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Oncology Clinical Development

Imatinib/STI571/Glivec®

Non-Interventional Study Protocol
CSTI571I2201

A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Philadelphia-positive (Ph+) Acute Lymphoblastic Leukemia (ALL) patients treated with chemotherapy + imatinib (+/-) hematopoietic stem cell treatment (+/-)HSCT)

Protocol version identifier	02 (Amended protocol)
Date of last version of protocol	27-Mar-2017 (Clean)
EU PAS register number	ENCEPP/SDPP/6665
Active substance	imatinib mesylate [L01XE01]
Medicinal product	Glivec®
Product reference	EU/1/01/198/001-013
Procedure number	EMEA/H/C/000406

Marketing authorization holder(s)	Novartis Pharma Services AG
Joint PASS	No
Research questions and objectives	Positive benefit-risk profile of imatinib in combination with chemotherapy in newly diagnosed pediatric Ph+ ALL patients is based on a limited number of patients. The primary objective is to evaluate long-term clinical outcome measured by event-free survival (EFS). Secondary objectives include overall survival (OS) and safety in newly diagnosed Ph+ ALL pediatric patients treated with imatinib in combination of chemotherapy primarily in European countries. This multi-center, observational registry is not designed to test a formal hypothesis, but has been initiated as part of a post-marketing commitment.
Country (-ies) of study	European Countries, Non-EU Countries e.g. Russia, Ukraine - *(Feasibility ongoing)*
Authors	[redacted]

Table of contents

List of tables

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
ASH	American Society of Hematology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical
BCR	Breakpoint Cluster Region
BM	Bone Marrow
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CHR	Complete Hematologic Remission
CML	Chronic Myeloid Leukemia
CMO&PS	Chief Medical Office & Patient Safety
COG	Children's Oncology Group
CPO	Country Pharma Organization
CR	Complete Remission
CRF	Case Report/Record Form
CRO	Contract Research Organization
CSF-1R	Colony Stimulating Factor Receptor
CTCAE	Common Terminology Criteria for Adverse Events
DDR	Discoidin Derived Factors
eCRF	electronic Case Report/Record Form
EC	Ethics Committee
EDC	Electronic Data Capture
EFS	Event Free Survival
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FISH	Fluorescence in situ Hybridization
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HSCT	Hematopoietic Stem Cell Treatment
ICMJE	International Committee of Medical Journal Editors
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LPLV	Last Patient, Last Visit
LPFV	Last Patient, First Visit
MedDRA	Medical Dictionary for Regulatory Activities

MRD	Minimal Residual Disease
NIS	Non-interventional Study
OS	Overall Survival
NI-PASS	Non- Interventional Post-Authorization Safety Study
PDGFR	Platelet-Derived Growth Factor Receptor
Ph+	Philadelphia Chromosome positive
PHI	Protected Health Information
PI	Principal Investigator
PMC	Post-Marketing Commitment
PRAC	Pharmacovigilance Risk Assessment Committee
RAP	Results Analysis Plan
REB	Research Ethics Board
RSI	Reference Safety Information
RT-PCR	Real Time - Polymerase Chain Reaction
RMP	Risk Management Plan
SAE	Serious Adverse Event
SCF	Stem Cell Factor
SDS	Standard Deviation Score
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TKI	Tyrosine Kinase Inhibitor
VHR	Very High Risk
WBC	White Blood Cell
WHO	World Health Organization

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
Main protocol author(s)	[redacted], [redacted] Novartis Pharmaceuticals Corporation [redacted], [redacted] Novartis Pharma Services AG [redacted], [redacted] Novartis Pharma Services AG [redacted], [redacted] Novartis Pharmaceuticals Corporation [redacted], [redacted] Novartis Pharmaceuticals Corporation
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2 Abstract

Title	A European observational registry collecting efficacy and safety data in newly diagnosed pediatric Ph+ Acute Lymphoblastic Leukemia (ALL) patients treated with chemotherapy + imatinib ± HSCT
Version and Date	02 (amended protocol) – 27-Mar-2017
Name and affiliation of main author	[redacted], Novartis Pharmaceutical Corporation
Rationale and background	The purpose of this non-interventional, observational study is to collect long-term efficacy and safety data of imatinib in combination with chemotherapy with or without hematopoietic stem cell treatment (±HSCT) in newly diagnosed Ph+ ALL pediatric patients. This registry was requested by the EMA as a post-marketing commitment to the type II variation EMEA/H/C/000406/II/80, related to the limited size of the safety database. EMA requested additional efficacy and safety data in the target population. This is an EMA imposed non-interventional post-authorization safety study (NI-PASS), conducted per GVP module VIII.
Research question and objectives	Positive benefit-risk profile of imatinib in combination with chemotherapy in newly diagnosed pediatric Ph+ ALL patients is based on a limited number of patients. The primary objective is to evaluate long-term clinical outcome measured by event-free survival (EFS). Secondary objectives include overall survival (OS) and safety in newly diagnosed Ph+ ALL pediatric patients treated with imatinib in combination with chemotherapy, primarily in European countries. This multi-center, observational registry is not designed to test a formal hypothesis, but has been initiated as part of a post-marketing commitment.
Study design	This study is an observational, multi-center disease registry to collect efficacy and safety data in Ph+ ALL pediatric patients treated with chemotherapy + imatinib, with or without hematopoietic stem cell treatment (±HSCT), primarily in European countries. The study concept was endorsed by the EMA as part of the post-marketing commitment EMEA/H/C/000406/II/80 and the design is aligned with ensuing discussions, as well as routine medical practice in the treatment of newly diagnosed Ph+ ALL in pediatric patients across Europe. For each patient enrolled in the registry, a minimum of 5 years observational follow-up data will be collected or such available data until early discontinuation, as measured from the date of start of imatinib treatment.

Population	The study population will include male or female pediatric patients (ages 1 to <18 years old) with documented, newly diagnosed Ph+ ALL who enrolled into this registry within 6 months of diagnosis or were enrolled in a clinical trial within 6 months of diagnosis (although no earlier than Jan-2012), and who were previously treated or are currently on treatment with chemotherapy + imatinib ± HSCT. Long term safety and efficacy data will be collected such that the observational follow-up data for each patient will be a minimum of 5 years from start of imatinib treatment. The registry has a planned enrollment of a minimum of 50 patients.
Variables	EFS, defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death. OS, defined as time from diagnosis to death from any cause. Safety defined as adverse events and serious adverse events in the observation period.
Data sources	The data for this study will be retrieved from hospital discharge files, clinical records and electronic medical records.
Study size	50 patients
Data analysis	All data analyses will be performed by Novartis personnel and/ or designee. All data summaries and analyses will have descriptive purposes only. Patient efficacy, safety and tolerability outcomes of patients treated with chemotherapy + imatinib will be summarized overall, by HSCT (yes/ no) and risk group (good risk– induction responder/ poor risk– induction non-responder).
Milestones	Start of data collection: 14 July 2014 Study progress report(s): Yearly update (Q4) Planned final report of study results: June 2022

3 Amendments and updates

Amendment 2

The main purpose of this amendment is to change in the reference safety information for Glivec (imatinib).

Novartis has taken the decision to discontinue the use of the Investigator´s Brochure for Glivec® (imatinib), since Glivec has been on the market for more than 15 years (first registered in 2001) and has a well-established efficacy/safety profile. In addition, there is no further global clinical development planned for the compound.

As of the dispatch of the Glivec DSUR 006 in July 2017, the latest approved national/regional product label (e.g. in the EU Summary of Product Characteristics) will serve as the reference safety information (RSI) for the compound.

The Glivec Investigator's Brochure version 19 (dated 21-Jun-2016) is the final Investigator's Brochure for the compound.

At the time of this amendment, 44 patients were screened, 3 failed screening and 41 were enrolled. Enrollment was ongoing at the time of this amendment.

Amendment 1

The rationale for making the proposed changes in this amendment is based on the following points.

Accrual to this registry has been challenging for many reasons. First, Ph+ ALL in the pediatric population is a rare condition. As such, finding patients for the registry has been

more difficult than previously projected. In addition, imatinib is not yet available for all countries for the pediatric indication. Given these reasons, and in light of the need to provide adequate 5-year follow up on the study population in a timely manner, it has been decided to amend the number of patients to be studied from 100 to a minimum of 50. Other changes have been included now as well reflecting administrative updates. These are delineated in the table below.

At the time of this amendment, 17 patients were screened, 3 failed screening and 14 were enrolled. Enrollment was ongoing at the time of this amendment.

Table 3-1 Study protocol amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	01-Feb-2016	Section 4	Study milestone dates revised	Updated to reflect current status
1	01-Feb-2016	Section 6	Acute or chronic added to incidence of graft versus host disease	To be consistent with Section 7.7.4.3
1	01-Feb-2016	Section 7.1.1	Patient population reduced to a minimum of 50	Recruitment efforts during the first year confirmed the rarity of this patient population. The sample size has been changed to 50 pts accordingly.
1	11-May-2016	Section 7.1.4	Definition of end of study further clarified	Clarify each patient will have a minimum of 5 years of follow up from the start of imatinib treatment
1	01-Feb-2016	Section 7.2.5	Disease progression removed from the list of potential reasons for study discontinuation	Not applicable to this study
1	01-Feb-2016	Section 7.3.1.6	Added/clarified definitions of time to engraftment and engraftment failure	For clarity
1	01-Feb-2016	Section 7.3.1.8	Revised definition of AE reporting period	For consistency
1	01-Feb-2016	Section 7.3.1.9	Duration of treatment for assessment of drug exposure further defined	For clarity
1	01-Feb-2016	Table 7-1	Data collection schedule updated to include on treatment follow up and post end of treatment follow up	Provide more clarity surrounding time points for data collection during surveillance period as data are collected during and post imatinib treatment.
1	01-Feb-2016	Section 7.4.2.7	Clarified time point at which AE collection vs. medical history will be recorded	For consistency
1	01-Feb-2016	Section 7.5	Patient population reduced to a minimum of 50	Recruitment efforts during the first year confirmed the rarity of this patient population. The sample size has been changed to 50 pts accordingly.
1	01-Feb-2016	Section 7.7	Definition of treatment and other secondary endpoints updated	For clarity

Number	Date	Section of study protocol	Amendment or update	Reason
1	01-Feb-2016	Section 9	Revision of wording in safety section	As per revised NIS protocol template primary data collection version 2.0 date 15-Sep-2015
1	01-Feb-2016	Section 9.4	Removed statement regarding pregnancy outcomes for female partners of males taking the drug of interest	Not applicable to this study
2	13-Feb-2017	List of Abbreviations	"Investigator Brochure" and DS&E removed, CMO&PS and RSI added	Investigator's Brochure is being retired, nomenclature of safety group revised, new term introduced in amendment rationale (RSI)
2	13-Feb-2017	Section 5.3	Reference to Investigator's Brochure removed	Investigator's Brochure is being retired
2	13-Feb-2017	Section 9.2	Reference to Investigator's Brochure removed	Investigator's Brochure is being retired
2	13-Feb-2017	Section 9.3	Reference to Investigator's Brochure removed	Investigator's Brochure is being retired
2	22-Mar-2017	Section 7.3.1.8	DS&E replaced by CMO&PS	Nomenclature updated
2	27-Mar-2017	Section 7.6.1	Replaced "violations" with "deviations"	Provide consistency throughout the document
2	22-Mar-2017	Section 7.6.1.1	DS&E replaced by CMO&PS	Nomenclature updated
2	22-Mar-2017	Section 7.6.1.2	DS&E replaced by CMO&PS	Nomenclature updated
2	22-Mar-2017	Section 9.1	DS&E replaced by CMO&PS	Nomenclature updated
2	22-Mar-2017	Section 9.3	DS&E replaced by CMO&PS	Nomenclature updated
2	22-Mar-2017	Section 9.4	DS&E replaced by CMO&PS	Nomenclature updated

4 Milestones

Table 4-1 Study milestones

Milestone	Planned date
Start of data collection	14 July 2014
Planned study progress report(s)	Yearly update (Q4)
Planned final report of study results	June 2022

5 Rationale and background

5.1 Study rationale and purpose

Efficacy and safety data from studies COG-AALL0031 (*a Phase III, Children's Oncology Group pilot study for the treatment with imatinib of very high risk acute lymphoblastic leukemia in children and adolescents* - 92 imatinib-treated patients STI571I2301) and EsPhALL (*a Phase II/III, open label, randomized study to compare safety and efficacy of imatinib with chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia* - 128 imatinib-treated patients STI571AIT07) was supportive of a positive benefit/ risk ratio of imatinib in combination with chemotherapy in newly-diagnosed pediatric Ph+

ALL patients. Data from these two studies were submitted to Health Authorities worldwide and as a result imatinib received approval for the indication of newly diagnosed pediatric Ph+ ALL in combination with chemotherapy.

Upon review of data from studies COG-AALL0031 and EsPhALL, EMA issued an approval for the indication and requested additional data as a post-marketing commitment to the type II variation EMEA/H/C/000406/II/80, in order to address the limitations related to the limited size of the studies. The variation type II/80 was to extend the indication for the treatment of pediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy. The precise uncertainties stemmed from the COG-AALL0031 study design (a non-standard phase III confirmatory trial), the sample size (50 assigned to the proposed treatment regimen (cohort 5), influence of the risk factors among the cohorts and the use of historical controls. Given that current medical practice recommends the use of TKIs in the treatment of Ph+ ALL in children, the EMA acknowledged that a true comparative phase III study was unfeasible. In order to provide additional data in this population and address these uncertainties, the EMA requested this "Non-Interventional, Post-Authorization Safety Study (NI-PASS)", which will be conducted primarily in Europe.

The purpose of this non-interventional, observational study is to collect long-term data relative to the efficacy and safety of imatinib in combination with chemotherapy ± HSCT in newly diagnosed Ph+ ALL pediatric patients. The term registry is used synonymously with the terms non-interventional study (NIS) and observational study in this instance, and thus does not involve any kind of intervention, experimental or otherwise.

5.2 Overview of Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL)

Acute lymphoblastic leukemia (ALL) is the most common malignancy in the pediatric population (approximately 80% of childhood leukemias and 25% of all pediatric cancers), with an annual incidence rate of 1-4 new cases per 100,000, with a peak incidence at ages 2-5 years (Pui et al. 2008, Stanulla and Schrappe, 2009). Philadelphia positive acute lymphoblastic leukemia (Ph+ ALL) is characterized by the presence of the Philadelphia chromosome, a reciprocal translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)) resulting in the fusion of the breakpoint cluster region (bcr) gene on chromosome 22 with c-abl gene sequences translocated from chromosome 9 and the expression of the BCR-ABL protein. Ph+ ALL accounts for up to 5% of pediatric ALL (Faderl et al. 2002).

Factors affecting the risk of ALL relapse include age, white blood cell (WBC) counts at diagnosis, presence and type of genetic abnormalities, and response to initial induction therapy. With regard to clinical factors, a poorer outcome is associated with children <1 year and >9 years of age and those with an increasing leukocyte count (Pui et al. 2006, Pui et al. 2008). Pediatric patients with B-lineage ALL are categorized as low risk, standard risk, high risk or very high risk (VHR) (Pui 2001a, Pui et al. 2001b). Pediatric Ph+ ALL is a subtype of VHR ALL, characterized by an older age (median 9-10 years vs. approximately 4-years for all pediatric ALL patients) and higher WBC counts at diagnosis. The presence of the Ph+ chromosome renders a patient very high risk ALL with a high risk of relapse and poor prognosis.

The treatment of ALL is not homogenous. Patients with high risk disease are at higher risk of relapse and receive more intensive chemotherapy than low risk patients. There is no standard chemotherapy regimen in ALL. Treatment of newly diagnosed ALL patients typically consists of several treatment phases, i.e. induction, consolidation, and maintenance. Prior to the development of imatinib, Ph+ ALL patients were treated with intensive chemotherapy followed by hematopoietic stem cell transplant (HSCT), ideally with a matched related donor, as this was shown to result in improved event-free survival (EFS) compared to either HSCT with other donors or chemotherapy alone (Arico et al. 2000).

Data from the literature show minimal improvements in patient outcomes over time due to improved chemotherapy regimens and transplantation. In 2000, Arico et al reviewed the medical records of 326 children with Ph+ ALL who were treated with intensive chemotherapy only, with or without bone marrow transplantation, by 10 study groups or large single institutions from 1986 to 1996 (Arico et al. 2000). In 2010, the same group performed a similar analysis on 610 children treated during the following decade, from 1995 to 2005 (Arico, 2010). The 7-year event-free survival and overall survival rates were only slightly superior in the 2010 cohort compared with the previous cohort (32% vs 25% EFS and 45% vs 36% OS). This comparison shows only modest improvements with more intensive and current treatment regimens.

The positive benefit-risk profile of adding imatinib to chemotherapy in Ph+ ALL pediatric patients was shown in studies COG-AALL0031 and EsPhALL. Study COG-AALL0031 showed remarkable results with respect to the primary efficacy endpoint of EFS and superior efficacy outcomes versus historical control data in patients treated only with chemotherapy ± HSCT (Section 5.3.1).

5.3 Overview of imatinib

Imatinib (Glivec®, known as Gleevec® in US/Canada); 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamidemethanesulfonate, STI571) is a small molecule protein-tyrosine kinase inhibitor that potently inhibits the activity of the BCR-ABL1 tyrosine kinase (TK), as well as several receptor TKs: c-KIT, the receptor for stem cell factor (SCF), the discoidin domain receptors (DDR1 and DDR2), the colony stimulating factor receptor (CSF-1R) and the platelet-derived growth factor receptors α and β (PDGFR-α and PDGFR-β). Glivec® consequently inhibits the cellular events mediated by activation of these receptor kinases.

Imatinib is currently approved in over 110 countries for the treatment of both hematological malignancies and solid tumors. Imatinib is already approved for pediatric indications (pediatric patients with newly diagnosed Ph+ CML for whom bone marrow transplantation is not considered as the first line of treatment, for pediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in blast crisis or accelerated phase) at a recommended dose of 340 mg/m^2 daily. In addition, Imatinib is currently approved in the EU for the treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy at a recommended dose of 600 mg/day. Imatinib is also approved as monotherapy in the EU and US for the treatment of adult patients with relapsed or refractory Ph+ ALL.

A full overview of imatinib, including a detailed description of efficacy and safety data from non-clinical experience can be found in the Summary of Product Characteristics (SmPC).

5.3.1 Clinical experience of imatinib in pediatric Ph+ ALL

The imatinib pediatric Ph+ ALL submission presented efficacy data from pivotal Study COG-AALL0031 in 92 patients treated with imatinib in combination with chemotherapy, 50 of whom received continuous imatinib in combination with chemotherapy. These efficacy data were compared with data from 120 Ph+ ALL historical control patients. Results from Study COG-AALL0031 demonstrated improved event free survival (EFS) (estimated EFS rate at 48 months was 69.6% in cohort 5, more than twice that of the historical control group at 31.6%; HR=0.28 and log rank p<0.0001) for pediatric patients with newly diagnosed Ph+ ALL when treated with imatinib continuously in combination with intensive chemotherapy compared to historical control patients treated with chemotherapy alone. The beneficial effects of imatinib were also reflected in the overall survival (OS) results (estimated OS rate at 48 months was 83.6% in cohort 5 compared to 44.8% in the historical control group; HR=0.23, log-rank p<0.0001).

The safety data presented in the submission included 220 patients treated with imatinib from both pivotal Study COG-AALL0031, (92 imatinib-treated patients) and supportive Study EsPhALL (128 imatinib-treated patients). In addition, comparison of safety data was made with data from 65 Very High Risk (VHR) Ph-negative patients included in COG-AALL0031 who received a similar backbone chemotherapy regimen without imatinib therapy. The safety profile of imatinib observed in pediatric Ph+ ALL studies COG-AALL0031 and EsPhALL was consistent with the known safety profile for this compound in both adult and pediatric indications. No new safety concerns were identified for imatinib use in these studies.

Overall, efficacy and safety data presented in the submission was supportive of a positive benefit/risk ratio in pediatric Ph+ ALL patients.

A combined submission package of the COG-AALL0031 and EsPhALL study data resulted in the approval of the following indication EMEA/H/C/000406/II/80: Imatinib is indicated for pediatric patients with newly diagnosed Ph+ ALL integrated with chemotherapy. This indication was approved by the European Commission on 28-Jun-2013 based on a positive benefit-risk profile. The EMA has also requested to collect long-term efficacy and safety data as a post-marketing commitment (PMC) to this type II variation EMEA/H/C/000406/II/80. This pediatric registry would fulfill this PMC.

6 Research question and objectives

The main objective is to collect data to describe long-term clinical outcomes measured by event-free survival (EFS), overall survival (OS) and long-term safety in newly diagnosed Ph+ ALL pediatric patients treated with imatinib in combination with chemotherapy

This multi-center, registry is not designed to test a formal hypothesis, but has been initiated as part of the post-marketing commitment to the type II variation EMEA/H/C/000406/II/80, in order to address the limitations related to the limited size of the efficacy and safety database (up to 92 patients evaluated for efficacy and 220 patients evaluated for safety in prospective studies).

Objectives and related main variables under study are described in Table 6-1 below.

Table 6-1 Objectives and related main variables

Objective	Main Variables	Analysis
Primary		Refer to Section 7.7
To evaluate long term clinical outcome measured by event-free survival (EFS, events defined as: relapse, death , secondary malignancies)	EFS, defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death.	
Main secondary		
To evaluate overall survival	OS, defined as time from diagnosis to death from any cause.	
To evaluate safety	Adverse events and serious adverse events in the observation period.	
Other secondary		
To evaluate hematological remission status	Hematological remission status. Complete hematological remission requires that all of the following are present: a) Adequate bone marrow cellularity with a blast count < 5%, b) No peripheral blood blasts, c) ANC ≥1500/µl, d) Platelet count ≥100.000/µl, e) No evidence of extramedullary involvement	
To evaluate minimal residual disease (MRD) response	MRD response evaluated via detection of BCR-ABL transcript (e.g. determined via quantitative real-time PCR of mononuclear bone marrow and peripheral blood cells or detection by flow cytometry).	
To evaluate duration of complete remission	Complete remission and duration of complete remission (CR, defined as <5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes).	
To evaluate time to transplantation, time to engraftment, engraftment failure, graft versus host disease	Transplant and time to transplant from diagnosis. Time to engraftment and engraftment failure Incidence of graft versus host disease (acute and chronic)	
To assess growth and development	Standard measures of growth and development e.g. general physical examination, height, weight, and Tanner staging.	

7 Research methods

7.1 Study design

7.1.1 Description of study design

This study has been designed as an observational, multi-center registry to collect efficacy and safety data in Ph+ ALL pediatric patients (ages 1 to <18 years old) treated with chemotherapy + imatinib, with or without hematopoietic stem cell treatment (±HSCT) primarily in European countries. The study concept was endorsed by the EMA as part of the post-marketing commitment EMEA/H/C/000406/II/80 and the design is aligned with ensuing discussions, as well as current medical practice in the treatment of newly diagnosed Ph+ ALL in pediatric patients across Europe.

A minimum of 50 pediatric patients meeting eligibility criteria after informed consent signature will be enrolled into the registry primarily from European countries, with some limited recruitment from non-EU countries, e.g. Russia, Ukraine. Due to the descriptive nature of this registry and the lack of a specific hypothesis to be tested, no formal sample size calculation exists. Medical feasibility is ongoing, although enrollment in Europe is estimated at a rate of 20 patients per year (or less). Enrollment may be supported through cooperation with approved, clinical trials (e.g. EsPhALL Study). The EsPhALL Study is an ongoing Phase II/III, open label, randomized study designed to compare safety and efficacy of imatinib with chemotherapy in pediatric patients with Ph+/BCR-ABL+ acute lymphoblastic leukemia. The trial is registered with EudraCT (2004-001647-30) and clinicaltrials.gov - number NCT00287105.

The registry will capture an observational follow-up period of minimum 5 years for each enrolled patient, or such information until early patient discontinuation (Section 7.1.4), as measured from the date of start of imatinib treatment. For the period whilst the database is open, retrospective additions to or revisions of the entered data will be possible at any time as additional or corrective data emerges. For patients meeting all inclusion criteria, enrollment is defined as having occurred on the date of patient inclusion into the registry (i.e. signature of informed consent).

No prospective clinical, instrumental or laboratory assessments/ interventions will be performed other than those required for disease management according to local best practice or locally approved summary of product characteristics or as stipulated in a clinical trial protocol, if a patient is taking part in a clinical trial in parallel with this registry (e.g. EsPhALL Study).

The population will include patients at different stages of chemotherapy + imatinib treatment upon their enrollment into this registry (Section 7.2.1). For the purposes of this registry, and in order to achieve its objectives, the notions of “baseline” and “follow-up” are entirely independent of the timing/ date of patient registry enrollment.

- The notion of "baseline" will consist of patient pre-treatment information from the time of diagnosis until just prior to start of treatment with imatinib.
- The notion of "follow-up" information will comprise any data collected by the treating physician and/ or designee from the start of imatinib onwards (i.e. post-"baseline"), regardless of whether this was prior to or after the date of registry enrollment.

Patient follow-up visits (whether prior to or after registry enrollment) will be scheduled according to the standard practice of the site and to the treating physician's best judgment or as specified in the visit schedule of any clinical trial in which the patient may be or may have been enrolled. Where disease evaluation is performed frequently, any follow-up information collected that is relevant to the objectives of this registry should be recorded in the database. Data will be collected such that the observational follow-up for long term safety and efficacy will be a minimum 5 years for each enrolled patient or such available data until early patient discontinuation.

Efficacy assessments will include standard long-term outcomes such as Overall Survival (OS) and Event Free Survival (EFS) (Section 7.4.2.3). Minimal Residual Disease (MRD) will be assessed at appropriate time points (Section 7.4.2.5). In terms of long-term safety, adverse events and serious adverse events in the observation period will also be collected.

Disease management, disease status and therapeutic interventions will be recorded. Follow-up will capture patient and disease status, response to treatment and treatment/ regimen changes at a frequency defined by the standard practice of each site.

Designated registry staff will enter the data into an electronic Case Report Forms (eCRFs) through a web-based internet system using fully validated software that conforms to regulatory requirements for electronic data capture. For each patient enrolled in this registry a minimum of a once yearly update of data in the registry database must occur (12 ±2 month intervals).

7.1.2 Rationale for registry design

The study objective is to provide additional data to support the positive benefit-risk profile of imatinib in newly diagnosed pediatric Ph+ ALL patients. ALL is a common malignancy in the pediatric population but Ph+ ALL only accounts for up to 5% of pediatric ALL, which makes it a rare disease. Therefore, the conduct of multiple or large clinical trials in this patient population is not feasible. In addition, considering the remarkable benefit shown by the addition of imatinib to chemotherapy in Study COG-AALL0031 (Schultz et al. 2009), newly diagnosed Ph+ ALL pediatric patients have been treated with imatinib in clinical practice for some time and a prospective randomized trial with a "no imatinib" arm would be unethical in this patient population.

The NI-PASS registry design has been requested by EMA. In such, the medicinal product, imatinib, should be prescribed in a usual manner, according to the terms of the marketing authorization. The therapeutic strategy assigned to the patient is not proscribed by this registry protocol, but should fall within current medical practice. In order to clearly separate the decision to prescribe medication from the decision to include a given patient in this registry, there will be no central provision of medication. In summary, given the rarity of the disease, current clinical practice and unfeasibility of a randomized design, an observational study in

imatinib-treated patients is the optimal way to obtain prospective data in a standardized manner and address the study objective. A registry design permits the large scale capture of information across a sizeable international cohort of pediatric patients with newly diagnosed Ph+ ALL, producing a representative dataset without bias towards demographic or social characteristics.

7.1.3 Timing of interim analyses / study status reporting

Per EMA agreement, a study status update of the registry will be provided annually for the duration of the study. A final analysis will be performed after registry end of study.

7.1.4 Definition of the end of study

The end of study is defined as the point when a minimum of 5 years of observational follow-up data are available for each enrolled patient, or such available data until early discontinuation (Section 7.2.5), as measured from the date of start of imatinib treatment.

7.2 Setting

7.2.1 Population

The study population will include male or female pediatric patients (ages 1 to < 18 years) with documented, newly diagnosed Ph+ ALL, who enrolled into this registry within 6 months of diagnosis or were enrolled in a clinical trial within 6 months of diagnosis (although no earlier than Jan-2012), and who were previously treated or are currently on treatment with chemotherapy + imatinib ± HSCT.

Data from patients participating in past or present interventional or observational studies can be included in this registry. Any concurrent participation of pediatric patients from Ph+ ALL studies is subject to the aforementioned studies' alignment with the inclusion criteria listed in Section 7.2.2. Any specific criteria in the concurrent clinical trial protocol explicitly excluding a patient from participating in a registry would render the patient ineligible for this registry. Enrollment of patients into this registry from the EsPhALL Study has been discussed with and endorsed by EMA.

The enrollment of patients already on treatment when entering the registry population introduces the risk of selection bias, since such patients may have different characteristics to those who progressed and died before registry opening. As a consequence, every effort will be made to obtain data for this registry from all patients meeting the inclusion criteria, who enrolled in the EsPhALL Study from Jan-2012 onwards. This would include patients who may have died before registry opening, although this is subject to parent/ legal guardian consent and local regulations. Any chemotherapy regimen in combination with imatinib is permissible.

The investigator or designee must ensure that only patients who meet all of the following inclusion criteria are enrolled in the study.

7.2.2 Inclusion Criteria

Patients eligible for inclusion in this registry have to meet **all** of the following criteria:

1. Male or female, pediatric patients aged greater than 1 year (≥365 days) and less than 18 years old (<17 years, 365 days) at diagnosis.
2. Documented, newly diagnosed Philadelphia Chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL).
   - Recorded presence of t(9;22)(q34;q11) is required e.g. determined via institutional cytogenetics or FISH and/ or of the presence of BCR-ABL fusion transcript identified by RT-PCR or FISH.
3. Enrolled into this registry within 6 months of diagnosis or enrolled in a clinical trial within 6 months of diagnosis, although no earlier than Jan-2012.
4. Previously treated or currently on treatment with any chemotherapy regimen + imatinib (of an HA-approved formulation or HA-approved Glivec® generic) ± HSCT.
5. Written informed consent obtained prior to any information being entered into the registry (parent / legal guardian consent, where applicable).
   - Assent from a patient enrolled as a minor by parent / legal guardian consent **must** be obtained wherever possible. Obvious child dissent **must** be respected.
   - A patient enrolled as a minor by parent / legal guardian consent **must** be re-consented as an adult upon reaching the legal age of maturity during the course of the registry (legal age of maturity defined by local regulations).
   - Patients fulfilling the inclusion criteria, but who have died prior to registry opening and without the opportunity to give consent, may still be eligible for inclusion, subject to local requirements regarding the consent process.

The registry participating physician must assess whether there are any third-party agreements limiting the clinical trial patient's data collection as part of the non-interventional study given that no identification of proprietary treatment information will take place.

7.2.3 Exclusion Criteria

There are **no** exclusion criteria for this non-interventional study.

Patients may voluntarily withdraw from the registry at any time.

7.2.4 Reasons for non-inclusion

The reasons for non-inclusion in the registry will be recorded during pre-screening and classified as:

- Did not meet diagnostic criteria
  - Patients for whom the presence of t(9;22)(q34;q11) could not be determined/ confirmed or for whom diagnosis occurred outside of the specified age range or for whom diagnosis was greater than 6 months before first treatment.
- Subject consent not given (e.g. either by parent/ legal guardian or subject themselves)

- Alternative treatment choice (e.g. physician's decision not to treat with imatinib or to treat with a non-HA-approved, Glivec® generic).
- Unknown
- Other *(*please specify*)*

7.2.5 Reasons for discontinuation

The reasons for discontinuation from participation in the registry will be collected and classified as:

- Death
  - For patients who discontinue due to death, then 'Death' will be recorded as reason for discontinuation. Patient's date of death, cause of death and phase of disease during which death occurred will be recorded, as permitted by local regulations.
- Lost to follow up
  - Patients lost to follow up should be recorded as such on the CRF. For patients who are lost to follow-up, the treating physician and/ or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.
- Subject withdrew consent
- Administrative problems
- Treatment duration completed / condition no longer requires treatment
- Protocol deviation

7.3 Variables

A tabular overview of the main variables and their relationship to the defined objectives are outlined in Table 6-1.

The corresponding data collection schedule at each patient visit is contained within Table 7-1.

Detailed assessment information and the data to be collected, if available, are outlined in Section 7.4.2.

7.3.1 Outcomes of interest

7.3.1.1 Event free survival

- Event free survival is defined as time from diagnosis to relapse at any site, development of a second malignant neoplasm or death (Section 7.4.2.3)
  - Relapse at any site defined as BM (e.g. via bone marrow assessment) or CNS (e.g. via cerebro-spinal fluid exam) or testis or other sites or any combination.
  - Second malignant neoplasm defined as presence of any secondary malignancy.

7.3.1.2 Overall survival

- Overall survival is defined as time from diagnosis to death from any cause. i.e.Death information:- date and major cause (if applicable).

7.3.1.3 Hematological remission status

- Standard hematology panel, including required laboratory parameters to define complete hematological remission. Parameters for complete hematological remission defined in Section 7.4.2.4.

7.3.1.4 Minimal residual disease (MRD) response

- MRD response assessed via the detection of BCR-ABL transcript, collected at specified time-points. Time-points defined fully in Section 7.4.2.5. MRD response is defined as any negative level of MRD, i.e. MRD <0.01%.

7.3.1.5 Complete remission

- Complete remission is defined as < 5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes.
- The duration of complete remission is defined as the time from the date of first complete remission to the date of loss of complete remission (Section 7.4.2.4).

7.3.1.6 Time to transplant, time to engraftment, engraftment failure, graft versus host disease

- Time to transplant is defined from the date of diagnosis until the date of the transplant procedure.
- Time to engraftment (neutrophil, platelet and both neutrophil/platelet engraftment) is defined as the time from the date of transplant to the date of engraftment.
- Engraftment failure is defined as either definitive engraftment failure or the absence of engraftment.
- Presence/ absence of graft versus host disease; chronic or acute (Section 7.4.2.6).

7.3.1.7 Assessment of growth and development

- Physical examination information, including the standard growth & development measures of height and weight, and sexual maturity (Section 7.4.2.7, Section 7.4.2.9 and Section 7.4.2.10).

7.3.1.8 Safety

- Adverse events (including serious adverse events) from start of imatinib (Glivec®) treatment.

Solicited safety information including serious adverse event reports, if any, will be handled through the Chief Medical Office and Patient Safety (CMO&PS) drug safety surveillance process (Section 9).

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a patient starts imatinib treatment.

All adverse events are to be collected and recorded for this registry regardless of relatedness (suspected or non-suspected). In order to comply with the 2012 EMA legislation on adverse event reporting in non-interventional trials, adverse events that are suspected to be related to

imatinib (Glivec®) are required to be reported to competent health authorities. Adverse events identified as part of this registry will be included in the annual study progress reports to the EMA.

In the context of this registry, adverse events will be collected in the clinical database (eCRF) from the date of start of imatinib (Glivec®) treatment. For further details on AE collection and reporting, including laboratory abnormalities, refer to Section 9. Accurate reporting of SAEs occurring during this period will be verified in accordance with the Site Monitoring Plan (Section 7.8.3).

- Information on all AEs is included in the individual patient eCRFs which must be updated in the registry database on a periodic basis, but not later than one month of new information becoming available.

For the duration of the registry, SAE reporting should continue via normal procedures, through the local Novartis CMO&PS office, as detailed in Section 9. Reporting and follow-up is independent of participation in the registry, although reconciliation will occur.

7.3.1.9 Drug Exposure

An assessment of imatinib (Glivec®) exposure will be calculated using the duration of treatment (date of first dose of imatinib until the last dose of imatinib), captured within the dose administration record (Section 7.4.2.11). The concomitant antineoplastic therapy (chemotherapy) regimen will be recorded on the Antineoplastic therapy – Medications CRF.

7.4 Data sources

The data for this registry will be retrieved from hospital discharge files, clinical records and electronic medical records (e.g. laboratory reports of baseline assessment data etc.).

Initiation of the participating sites will be performed by a Novartis representative and/ or designee. Before registry initiation, a Novartis representative and/ or designee will review the protocol and eCRF with the treating physicians and their staff.

Sites enrolling patients in this registry will record data on eCRFs designed by a Novartis representative and/ or designee. The database will capture, perform standard edit checks and store the data.

Concomitant or prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List. Relevant medical history/ current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data will be transferred to Novartis on a monthly basis as defined in Section 9 of this protocol. Clinical data will be transferred to Novartis on once yearly (minimum).

7.4.1 Data collection schedule

This is a non-interventional registry and does not impose a therapy protocol, diagnostic/ therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and the types of assessments performed for disease evaluation, and only these data will be collected as part

of the registry. The treating physician and/ or designee are asked to complete the appropriate electronic Case Report Form (eCRF) at every patient visit, where possible. For each patient enrolled in the registry a minimum of a once yearly update (12 ±2 month intervals) of data in the registry database must occur to ensure an ongoing data stream, with the exception of safety data which should be entered within a month of new information becoming available. Where disease evaluation is performed frequently, any follow-up information collected that is relevant to the objectives of this registry should be recorded in the database. Long term safety and efficacy data will be collected such that the observational follow-up for each patient will be a minimum of 5 years from start of imatinib treatment or such available data until early patient discontinuation (Section 7.2.5).

Table 7-1 is a data collection schedule that outlines all the assessment information required by the registry and indicates with an "X", the visits when they are recorded. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column). The expectation is that laboratory assessments/ interventions shown are those required for the standard disease management of pediatric Ph+ ALL, according to local best practice.

- Where complete laboratory assessments/ interventions are not performed, it will be acceptable to indicate not done.

For each patient discontinuation, the reason for discontinuation should be determined.

Table 7-1 Data collection schedule

	Category	Protocol Section	Screening & Enrollment	Diagnosis / Baseline	Surveillance Period			Study Evaluation Completion	Survival follow-up
					On Treatment Follow-Up	End of study Treatment (EOT)	Post-Treatment Follow-Up		
					Visit Dates	EOT Date	Visit Dates	EOS Date	SURV Visit
Follow-up Visit			**1**	**2**	**601**	**777**	**602**	**778**	**888**
Obtain Informed Consent	D	8	X						
Patient history									
Inclusion/ exclusion criteria	D	7.2.2	X						
Demography	D	7.4.2.1	X						
Relevant medical history / current medical conditions	D			X					
Prior / Concomitant medications	D			X	X	X			
Concomitant antineoplastic therapy	D			X	X	X			
History and diagnosis of disease	D			X					
Induction Response [Poor / Good]	D	7.4.2.2		X					
Physical examination									
General Physical Examination	S	7.4.2.7		X	X	X	X	X	
Performance status	D	7.4.2.8		X	X	X	X	X	
Vital Signs [Height / Weight]	D	7.4.2.9		X	X	X	X	X	
Development & Growth [Tanner Staging]	D	7.4.2.10		X	X	X	X	X	
Laboratory assessments									
Response status [Efficacy]	D	7.4.2.3		X	X	X	X	X	

	Category	Protocol Section	Screening & Enrollment	Diagnosis / Baseline	Surveillance Period			Study Evaluation Completion	Survival follow-up
					On Treatment Follow-Up	End of study Treatment (EOT)	Post-Treatment Follow-Up		
					Visit Dates	EOT Date	Visit Dates	EOS Date	SURV Visit
Follow-up Visit			**1**	**2**	**601**	**777**	**602**	**778**	**888**
Hematology	D	7.4.2.4		X	X	X	X	X	
BM assessment / cytogenetics	D			X	X	X	X	X	
MRD assessment	D	7.4.2.5		X	X	X	X	X	
Extramedullary involvement [Cerebro-spinal Fluid Exam]	D			X	X	X	X	X	
Safety									
Adverse events / Serious adverse events	D	7.3.1.8		X	X	X	X	X	
Drug administration (imatinib dosing)	D	7.4.2.11		X	X				
Surgery									
Transplantation and engraftment [Hematopoietic Stem Cell Treatment (HSCT)]	D	7.4.2.6			X	X	X		
End of study treatment (EOT)	D					X			
Study Evaluation Completion	D							X	
Overall Survival	D	7.3.1.2							X

7.4.2 Assessments

7.4.2.1 Patient demographics and other pre-treatment characteristics

- Demographic information and other background or relevant medical history (i.e. age at diagnosis, sex, race, extent of disease)
- Information relating to patient eligibility and inclusion criteria (i.e. date of diagnosis, date of obtained informed consent).
- Details of all relevant prior concomitant medications, post-diagnosis.
- Updated information and details of new concomitant medications and significant non-drug therapies.
- Concomitant antineoplastic therapy details (i.e. full chemotherapy regimen).

7.4.2.2 Induction response

The patient response to induction treatment provides a measure of the patient-risk category. The commonly used definitions of good-risk (induction-responder) / poor-risk (induction non-responder) suggested below are adopted from Biondi et al. 2012. If this is not the definition that was used for a patient, information will be obtained with respect to the definition of risk.

- **Good-Risk Group**: Patients with both early response and complete remission at the end of induction e.g. Blast cell count < 1000/µl in peripheral blood after 7 days of Prednisone given in combination with chemotherapy drug(s) before induction is instituted **or** have M1/M2 BM at day 15 (after start of chemotherapy) **or** M1 BM at day 21 **and** achieve CR after induction period.
- **Poor-Risk Group**: Patients with poor early response to induction treatment **or** absence of complete remission at the end of induction e.g. Blast cell count ≥ 1000/µl in peripheral blood after 7 days of Prednisone given in combination with chemotherapy drug(s) before induction is instituted **or** have M3 BM at day 15 **or** M2/M3 BM at day 21 **or** do not achieve CR after induction period.
    - M1: <5% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.
    - M2: 5-25% blasts, counting all nucleated cells, including erythropoiesis. In case of regenerating marrow with a high erythropoietic predominance, at least a total count of 100 non-erythropoietic cells should be counted.
    - M3: >25% blasts in a BM aspirate.

7.4.2.3 Efficacy response

The efficacy of treatment with chemotherapy in combination imatinib (Glivec®) will be evaluated from diagnosis, and based on the tests performed (e.g. extramedullary, cerebro-spinal fluid exam, hematological, MRD assessment data) by the treating physician and/ or designee for each patient to assess incidence of relapse and secondary malignancy.

7.4.2.4 Hematological response

Peripheral blood will be used to assess hematological response. Complete hematological remission requires that **all** of the following are present:

- Adequate bone marrow cellularity with a blast count < 5%
- No peripheral blood blasts
- ANC ≥ 1500/µl
- Platelet count ≥ 100.000/µl
- No evidence of extramedullary involvement

The loss of complete remission and thus the end of the duration of complete remission is defined as:

- ≥ 5% blasts in bone marrow aspirate regardless of proportion of mature lymphocytes.

Progressive disease (relapse) is defined as the new appearance of **any** of the following:

- ≥ 25% blasts in bone marrow aspirate
- Any increase of at least 25% in the absolute number of circulating leukemic cells.
- ≥ 30% increase of Ph+ metaphase cells as assessed by standard cytogenetic analysis.
- Development (evidence) of extramedullary disease
- Other laboratory or clinical evidence of disease progression.

7.4.2.5 Molecular response

MRD assessments to detect BCR-ABL transcript will be evaluated at specific time-points (if available) to provide a measure of the molecular response. Biondi et al. 2012 define the 5 time-points as the following: post-frontline induction; pre-consolidation block 1, pre-consolidation block 2, pre-consolidation block 3, post-consolidation.

MRD assessments may be performed for example via quantitative real-time PCR of mononuclear bone marrow and peripheral blood cells or detection by flow cytometry. Data should be provided if available at the aforementioned time-points.

7.4.2.6 Transplant and engraftment

- Transplant (i.e. date of transplantation, phase of transplantation, type of transplantation, source of transplantation, relationship to donor).
- Time to engraftment, engraftment failure (i.e. date, neutrophil/platelet engraftment success – yes/ no, engraftment failure – yes/no).
- Presence of graft versus host disease (i.e. chronic graft versus host disease presence – yes/ no, acute graft versus host disease presence – yes/no).

7.4.2.7 Physical examination

A general physical examination would include the examination of general appearance, and vital signs (e.g. blood pressure [BP] and pulse), although the extent of the examination is at the discretion of the treating physician and/ or designee.

Significant findings that were present prior to first dose of imatinib must be included in the Relevant Medical History page on the patient's eCRF. Significant new findings that begin or worsen after start of treatment with imatinib (Glivec®) must be recorded on the Adverse Event page of the patient's eCRF.

7.4.2.8 Performance status

Performance status may be measured using the Lansky/ Karnofsky Performance Status Score. Wherever possible, the same performance scale used at baseline assessment should be maintained for the duration of follow-up.

7.4.2.9 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be captured in the database, if available.

7.4.2.10 Tanner stage and development assessments

Tanner staging will be evaluated as a measure of pubertal status (Tanner 1-5). Data corresponding to the age of menarche for girls and the age of adrenarche for boys will be captured, if available.

7.4.2.11 Dose administration record

Full and complete imatinib (Glivec®) dosing data from medical charts/ prescription records (historic and/ or current) should be recorded, if available. Detailed information including total daily dose, regimen and dose changes (e.g. dosing errors) to be captured wherever possible.

7.5 Study size

This is a multi-center, observational registry that is not designed to test a formal hypothesis and therefore there is no formal sample size calculation. The registry has a planned enrollment of a minimum of 50 patients.

7.6 Data management

7.6.1 Data collection methods and tools

Designated staff will enter the data required by the registry into a secure web-based internet system using a Novartis-designed eCRF with fully validated software that conforms to 21 CFR Part 11 and regulatory requirements for electronic data capture (EDC). Registry site staff will not be given access to the EDC system until they have been trained. An international Contract Research Organization (CRO) will administer and manage the web-based system and review the data for completeness and accuracy.

Each subject in the study is uniquely identified by a **9 digit subject number** which is a combination of his/ her **4-digit center number** and **5-digit subject number**. The center number is assigned by Novartis to the registry site. Upon signing the informed consent form, the subject is assigned a subject number by the treating physician and/ or designee. For studies using electronic CRFs, only the assigned 5-digit subject number (excluding the leading zeros)

should be entered in the field labeled "Subject ID" on the EDC data entry screen. Once assigned to a subject, a subject number will not be reused.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Novartis personnel (or designated CRO) will review the data entered by registry staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the registry site via the EDC system. Designated registry site staff is required to respond promptly to queries and to make any necessary changes to the data. Queries are expected to be minimal since the web-based system will have automatic validation programs to check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the registry site staff.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and made available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Further information on quality control, data quality assurance, data recording and document retention and site monitoring are explained in Section 7.8.

7.6.1.1 Treating physician / investigator

Treating physician and/ or designated registry staff are responsible for providing adequate patient care and accurate patient data. The following are data handling responsibilities for the treating physicians and/ or their designated staff:

- Record and maintain accurate patient data in medical charts, research records or files.
- Record and ensure patient data entered into the registry is accurate; obtain missing data and clarify discrepancies with the treating physicians and/ or their designated staff on an ongoing basis.
- Provide missing information and responses to queries to clarify discrepancies (as required).
- Enter, update and complete registry data collection pages on an ongoing basis, the data will be subsequently transferred electronically to the Novartis global clinical team.
- Enter and/ or update patient registry data a minimum of once yearly (12 ±2 month intervals) for the duration of the registry (if necessary).

- Ensure all AE information is included in the individual patient eCRFs which must be updated in the registry database on a periodic basis, but not later than one month of new information becoming available.
- Contact Novartis CMO&PS office in their local country regarding SAEs, and provide information on SAEs to investigators and/ or Novartis representative and/or designee as needed (as outlined in Section 9).

7.6.1.2 Novartis

Novartis responsibilities in regards to data handling are specified below:

Novartis global clinical study team

- Development of electronic Case Report Form.
- Ensure all patients are assigned a unique patient number.
- Review and check the registry database for missing data, inconsistencies, and any obvious discrepancies.
- Contact the treating physician and/ or designee, for updated information; any queries generated will be documented.
- Process and record in the database any discernible manual protocol deviations.
- Archive data according to Novartis standard operating procedures.

Novartis Chief Medical Office and Patient Safety

- Contact treating physician and/ or designee, or Novartis representative and/ or designee for SAE information or additional follow-up, as needed (as outlined in Section 9).

7.7 Data analysis

All analyses will be performed by a Novartis representative and/or designee.

All data summaries and analyses will have descriptive purposes only with no formal inferential testing.

Due to the observational nature of this registry, it is expected that some specific endpoints may not be available at all time points and for the entire population. Unless otherwise specified in the Reporting Analysis Plan, the analyses will be performed on available data.

Patient efficacy, safety and tolerability outcomes of patients treated with chemotherapy + imatinib will be summarized overall, by HSCT (yes/no) and by risk group (good-risk/induction-responder) / (poor-risk/induction non-responder).

7.7.1 Analysis sets

The Full analysis set (FAS) comprises all patients who received at least one dose of imatinib + chemotherapy in the observational period.

The Safety set consists of all patients who received at least one dose of imatinib and with a valid post-baseline assessment. The statement that a patient has no AE constitutes a valid safety assessment. The occurrence of a death also constitutes a valid safety assessment. The safety set will be the population used in the assessments of safety. Patients with no post-baseline safety assessment will be listed.

7.7.2 Patient demographics/ other baseline characteristics

Demographic and other baseline data will be summarized descriptively. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

7.7.3 Treatments (study treatment, concomitant therapies)

Time on imatinib, duration of exposure, percentage of days on treatment, average dose intensity, and actual daily dose will be summarized using descriptive statistics for the Safety Set.

Chemotherapy exposure will be summarized using descriptive statistics for the Safety Set

Time on imatinib is defined as the time from first dose of imatinib to last dose of imatinib.

Duration of exposure to imatinib is defined as the time on imatinib minus the days with zero dose.

7.7.4 Efficacy analyses

The efficacy analyses will be performed using the FAS.

7.7.4.1 Primary endpoint

The **primary endpoint** will be event-free survival (EFS) considering the following events: relapse at any site, development of a second malignant neoplasm or death.

Event free survival is defined as the time from diagnosis to the earliest of these events.

Censoring date will be the date of last contact for patients who did not experience any of these events.

7.7.4.2 Main secondary endpoints

The main secondary efficacy endpoint will be overall survival (OS).

OS is defined as the time from diagnosis to death from any cause.

Censoring date will be the date of last contact for patients who are still alive.

7.7.4.3 Other secondary endpoints

The other secondary efficacy analyses will be the evaluation of the following outcomes:

1. Rate of Complete Remission (CR)
   CR is defined in Section 7.3.
2. Duration of first complete remission
   This is defined as the time between date of first complete remission to the date of loss of first complete remission.
3. Rate of Complete Hematological Remission
   CHR response (Complete Hematological Remission) is defined in Section 7.3.
4. Rate of MRD response
   MRD response (Minimal residual Disease) is defined in Section 7.3.
5. Time to first transplantation
   This is defined as the time from date of diagnosis to the date of first transplantation.
6. Time to engraftment (neutrophil, platelet and both neutrophil/platelet)
   This is defined as the time from date of transplant to the date of engraftment.
7. Rate of engraftment failure
8. Rate of acute Graft versus Host disease
9. Rate of chronic Graft versus Host disease

7.7.4.4 Methods of analysis

The efficacy endpoints will be summarized descriptively for the FAS.

Time to event endpoints (OS, EFS, transplant, engraftment) will be described using Kaplan Meier plots and associated statistics such as estimated survival rates by time points and medians along with 95% confidence intervals.

Event rates will be provided with 95% confidence intervals using Pearson-Clopper method.

On top of these analyses, analyses with a different definition of endpoint or on different subgroups will be performed:

- Analyses of OS and EFS will be performed taking into account the occurrence of transplantation procedure (by censoring at time of transplant for example). This is to avoid that prolongation in time to event after transplantation is taken as an Imatinib success.
- OS and EFS will be performed on the following subgroups:
  - subgroups based on age (with age categories selected to allow pubertal vs pre-pubertal differentiation),
  - subgroups based on peripheral lymphoblast count,
  - subgroups based on enrollment into approved clinical studies
  - subgroups based on type of transplant donor
- Time to transplant will be analyzed and presented according to type of transplant donor (autologous, allogeneic, syngeneic, other).

In addition, an analysis will be performed to evaluate the influence of prognostic factors (age, leukocyte count and early response, type of donor etc.) on efficacy outcome: these could include analyses of the impact of prognostic factors either on the odds of non-response to induction therapy by using logistic regression modeling or on time to event variables using cox regression modeling.

The association between MRD with other endpoints such as OS and EFS will be explored.

7.7.5 Safety analyses

The safety analyses will be performed using the safety set.

7.7.5.1 Growth and development

Growth and development data collected during the study will be summarized descriptively at each relevant time point. These data consist of height, height velocity (difference of height over 1 year), weight, weight velocity (difference of weight over 1 year) reported as standard deviation score (SDS, also called z-score), the age at thelarche (Tanner stage 2 for breast development) and menarche for girls, the age of adrenarche for boys as well as the Tanner stage assessment.

7.7.5.2 Adverse events (AEs)

The incidence of - adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.

7.7.5.3 Laboratory abnormalities

Novartis will not have access to individual laboratory values. Clinically relevant laboratory abnormalities will be captured as AEs. There is then no intent to perform specific lab values analyses.

7.7.5.4 Other safety data

Other clinically relevant abnormal safety data collected (e.g. vital signs) will be captured as AEs. No specific analyses will be performed.

7.8 Quality control

Queries related to the completeness and accuracy of the data entered will ensure data quality and integrity. The web-based system will have automatic validation programs to check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the registry site staff.

7.8.1 Data quality assurance

Novartis Data Management and/ or designee will assure database quality by reviewing the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the Data Handling Plan.

7.8.2 Data recording and document retention

Each participating site will maintain appropriate medical and research records for this registry, in compliance with standard practice, regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored registry, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the registry staff at the site under the supervision of the site Principal Investigator. The study case report form (eCRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded. Any missing data must be explained. Any change or correction to a paper eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Registry unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

7.8.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on eCRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/ exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

7.9 Limitations of the research methods

The research method outlined in this protocol serves as a compromise between a population-based registry assessing the entirely of the pediatric patient population treated with imatinib in this indication, and an interventional, clinical trial, which would not reflect the breadth of the standard clinical setting.

A non-interventional, observational study design is implicitly associated with known limitations, including difficulty to control external variables and the availability/ completeness of data. In an effort to mitigate these potential limitations, this protocol is well-aligned with the current treatment paradigm and indicates precise data collection requirements to successfully respond to the stated objectives.

In an effort for the registry population to be as representative as possible of the patient population as a whole, no exclusion criteria have been defined. Furthermore, any standard concomitant chemotherapy regimen is permissible. Although this enhances the relevance of the study, it does create a source of non-homogeneity with respect to adverse events related to concurrent chemotherapy. Reasons for non-inclusion will also be identified to permit a possible analysis of any potential bias.

It is recognized that the study is single arm (imatinib + chemotherapy) and lacking a contemporary, external control. Given that current standard medical practice recommends the use of TKIs in the treatment of Ph+ ALL in children, it has previously been acknowledged

that the introduction of such a control would be unfeasible and possibly unethical. Nevertheless, this limitation is recognized by the study team.

7.10 Other aspects

Not applicable – all aspects are addressed in previous sections.

8 Protection of human patients

As a non-interventional, observational study, with no prospective clinical, instrumental or laboratory assessments/ interventions other than those required for disease management according to local best practice, patients are not at risk as a result of participating in this registry.

8.1 Protection of data confidentiality

Information about patients in the registry will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the patient of the following:

- What protected health information (PHI) will be collected from patients in this registry
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the registry participating physician, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization.

The data collection system for this disease registry will use built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Key sensitive personal identifiable information (e.g. exact date of birth), will be collected only in countries where it is allowed by local regulations. Each registry participating physician will have access to the data generated from his/ her patient. Patients will be identified by a unique ID key. Only physicians will be able to link patients to their ID key. It is the responsibility of each site to keep this list confidential and to update it accordingly for the purpose of facilitating data validation.

The registry participating physician must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

8.2 Early study termination

The registry can be terminated at any time for any reason by Novartis. Any early registry termination will always be in agreement with the EMA.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The registry participating physician will be responsible for informing IRBs and/or ECs of the early termination of the trial.

8.3 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the registry data are credible and responsibly reported.

This registry was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

8.4 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before registry start. Prior to registry start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

8.5 Informed consent procedures

Eligible patients may only be included in the registry after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the registry to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

According to local regulations, any child under the age of consent (for that region) must get consent from the legal guardian. Where applicable, children should also provide 'assent' after being provided with appropriate information about the registry (age of assent determined by the ethics committee or local requirements).

Informed consent must be obtained before any registry data is collected. The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to participating physicians, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this registry and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the participating physicians must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

If applicable and according to local regulations, the physician must explain to each patient (or legally authorized representative) the nature of the registry, its purpose, the requirement to report SAEs to Novartis per ICH guidelines, and the expected duration. Each patient must be informed that participation in the registry is voluntary and that he/ she may withdraw from the program at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

9 Management and reporting of adverse events/adverse reactions

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – must be collected and recorded in the registry database, irrespective of causal association. All safety data AEs and SAEs occurring in association with exposure to imatinib (Glivec®), also have to be notified for recording in the Novartis safety database.

Adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder; these will not be recorded in the Novartis safety database.

9.1 Adverse event definitions and reporting

An adverse event (AE) is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) in a patient administered imatinib (Glivec®) that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of imatinib (Glivec®), whether or not related to the medicinal product(s).

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy or require changes in medication(s) dose.

Adverse events that begin or worsen during imatinib (Glivec®) administration should be recorded in the Adverse Events CRF. Conditions that were already present at the time of diagnosis and until the first dose of imatinib (Glivec®) should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE).

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, all adverse events should be recorded on the Adverse Events case report/case record form (CRF) with the following information:

1. the severity grade (CTCAE Grade 1-4)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken with respect to imatinib (Glivec®) treatment during registry period (no action taken, dose adjusted/ temporarily interrupted, permanently discontinued, unknown, not applicable)
5. whether medication or therapy was given (concomitant medication taken, non-drug therapy given)
6. whether it constitutes a serious adverse event (SAE) as defined in Section 9.3.

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during lactation or breast-feeding,
- Lack of effectiveness
- Overdose
- Intentional drug abuse and misuse
- Medication error including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Unexpected beneficial effect
- Off-label use
- Withdrawal or rebound symptoms
- Treatment non-compliance (with clinical symptoms)

Note: Occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Novartis CMO&PS as a spontaneous report.

All adverse events should be treated appropriately. Any treatment of any adverse event (e.g. concomitant medication or non-drug therapy) should be recorded on the Adverse Event CRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication introduced or adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method, should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

Information on all AEs is included in the individual patient eCRFs which must be updated in the registry database on a periodic basis, but not later than one month of new information becoming available. Information on non-serious AEs is then transferred from the study database to Novartis CMO&PS by the CRO Data Management on a periodic basis but not less frequently than monthly.

Information about common adverse effects already known about the medicinal product can be found in the Summary of Product Characteristics (SmPC). This information will be included in the patient informed consent and should be discussed with the patient prior to the study start and during the study as needed.

9.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be

required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Full details of all laboratory test abnormalities (e.g. biochemistry values) associated with imatinib treatment can be found in the Summary of Product Characteristics (SmPC).

9.3 Serious adverse event definitions and reporting

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Transmission of infectious agent via medicinal product

In addition, as a Risk Management Plan (RMP) exists for imatinib (Glivec®) any events of special interest must be sent to Novartis CMO&PS within the same timelines as a serious adverse event in order to facilitate required follow-up.

To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to treatment with imatinib (Glivec®). Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Novartis Non-Interventional Study SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the Non-Interventional Study SAE Report Form and send the completed, signed form by fax within 24

hours to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. The telephone and telefax number of the contact persons in the local department of CMO&PS, specific to the site, are listed in the treating physician or other involved health care health care professional folder provided to each site. The original copy of the Non-Interventional Study SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original Novartis Non-Interventional Study SAE Report was sent, using a new Novartis Non-Interventional Study SAE Report stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Package Insert (new occurrence) a local Novartis Chief Medical Office and Patient Safety (CMO&PS) associate may urgently require further information from the treating physician for Health Authority reporting.

9.4 Pregnancies

To ensure patient safety, any occurrence of a pregnancy in a patient on imatinib (Glivec®) must be reported to Novartis within 24 hours of learning of its occurrence. Any SAE experienced during pregnancy must be reported on the SAE Report Form. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis CMO&PS Department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to imatinib (Glivec®) should be reported. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the imatinib (Glivec®) for any pregnancy outcome. Full contraception guidance is provided on the Glivec® label.

10 Plans of disseminating and communicating study results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov and the EU PAS Register. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For non-interventional PASS studies, the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

In qualifying as an ENCePP study, this study will be registered in the electronic EU PAS Register before the study commences, following approval by Pharmacovigilance Risk Assessment Committee (PRAC).

11 References (available upon request)

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Annex 1 – List of stand-alone documents

None.

Annex 2 – ENCePP checklist for study protocols

sti571i2201--ENCePP checklist for study protocols is attached to this document.

CREDI Electronic Document Identifier: [090095a885143744]

Annex 3 – Additional information

Not applicable – all aspects are addressed in previous sections.