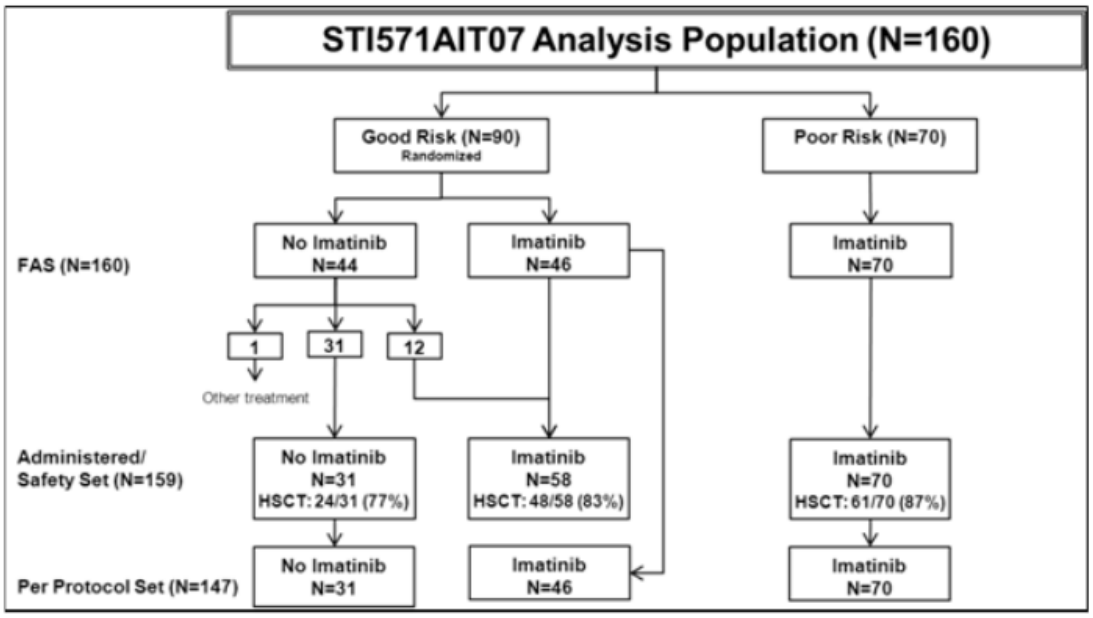
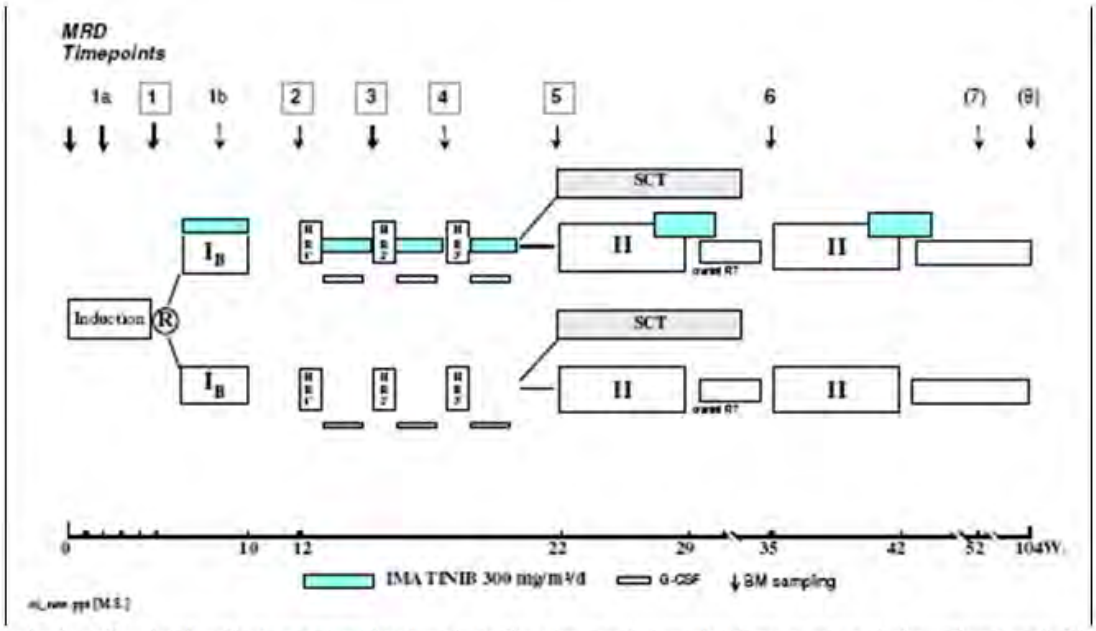
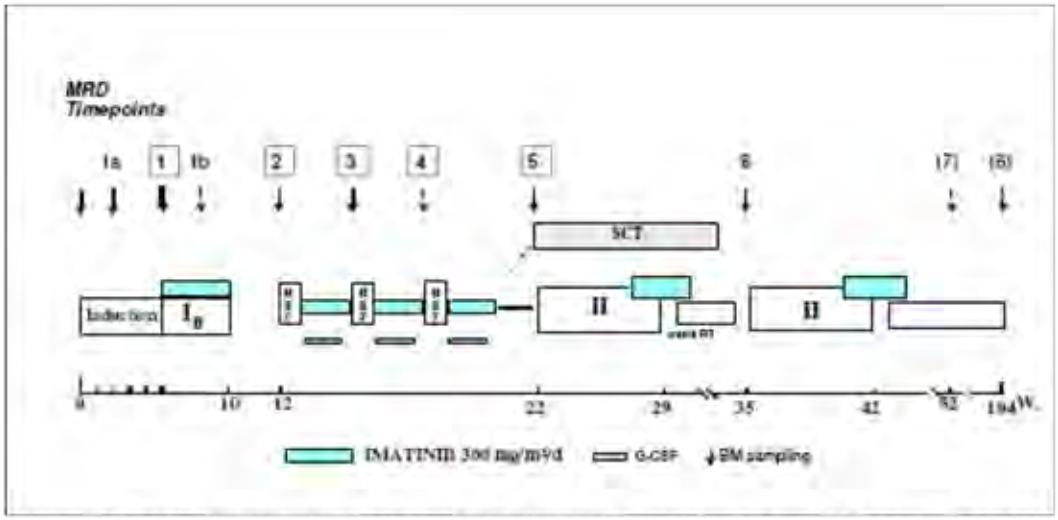


Figure 11: Treatment of Good risk Ph+ ALL with or without imatinib



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 12: Treatment of Poor risk Ph+ ALL with or without 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).

8.2. Exposure

In relation to exposure in the pivotal study median exposure to Imatinib for cohorts 1 to cohort 5 among patients who did not undergo HSCT range from 176 days for cohort 1 to 708 days for cohort 5. In the non HSCT Philadelphia negative patients the median exposure to chemotherapy was 783 days and this is illustrated in Table 17.

Table 17: 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.

Among the PH positive ALL patients receiving per protocol HSCT the overall median intermittent exposure prior to HSCT was 42 days and with a range of 21 to 77 days and median exposure to Imatinib following HSCT was 169 days with a range of 14 to 192 days. Among the Ph positive patients the overall median Imatinib exposure prior to patients receiving off protocol HSCT was 53 days with a range of 28 to 165 days.

Duration of follow up from start of consultation 1 to the end of study including follow up after discontinuation of treatment is indicated in Table 18. As indicated in Table 19 65% of all patients had at least one treatment block delayed for more than 14 days. The most frequent reason for this being delayed neutrophil count recovery.

Table 18: Duration of follow-up (Safety set - STI571I2301

Follow-up time (months)	Cohort 1+2 N=19	Cohort 3+4 N=23	Cohort 5 N=50
Mean (SD)	38.9	43.9	37.2
Minimum	10	10	5
Q1	22.4	23.2	34.1
Median	26.2	54.0	40.5
Q3	62.0	56.8	46.1
Maximum	70	65	55

Follow-up is the time from start of Consolidation 1 to death or last contact. No patient was censored.
Patients who received HSCT and those who did not are included in this analysis.

Table 19: 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]

In relation to study AIT07 overall treatment exposure for Imatinib plus chemotherapy or chemotherapy alone is summarised in Table 20. Median duration of treatment was similar for all patient groups.

Table 20: Overall treatment exposure* (Safety set STI571I2301)

	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.

Overall 24 or 77.4% of the good risk patients who received chemotherapy alone, 48 or 82.8% of the good risk patients received Imatinib plus chemotherapy and 61 or 87.1% of the poor risk patients who received Imatinib plus chemotherapy underwent HSCT. In total 109 or 85.2% of patients who received Imatinib plus chemotherapy in both good and poor risk patients underwent HSCT in this study. Patients undergoing HSCT did not receive Imatinib post HSCT.

The median duration of follow up was similar for good risk patients receiving chemotherapy alone at 38 months with a range 2 to 72 and patients receiving Imatinib plus chemotherapy at 35 months with a range of 2 to 79. As expected follow time was poor for the poor risk patients at 23 months with a range of 4 to 79 months. Patients who received Imatinib from start of study treatment were followed up to a maximum of 79 months with a median of 30 months.

The incidence of treatment delay of at least one week was similar among good risk and poor risk patients who received Imatinib at 25 patients or 43% and 25 patients or 36% respectively. This is illustrated in Table 21.

Table 21: 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]

Baseline demographic characteristics for the pivotal study 2301 have been presented and are indicated in Table 22 for study AIT07.

Table 22: Demographics at baseline (Safety set - STI571AIT07)

	Good risk		Poor risk	All with imatinib
	No imatinib	Plus imatinib	Plus imatinib	
	N=31	N=58	N=70	N=128
Baseline age (years)				
Mean (SD)	8.9 (4.1)	8.4 (4.9)	10.3 (4.3)	9.4 (4.7)
Minimum	1.5	1.6	2	1.6
Q1	6.8	4.1	6.4	5.3
Median	9.0	7.6	11.1	10.0
Q3	12.1	12.8	13.8	13.4
Maximum	16.1	17.9	16.8	17.9
Age-groups - risk group – n (%)				
<10 years	21 (67.7)	35 (60.3)	29 (41.4)	64 (50.0)
≥ 10 years	10 (32.3)	23 (39.7)	41 (58.6)	64 (50.0)
Age-group–according to pediatric investigational plan (PIP) – n (%)				
<2 years	2 (6.5)	5 (8.6)	0	5 (3.9)
Baseline age (years)				
2-<12 years	21 (67.7)	34 (58.6)	38 (54.3)	72 (56.3)
12-<18 years	8 (25.8)	19 (32.8)	32 (45.7)	51 (39.8)
≥ 18 years	0	0	0	0
Sex – n (%)				
Male	17 (54.8)	40 (69.0)	44 (62.9)	84 (65.6)
Female	14 (45.2)	18 (31.0)	26 (37.1)	44 (34.4)
Risk classification				
Standard Risk	10 (32.3)	22 (37.9)	10 (14.3)	32 (25.0)
High Risk	20 (64.5)	36 (62.1)	59 (84.3)	95 (74.2)
Not applicable(T-ALL)[b]	1 (3.2)	0	1 (1.4)	1 (0.8)
WBC (/nL) at diagnosis [a,c]				
N	30	57	69	126
Mean (SD)	83.0 (136.5)	69.6 (97.7)	150.5 (148.1)	113.9 (133.6)
Minimum	3.0	1.0	2.2	1.0
Q1	7.8	5.5	44.0	13.1
Median	26.2	23.7	101.0	71.1
Q3	94.7	99.5	212.0	160.0
Maximum	600.0	469.8	605.0	605.0
<50,000/nL	19 (61.3)	35 (60.3)	20 (28.6)	55 (43.0)
≥ 50,000/nL to <100,000/nL	4 (12.9)	8 (13.8)	14 (20.0)	22 (17.2)
≥ 100,000/nL	7 (22.6)	14 (24.1)	35 (50.0)	49 (38.3)
Not known	1 (3.2)	1 (1.7)	1 (1.4)	2 (1.6)

[a] NCI Standard-risk category included patients aged <10 years who had a WBC count at diagnosis <50000/μL. Therefore, patients aged ≥ 10 years or those who had a WBC count at diagnosis ≥50000/uL were classified as High risk.
[b] Risk classification was considered not applicable for patients who had T-ALL (leukemic cells formed from T-lymphocytes).
[c] The summary statistics for WBC are presented in nL for better readability.

In relation to patient disposition in the pivotal study 2301 approximately half the patients in each group completed patient protocol treatment and the proportion of patients that discontinued protocol treatment prior to completing therapy was similar for both the Ph positive and Ph negative patients as indicated in Table 23.

Table 23: 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).

Patient disposition for study AIT07, of the total of 229 patients 178 were enrolled and assigned to either good risk i.e. 108 or poor risk i.e. 70. The remaining patients were outside of this protocol. All 70 patients assigned to the poor risk group received Imatinib plus chemotherapy and of the 108 good risk patients 90 were randomised to Imatinib plus chemotherapy i.e. 46 and chemotherapy alone i.e. 44. As indicated in Table 24.

Table 24: 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.]

8.3. Adverse events

Adverse event reporting was as per NCI common terminology criteria including relevant grading.

Reviewing the overall incidence of adverse effects in Study 2301 the incidence of non-targeted AE at least grade 3 by system organ class and preferred term in Ph positive patients treated with chemotherapy plus Imatinib as well as the Ph negative patients who received chemotherapy alone is indicated in Table 25.

Table 25: 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	N=19 n (%)	N=23 n (%)	N=50 n (%)	N=92 n (%)	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.

The proportion of patients experiencing adverse events were generally higher in those receiving chemotherapy plus Imatinib although as noted except for the Ph negative patients who did not receive Imatinib the incidence of lymphopenia, infection, hyperglycemia and hypocalcaemia was higher.

A selection of toxicities that were considered by the sponsor to be targeted toxicities and the incidence of these of at least grade 3 for patients who received chemotherapy plus Imatinib as well as the Ph negative patients who did not receive Imatinib is indicated in Table 26.

Table 26: 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 most regular of these were increased ALT, AST and haemorrhage. Because of this increased incidence of elevated liver enzymes the duration of Imatinib was adjusted from 21 days per cycle to 14 days per cycle for maintenance cycles 5 to 12. Comparison of the enzyme elevations before and after the adjustment is indicated in Table 27 which indicates a decreased incidence of grade 3 and 4 ALT elevation, AST elevation and bilirubin elevation.

Table 27: 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.

8.3.1. Analysis of adverse events within the Ph+ treatment blocks

As illustrated in Table 28 a number of PH positive ALL patients with grade 3, 4 or 5 adverse events by cohort and treatment block is indicated at the shaded cells which correspond to Imatinib integrated with chemotherapy. There is a high incidence of adverse events overall in each treatment block as expected due to the intensive chemotherapy regimen.

Table 28: 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.

8.3.2. Common adverse events in study STI571AIT07

Reviewing adverse events for study AIT07 most patients experienced at least one adverse event during the study and these are consistent with the established safety profile of Imatinib. Again the most frequent were decreased white blood count, haemoglobin, platelet count and neutrophil count as well as infections as indicated in Table 29. For those good risk patients who received Imatinib compared to those who did not there was an increased incidence of neutropenia, infection, increased hepatic enzymes, decreased anti-thrombin 3, gastritis, proteinuria and euphoric mood.

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].

8.3.3. Adverse events suspected to be drug-related

Reviewing adverse events suspected to be drug related for study 2301, Table 30 indicates the most frequent adverse events for those who were at least grade 3 suspected to be related to Imatinib as assessed by the investigator. The suspected adverse events of myelosuppression and hepatotoxicity were consistent with the established safety profile of Imatinib. There were no consistent trends observed of increased or decreased frequency of suspected adverse events according to cohorts and treatment block.

Table 30: 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=6	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)
Reinduction 2	n=3	n=7	n=8	n=6	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=6	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.

Information related to events suspected to be drug related was not collected for study STAIT07.

8.3.4. Deaths

In relation to deaths, in study 2301 the deaths and reasons for these are indicated in Tables 31 and 32.

Table 31: 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]

Table 32: 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]

It is noted that four occurred on therapy or within 30 days of the last treatment. Of these, two were in patients who were receiving chemotherapy and Imatinib and both were related to infection. A further death was related to infection together with respiratory haemorrhage and failure. The final death was also associated with neutropenic infection.

It is noted the most common cause of death was progression of malignancy and in particular this was three times more common in the Philadelphia negative patients. It is also noted that patients in cohort 5 with the longest duration of Imatinib exposure experienced a lower incidence of deaths than patients in the other 4 cohorts including those deaths related to progressive disease, infection, haemorrhage and unknown.

In relation to study AIT07 as indicated in Table 33 a total of 41 deaths occurred during the study with a higher frequency in the poor risk patients (34.3%) compared to the good risk with no Imatinib (25.8%) or in good risk with Imatinib (15.5%). The reasons for the deaths were generally similar across treatment groups. Again the most common was progressive malignant disease.

Table 33: 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)
No	1 (12.5)	2 (22.2)	5 (20.8)	7 (21.2)
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]

8.3.5. Serious adverse events

In relation to serious adverse events the frequency of these by system organ class for the pivotal study 2301 was higher for cohort 5 patients excluding HSCT at 50% and for all cohort patients who received per protocol HSCT at 33.3% and indicated in Table 34 (AdEERS: Adverse Event Expedited Reporting System).

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	All cohorts per protocol HSCT *
	N=30	N=21
	n (%)	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.

In relation to serious adverse events for study AIT07 the proportion of patients who experienced serious adverse events were similar for patients who received Imatinib at 31.3% versus 32.3% for patients not treated with Imatinib. The proportion of patients experiencing serious adverse events was lower in the good risk Imatinib group at 27.6% than in the good risk no Imatinib group at 32.3%. This latter figure was similar to that for the poor risk group at 34.3% all who had received Imatinib. This is illustrated in Table 35. Infections were the most commonly reported serious adverse events in both risk groups.

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]

8.3.6. Discontinuations due to adverse events

In relation to discontinuations due to adverse events for study 2301 the percentage of discontinuations was low when Imatinib was added to the chemotherapy regimen. Four patients (4.3%) in the Ph+ group (two patients in cohorts 3 + 4 and 2 patients in cohort 5) and one patient in the Ph- group were discontinued prematurely from the study due to toxicity.

In relation to study AIT07 only one patient discontinued due to toxicity which is considered to be related to one of the chemotherapy agents i.e. Asparaginase and not causally related to Imatinib.

8.4. Clinical laboratory evaluations

In relation to clinical laboratory evaluations for the two studies only limited documentation of abnormalities was provided for the two studies.

In relation to study 2301 assessment of the neutrophil counts revealed that most Ph positive ALL patients had a drop in absolute neutrophil count to less than 750 per microlitre at some time regardless of Imatinib administration. For Consolidation 1 this was 85.7% (cohort 1), 58.3% (cohort 2), 54.5% (cohort 3), 72.7% (cohort 4) and 82% for cohort 5. Recovery time from neutropenia was similar across cohorts ranging from 3 to 35 days. These recoveries tended to be longer with more prolonged chemotherapy. There was no apparent difference in the incidence of neutropenia or time to recovery related to the incorporation of Imatinib into each treatment course.

In respect of thrombocytopenia patients with platelets less than 75,000 per microlitre at any time varied in all cohorts via treatment block being highest in Consolidation 2 and Intensifications 1 and 2 and lowest in Maintenance 5 to 12. The overall median time to recovery range was 5.5 to 17 days and was similar in cohort 5. In general there is no difference between treatment blocks.

Assessment of haematological values for study AIT07 showed decreased white blood count, haemoglobin and platelet count observed in over 90% of the patients in both groups with or without Imatinib. There were no significant differences observed across the treatment groups.

8.5. Safety in special groups and situations

8.5.1. Subgroup evaluation of adverse events-Study STI571I2301

Review of adverse events for study 2301 in relation to age noted there were 15 patients aged less than 4 years including 3 who were 1 to 2 years old. Analysis of adverse events for those who were less than 4 versus those that were aged higher than 4 years of age is summarised in Table 36.

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]

In the group of patients less than 4 years in cohort 5 involving 11 patients there were no deaths during or within 30 days of discontinuing Imatinib therapy. There were no discontinuations due to toxicity whereas in the age group greater than 4 years involving 39 patients there were 8 patient deaths (20.5%) and 2 (5.1%) who discontinued due to toxicity. The frequency of adverse events and grade 3 or 4 adverse events were similar for the younger and older age groups.

The most regular adverse events in all age groups were related to investigations followed by infections and infestations for those patients less than 12 years and gastrointestinal disorders

for those 12 to 18 years. It is also noted in patients less than 12 years of age in cohort 5 the most frequent adverse events were decreased neutrophil count, decreased platelet count, decreased haemoglobin and increased ALT. No clinically relevant differences were observed concerning the frequency of adverse events in different age groups.

8.5.2. Subgroup evaluation of adverse events in study STI571AIT07

In relation to study AIT07 adverse events regardless of investigator causality assessment is summarised by age at diagnosis in Table 37. The overall incidence of adverse events was similar in the less than 4 years to the greater than 4 year age groups.

Table 37: Adverse events regardless of study drug relationship by preferred term and age at diagnosis (Safety set –STI571AIT07)

	Good risk				Poor risk		All	
	No Imatinib		Plus Imatinib		Plus Imatinib		Plus Imatinib	
	<4 years N=4 n (%)	≥ 4 years N=27	<4 years N=14 n (%)	≥ 4 years N=44	<4 years N=10 n (%)	≥ 4 years N=60	<4 years N=24 n (%)	≥ 4 years N=104
White Blood Cell Count[a]	4 (100)	24 (88.9)	14 (100)	43 (97.7)	9 (90)	56 (93.3)	23 (95.8)	99 (95.2)
Hemoglobin[a]	4 (100)	24 (88.9)	14 (100)	41 (93.2)	9 (90)	56 (93.3)	23 (95.8)	97 (93.3)
Platelet Count[a]	4 (100)	24 (88.9)	14 (100)	42 (95.5)	8 (80)	55 (91.7)	22 (91.7)	97 (93.3)
Granulocyte Count[a]	4 (100)	22 (81.5)	14 (100)	40 (90.9)	9 (90)	53 (88.3)	23 (95.8)	93 (89.4)
Infection	4 (100)	22 (81.5)	14 (100)	40 (90.9)	8 (80)	53 (88.3)	22 (91.7)	93 (89.4)
Pyrexia	3 (75)	22 (81.5)	11 (78.6)	39 (88.6)	8 (80)	53 (88.3)	19 (79.2)	92 (88.5)
Nausea	4 (100)	16 (59.3)	8 (57.1)	34 (77.3)	7 (70)	51 (85)	15 (62.5)	85 (81.7)
Hepatic Enzyme[b]	3 (75)	19 (70.4)	9 (64.3)	38 (86.4)	5 (50)	44 (73.3)	14 (58.3)	82 (78.8)
Vomiting	4 (100)	17 (63)	10 (71.4)	33 (75)	8 (80)	45 (75)	18 (75)	78 (75)
Stomatitis	2 (50)	20 (74.1)	10 (71.4)	32 (72.7)	7 (70)	45 (75)	17 (70.8)	77 (74)
Abdominal pain	2 (50)	17 (63)	9 (64.3)	32 (72.7)	7 (70)	41 (68.3)	16 (66.7)	73 (70.2)
Diarrhoea	3 (75)	13 (48.1)	8 (57.1)	21 (47.7)	6 (60)	32 (53.3)	14 (58.3)	53 (51)
Depression	0	11 (40.7)	5 (35.7)	20 (45.5)	2 (20)	32 (53.3)	7 (29.2)	52 (50)
Blood Bilirubin[b]	3 (75)	15 (55.6)	4 (28.6)	20 (45.5)	4 (40)	31 (51.7)	8 (33.3)	51 (49)
Skin Disorder	3 (75)	10 (37)	5 (35.7)	15 (34.1)	5 (50)	23 (38.3)	10 (41.7)	38 (36.5)
Activated PTT	2 (50)	8 (29.6)	7 (50)	15 (34.1)	4 (40)	19 (31.7)	11 (45.8)	34 (32.7)
Blood Glucose[b]	1 (25)	10 (37)	5 (35.7)	11 (25)	3 (30)	22 (36.7)	8 (33.3)	33 (31.7)
Antithrombin III[a]	1 (25)	4 (14.8)	4 (28.6)	13 (29.5)	3 (30)	15 (25)	7 (29.2)	28 (26.9)
Myalgia	1 (25)	3 (11.1)	4 (28.6)	7 (15.9)	2 (20)	20 (33.3)	6 (25)	27 (26)
Creatinine	2 (50)	9 (33.3)	1 (7.1)	12 (27.3)	2 (20)	12 (20)	3 (12.5)	24 (23.1)
Blood Fibrinogen	2 (50)	4 (14.8)	3 (21.4)	9 (20.5)	3 (30)	14 (23.3)	6 (25)	23 (22.1)
Weight[b]	1 (25)	11 (40.7)	3 (21.4)	9 (20.5)	1 (10)	12 (20)	4 (16.7)	21 (20.2)
Myopathy Toxic	1 (25)	7 (25.9)	5 (35.7)	10 (22.7)	0	10 (16.7)	5 (20.8)	20 (19.2)
Neurotoxicity	0	3 (11.1)	0	7 (15.9)	0	13 (21.7)	0	20 (19.2)
Gastritis	0	4 (14.8)	3 (21.4)	10 (22.7)	0	9 (15)	3 (12.5)	19 (18.3)
Oedema	1 (25)	6 (22.2)	1 (7.1)	5 (11.4)	3 (30)	10 (16.7)	4 (16.7)	15 (14.4)
Hematuria	1 (25)	3 (11.1)	2 (14.3)	4 (9.1)	1 (10)	6 (10)	3 (12.5)	10 (9.6)
Proteinuria	1 (25)	0 (0)	2 (14.3)	5 (11.4)	2 (20)	4 (6.7)	4 (16.7)	9 (8.7)
Melena	0	2 (7.4)	1 (7.1)	1 (2.3)	0	8 (13.3)	1 (4.2)	9 (8.7)
Euphoric Mood	0	1 (3.7)	3 (21.4)	5 (11.4)	0	3 (5)	3 (12.5)	8 (7.7)
Arrhythmia	1 (25)	1 (3.7)	0	4 (9.1)	1 (10)	3 (5)	1 (4.2)	7 (6.7)
Left Ventricular Dysfunction	1 (25)	1 (3.7)	1 (7.1)	1 (2.3)	1 (10)	3 (5)	2 (8.3)	4 (3.8)
Cardiac Failure	0	1 (3.7)	0	2 (4.5)	1 (10)	2 (3.3)	1 (4.2)	4 (3.8)
Gastric Ulcer	0	0	0	1 (2.3)	0	2 (3.3)	0	3 (2.9)
Thrombosis	1 (25)	0	0	1 (2.3)	0	1 (1.7)	0	2 (1.9)
Osteonecrosis	0	0	0	0	0	1 (1.7)	0	1 (1.0)

[a] Decrease in laboratory parameter
[b] Increase in laboratory parameter
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- The table includes treatment phases up to HR3 Block (Consolidation 3).
Source: [Study AIT07-Table 14.3-1.3]. [Study AIT07- Table 14.3-1.4]

8.6. Post-marketing data

In relation to post-marketing data a worldwide literature search was performed to capture any investigator reports on safety aspects which were not included in study reports. This did not provide any evidence of unexpected or unknown events that would be attributable to treatment with Imatinib, confirming the established safety and tolerability profile of Imatinib.

8.7. Evaluator's conclusions on safety

These two studies have essentially shown that the principal impact of adverse events relates to the intensive chemotherapy received by the patient. The addition of Imatinib resulted in a small increase in potential for selected toxicities in the pivotal study 2301 but not noted in study AIT07. Overall the safety profile of Imatinib when used in combination with chemotherapy appears to be consistent with the known safety profile of Imatinib and consistent with that previously determined for those adult patients with Ph positive ALL receiving Imatinib in conjunction with chemotherapy. There was no evidence that younger patients less than 4 years experienced a greater potential for adverse events in relation to the use of Imatinib.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The pivotal study 2301 certainly demonstrated evidence that the addition of Imatinib to chemotherapy following initial induction was associated with a prolongation in event free survival as the primary end point of this trial. Greater efficacy was apparent for the longer duration of administration of Imatinib as determined within cohort 5 and the estimated 48 month event free survival for this cohort was more than twice i.e. 69.6% that of historical controls i.e. 31.6% with an HR 0.28 and log rank $P < 0.0001$. There was also evidence of prolongation of overall survival at 48 months in relation to cohort 5 compared to historical controls i.e. 83.6% versus 44.8% with an HR of 0.23 and log rank $P < 0.0001$. There is also evidence of significant benefit for patients receiving the longest duration of Imatinib as in cohort 5 when compared with the shorter durations as in cohorts 1 and 2 with values being 0.0101 and also similarly for overall survival with a P value at 0.0091. It is of interest that there was a difference for overall survival in favour of cohort 5 excluding HSCT versus HSCT overall at the cohorts both off protocol HSCT and all HSCT showing that the therapeutic benefits in cohort 5 did not result from a therapeutic effect of HSCT and patients undergoing HSCT did not have better outcomes than patients receiving Imatinib in addition to chemotherapy alone in cohort 5.

These data for patients with Ph positive ALL following on earlier studies demonstrating benefit for the addition of Imatinib in Ph positive CML in the paediatric population. Nevertheless this evaluator still has concerns regarding the evidence of benefit for Imatinib in the pivotal study taking into account that the comparison is with historical controls which were conducted by the COG various years earlier and information regarding the nature and intensity of induction therapies for these studies is not provided. This raises the question as to whether the historical controls represent a comparable group to the study population.

9.2. First round assessment of risk

The safety profile of Imatinib observed in the studies 2301 and AIT07 were consistent with the known safety profile for this agent. The adverse events observed also confirmed that the Imatinib dosing regimen were therapeutically appropriate for the paediatric patient population and did not adversely impact known drug adverse event characteristics.

In study 2301 the overall incidence of preselected targeted toxicities and non-targeted adverse events were higher in the Ph positive ALL patients receiving chemotherapy plus Imatinib compared with Ph negative patients receiving chemotherapy alone. There was however an overall lower frequency of death i.e. 23.9% for patients who received Imatinib in contrast with the control group that did not receive Imatinib at 44.6%. There were no clinically relevant differences in the development of targeted toxicities and non-targeted adverse events between Ph positive and Ph negative ALL patients.

In study AIT07 the overall frequency of adverse events including those serious and non-serious were again similar between those patients receiving chemotherapy alone versus those who received chemotherapy plus Imatinib. There were no clinically relevant differences observed in the nature of adverse events across patient groups. There was a small increase in the frequency of adverse events between 5 to 10% when comparing the patients treated with Imatinib plus chemotherapy to those patients who received chemotherapy alone however the proportion of good risk patients experiencing serious adverse events was 27.6% and deaths 15.5% which was lower (in the population with Imatinib) then the population with chemotherapy alone at 32% and 25% respectively.

It is worth commenting that the four year evaluation data from the pivotal study has not shown any evidence of development of longer term adverse effects for this paediatric population. Nevertheless ongoing review of these patients remains appropriate.

It is also noted that the optimum long term duration of administration of Imatinib still remains somewhat uncertain both in terms of its potential use in induction as well as longer maintenance therapies for patients with Ph positive ALL.

9.3. First round assessment of benefit/risk balance

The efficacy results from the pivotal study 2301 has certainly shown benefit for the addition of Imatinib in improving both EFS and overall survival when compared to historical control. This was most apparent in those who received Imatinib for the longest duration of time. These favourable data are in line with that previously observed for paediatric patients with Ph positive CML and adult patients with Ph positive ALL. Nevertheless this evaluator has some reservation in relation to study 2301 in regards to the precise comparability of the historical control group to the study group.

Evaluation of adverse events from both the pivotal study 2301 and the supportive study AIT07 have shown no evidence of an increase potential for adverse events in the paediatric population receiving Imatinib compared to the known toxicity profile for Imatinib in both other paediatric populations and adult populations receiving this agent. There is if anything some evidence that both serious adverse events and deaths are perhaps reduced by the influence of Imatinib in combination with chemotherapy for this paediatric patient population.

10. First round recommendation regarding authorisation

On balance this evaluator considers it appropriate to approve Imatinib for the proposed new indication for the treatment of adult and paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia integrated with chemotherapy. This recommendation is made on the basis of the efficacy results and their comparability with adult patients with Ph positive ALL with the addition of Imatinib and the paediatric population with Ph positive CML with the addition of Imatinib. Nevertheless the reservations as stated above in relation to the historical control group remain. Certainly there is no evidence from evaluation of adverse events from the two studies assessed to raise extra concerns regarding the role of Imatinib for the Ph positive ALL paediatric population.

11. Clinical questions

This evaluator would seek additional information regarding the nature of induction chemotherapy for the various COG studies utilized as historical controls for the pivotal trial 2301.

Further information on the longer term influence of Imatinib administration both as part of induction therapy and maintenance therapy for Ph positive ALL would be of interest.

12. Second round evaluation of clinical data submitted in response to questions

[Note: The sponsor's response to the clinical questions were evaluated by the Delegate in the Overview for this application (see section on Risk-Benefit Analysis in the AusPAR for this application)]

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au