STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

A PHASE 2 MULTI-CENTER, HISTORICALLY-CONTROLLED STUDY OF DASATINIB ADDED TO STANDARD CHEMOTHERAPY IN PEDIATRIC PATIENTS WITH NEWLY DIAGNOSED PHILADELPHIA CHROMOSOME ACUTE LYMPHOBLASTIC LEUKEMIA

PROTOCOL CA180-372

VERSION 1.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

[redacted]

Research Hypothesis:

Dasatinib added to chemotherapy will demonstrate a superior 3-year event free survival (EFS) rate compared to chemotherapy alone in the external historical control trial Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster ALL 2000 (AIEOP-BFM 2000) and non-inferior 3-year EFS compared to continuous imatinib added to chemotherapy in the external historical control trial of the amended European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL).

Schedule of Analyses:

Interim monitoring of safety and efficacy will be done by an independent Data Monitoring Committee (DMC) for all subjects starting from the date each subject signs informed consent.

The DMC can recommend discontinuing the study due to excessive and unacceptable toxicities or to poor efficacy.

The analyses to be performed for the DMC and the schedules of reports and meetings are described in the DMC Charter. They don't include any comparison with historical controls.

This SAP will focus on all planned analyses for the final CSR.

2 STUDY DESCRIPTION

2.1 Study Design

CA180-372 is an open-label, multi-Center single-arm but Historically-Controlled study. Children and adolescents with newly diagnosed Ph+ ALL will be eligible and will receive dasatinib at a dose of 60 mg/m2 once daily in addition to the standard Associazione Italiana di Ematologia Pediatrica - Berlin-Frankfurt-Muenster (AIEOP-BFM) ALL 2000 chemotherapeutic standard multiagent chemotherapy protocol[8] for a maximum duration of 2 years.

Subjects who meet pre-defined criteria at specific time points in treatment (see section 4.3.3) may receive a hematopoietic stem cell transplant (HSCT) and will have the option to receive 12 additional months of post-HSCT dasatinib (not mandatory).

The components of treatment are divided into successive blocks as follows (see protocol section 4.1 for the complete list of individual agents). All block durations are approximate:

Phase I - For all subjects

1. Induction IA (4 - 5 weeks): During the first 2 weeks, the subjects will receive frontline acute lymphoblastic leukemia (ALL) induction chemotherapy (standard at the investigative center) outside the protocol. They will be enrolled in the study and start to receive Dasatinib at Day 15 when positive Philadelphia chromosome status is confirmed via cytogenetics, FISH or PCR prior to Day15).
2. Induction IB (28 days, 4 weeks)
3. Recovery period (Dasatinib continues, No chemotherapy given) (2 - 4 weeks)
4. Three successive Consolidation blocks (HR1, HR2, and HR3) of 21 days each
5. Recovery period (Dasatinib continues, No chemotherapy given) (14 days, 2 weeks)

Phase IIa - For the subjects who don't meet the criteria for HSCT:

6. Reinduction Block 1, including phase IIa and IIb (63 days, 9 weeks)
7. Interim maintenance (29 days, 4 weeks). Subjects with CNS3 disease at diagnosis will receive cranial irradiation during the Interim Maintenance period.
8. Reinduction Block 2 (63 days, 9 weeks)
9. Continuation therapy (62 weeks)

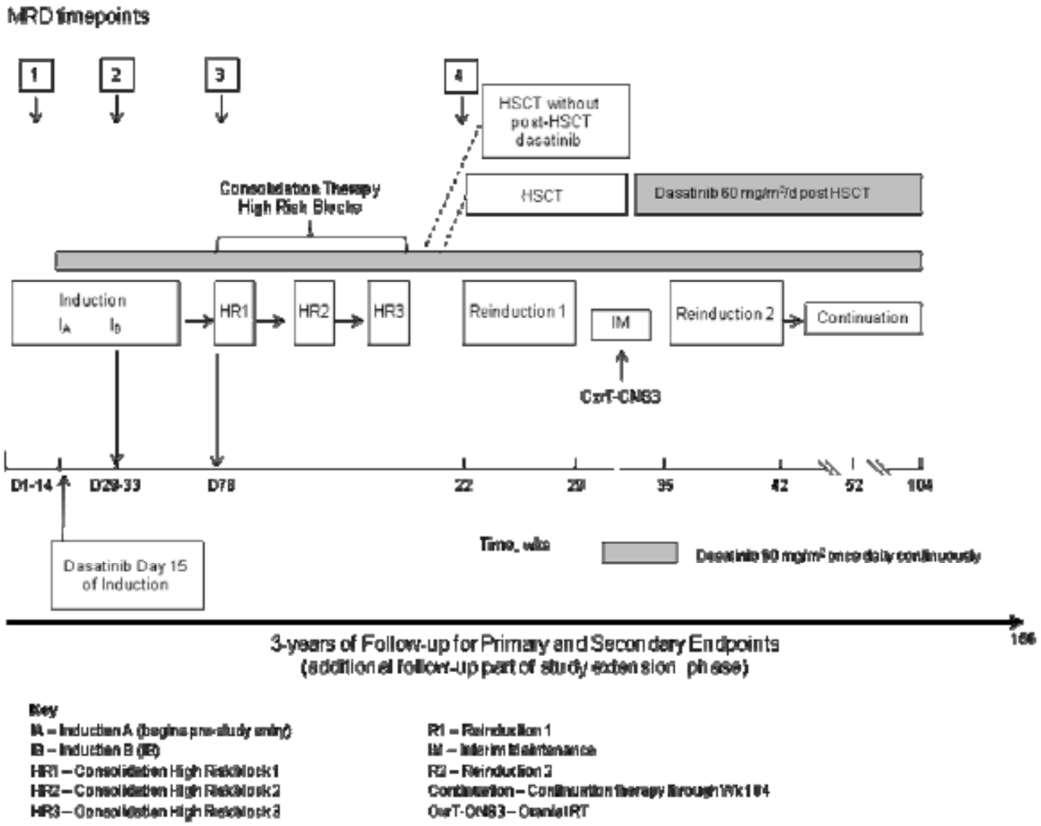
Phase IIb - For the subjects who meet the criteria for HSCT

The subjects who meet predefined criteria for HSCT mainly based on MRD response at key early time points in therapy (see section 4.3.3) may receive a HSCT following the Consolidation Block (HR3) instead of continuing the AIEOP-BFM ALL.

During the HSCT, subjects will not receive dasatinib. Following adequate engraftment of the HSCT, subjects have the option to receive 12 additional months of post-HSCT dasatinib 60 mg/m2 orally once daily (recommended but not mandatory).

A schematic of the study design is shown in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



The total intended duration of treatment (including chemotherapy and dasatinib) will be approximately 104 weeks (2 years). Subjects will be followed (including time on treatment) for at least 3 years for event-free survival and other secondary endpoints.

2.2 Treatment Assignment

After informed consent and subject assent has been obtained as per local guidelines, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Instructions on the use of the IVRS will be provided to the study site.

This is a single-arm open-label study where subjects will receive up to 24 months of study treatment during the trial. Since subjects with Ph+ ALL often experience delays in treatment due to toxicities associated with therapy, delays in starting treatment blocks are expected. Therefore, all start dates for the initiation of all treatment blocks are estimates, and should not be considered as strict requirements.

As subjects newly diagnosed with Ph+ ALL require urgent treatment, initial therapy for their disease will start outside the protocol with a chemotherapy regimen that is standard at the investigative center (referred to as induction therapy IA). Dasatinib at a dose of 60 mg/m2 once daily will be introduced on day 15 from initiation of treatment in all subjects in addition to ongoing chemotherapy (approximately until day 29 - 33). From the start of induction therapy IB, all subjects will follow the same treatment plan shown in the protocol Table 4.3A till end of HR3 where they either pursue the chemotherapy + Dasatinib or have a HSCT.

2.3 Blinding and Unblinding

Not applicable; this is an open label study.

2.4 Protocol Amendments

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
4	28-Oct-2013	Addition of mandatory supportive care measures during the 3 High Risk Blocks
3	31-Jul-2013	• Increase of the number of treated subjects from 75 to at least 75 and up to 90. • Incorporate recommendations for subject management and supportive care during High Risk (HR) Blocks 1-3
2	07-Dec-2012	• Introduce a new pediatric formulation of dasatinib (Powder of Oral Solution - PFOS) • BCR-ABL mutation status at baseline and at time of progression moved from being an exploratory objective to a secondary objective • Allow Philadelphia chromosome positivity from peripheral blood to be acceptable for study entry. • Expand the window for screening activities to 21 days. • Modify the definition of high risk group and low/standard risk group in response to Induction 1A treatment. The high risk group will be defined by a MRD ≥ 0.01%; low/standard risk will be defined as day 29 MRD <

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
		0.01%. This approach is consistent with the criteria used in other COG trials, and/or NCI risk group and being adopted by EsPhALL trials.
1	20-Sep-2011	Changing the statistical design of the trial to allow comparison to historical external controls. Specifically, the 3-year event free survival (EFS) of dasatinib plus chemotherapy will be compared to the 3-year EFS of chemotherapy alone from the Associazione Italiana di Ematologia Pediatrica-Berlin-Frankfurt-Muenster ALL 2000 (AIEOP-BFM 2000) trial and the 3-year EFS of imatinib plus chemotherapy from the European intergroup Study on post induction treatment of Philadelphia positive Acute Lymphoblastic Leukemia (EsPhALL). This analysis will improve the ability to interpret the safety and efficacy of dasatinib added to chemotherapy among other treatment options for pediatric leukemia.

2.5 Data Monitoring Committee

- An independent DMC will review safety and efficacy data for all subjects starting from the date each subject signs informed consent. These data will consist of tables and listings related to protocol deviations, subject disposition, demographics, deaths, extent of exposure and dose modifications for dasatinib, AEs, neoplasms, Complete Remission Rate and Event Rate for Event Free Survival.

- The DMC will monitor the study for effectiveness and safety as described below and can recommend discontinuing the study due to excessive and unacceptable toxicities or due to poor efficacy.

2.5.1 Monitoring for Effectiveness

Interim analyses will be conducted to protect against poor EFS. Under the exponential assumption, a three-year EFS rate of 78% (lower limit of the 95% confidence interval for an observed ≥ 88% EFS rate) translates to a hazard rate of 0.083. Interim analyses will be based on the estimated hazard rate, testing the null-hypothesis H_0 that the hazard rate <= 0.083 versus the alternative hypothesis H_1 that the hazard rate is > 0.083 (at an alternative of 0.119 which corresponds to a 3-year EFS of 70%).

Testing H_0: $S(3) \geq 0.78$ vs. H_1: $S(3) < 0.78$ where S(3) is the 3-year EFS rate.

Test statistic: Z_i = (lambda_hat) - lambda_0) / sqrt (lambda0/T_i)

Where:

Z_i = value of the test statistic at the time of the i-th interim analysis

lambda_hat = estimate of hazard rate at the time of i-th interim analysis

lambda_0 = hazard rate under the null hypothesis

T_i = Total time at risk for subjects at the time of i-th interim analysis

The αt^2 spending function will be used to maintain an overall one-sided Type I error rate of 10%. Based on 106 treated subjects, the total number of expected events is 30. Interim analyses will be performed when 33%, 66%, 100% (if prior to 3 year EFS landmark) of the expected information (events), respectively have been observed. The corresponding critical values (boundaries) are Z_c: 2.29, 1.76, and 1.37, assuming the three interim analyses will occur after reaching 10, 20, and 30 events, respectively. If Z_i at one of these interim looks is > Z_c, then the monitoring boundary would be crossed and the DMC can recommend the study be stopped for inferior EFS.

The DMC will monitor for effectiveness until all subjects are off-treatment.

2.5.2 Monitoring for Safety

The DMC may recommend termination of the entire study for any safety concern that is felt to outweigh potential benefits.

Safety review will occur after each new treatment related death. The DMC will be provided information on each new treatment related death and after review will decide if additional information is needed from the sponsor. The DMC will also meet at least once per year to review all available safety tables and listings and per the charter.

The DMC may recommend stopping the trial if the observed death rate is above the acceptable limit.

The tables below show the minimum number of treatment related deaths in induction (after day 15) and in continuous complete remission (CCR), excluding deaths after HSCT, at which the DSMB should evaluate stopping the study. The method applied for developing these guidelines follows a Bayesian approach, extending that of Metha and Caine[10, 11]. In these guidelines, the maximum acceptable level of probability of treatment related deaths in induction (IND) and in CCR were pIND = 3% and pCCR = 7% respectively. The number of failures is assumed to be taken from a binomial distribution. The prior distribution for the probability of the endpoint of interest was taken as a beta (1,1), corresponding to an uninformative uniform distribution. The stopping bounds reported in tables 2.5.2-1 and 2.5.2-2 below are the experimental results that give a posterior probability of 90% or more, of observing pIND ≥ 3% and pCCR ≥ 7%, respectively.

Table 2.5.2-1: Guidelines for early stopping due to treatment related mortality in Induction

No. of subjects on treatment p_{IND} = 3%	No. of Death Events
11 - 36	2
37 - 58	3
59 - 82	4
83 - 106	5

Table 2.5.2-2: Guidelines for early stopping due to treatment related mortality in CCR

No. of Subjects on Study p_{CCR} = 7%	No. of Death Events
11 - 15	2
16 - 25	3
26 - 35	4
36 - 45	5
46 - 56	6
57 - 67	7
68 - 78	8
79 - 90	9
91 - 101	10
102 - 106	11

3 OBJECTIVES

3.1 Primary

The primary objective is to compare the 3-year EFS of dasatinib plus chemotherapy with external historical controls, in hierarchical order, as follows:

1) Superiority over chemotherapy alone of AIEOP-BFM 2000
2) Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial
3) Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial

The trial will be considered positive if at least the first two comparisons are statistically significant.

3.2 Secondary

The key secondary objectives are to determine:

1. The safety and feasibility of dasatinib added to standard chemotherapy
2. Estimate the EFS of dasatinib plus chemotherapy (including 3 and 5-year rates)
3. Complete remission rates (< 5% blasts in bone marrow and no peripheral blasts) at end of induction

Other secondary objectives are to estimate:

1. The difference in 3-year EFS rate with the 3-year EFS rate of available historical controls such as the COG AALL0031 study
2. MRD levels (defined by PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements)
3. BCR-ABL mutation status at baseline and time of disease progression or relapse

3.3 Exploratory

[redacted]

4 ENDPOINTS

4.1 Primary Endpoint

The 3-year event-free survival (EFS) rate is the primary endpoint where EFS is defined as the time from the starting date of dasatinib until an event and will be computed using binomial proportions.

Events for EFS are defined as ANY first one of the following:

- Lack of complete response in bone marrow (see below definition)
- Relapse at any site

- Development of second malignant neoplasm
- Death from any cause

Response Criteria for EFS

Criteria for Response in Bone marrow (BM) are:

- M1: < 5% lymphoblasts (Complete Response in BM)
- M2: 5 - 25% lymphoblasts
- M3: > 25% lymphoblasts

For the primary analysis as described in protocol section 7.5.1, complete response (CR) in the bone marrow will be assessed between the start of dasatinib and completion of Consolidation Block 3 (HR3) / start of Reinduction 1. Three assessments are planned during that period:

- MRD2 at end of induction IA,
- MRD3 at end of IB / start of HR1, and
- MRD4 at end of HR3 /start of Reinduction 1.

(MRD1 is the screening assessment.)

- Subjects who reach CR within this window will be considered at risk for relapse or death without relapse.
- Those who do not reach CR (i.e. M1 bone marrow) between the start of dasatinib and the last day of Consolidation Block HR3/start of Reinduction 1 (Protocol II) will be considered as an event (resistant).
- For subjects who undergo HSCT, the date of the HSCT will not be considered as an event in the primary efficacy analysis. These subjects will continue to be followed for an event during and after HSCT.
- Subjects without valid BM results during this window (no BM done or no evaluable aspirate) will be considered having lack of complete response.

Relapse Criteria for EFS

Relapse is defined as any recurrence of disease, whether in the marrow or extramedullary site:

- CNS relapse: Positive cytomorphology and 5 or more WBC/μL in CSF, or any signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.
- Testicular relapse: Must be documented by testicular biopsy, in the absence of concomitant bone marrow or CNS relapse.
- Bone marrow relapse: An M3 marrow (>25% blasts), or peripheral blood with >25% blasts if bone marrow not available, after first CR has been achieved.

- Combined bone marrow + other site: >=5% blasts (or >25 % peripheral blood blasts if bone marrow not available) with other site of relapse.

Relapse should be histopathologically determined. All BM samplings, CSF evaluations, physical examinations and death information subsequent to achievement of a CR will be utilized to determine relapse, second malignancy and death for EFS analysis.

4.2 Secondary Endpoints

4.2.1 Safety and Feasibility

The safety and feasibility endpoint will include computation of frequencies of

(a) Treatment related deaths during induction as well as in subjects in complete remission

(b) All adverse events

(c) Laboratory abnormalities

(d) Dose interruptions, dose reductions and treatment discontinuations for dasatinib related toxicity

(e) Treatment block delays expressed in lapsed time (≤ 7 days, 8-14 days, etc.) will be summarized for start of dasatinib until start of HR1, and for start of HR1 until start of Reinduction (for subjects starting Reinduction):

- For start date of dasatinib (target day 15) to start date of HR1 (target day 78) a lapsed time of 63 days is exactly on target. If the lapsed time is <= 70 days, the delay is ≤ 7 days; if the lapsed time is 71-77 days, the delay is 8-14 days, etc.
- For start date of HR1 (target day 78) until start of Reinduction (target day 154) a lapsed time of 76 days is exactly on target). If the lapsed time is <= 83 days, the delay is ≤ 7 days; if the lapsed time is 84-90 days, the delay is 8-14 days, etc.

4.2.2 Event Free Survival (EFS)

The EFS endpoint is also considered for secondary/sensitivity analyses:

- Overall EFS analysis using Kaplan-Meier estimates of EFS probabilities (for overall EFS estimation and the 3-year and 5-year Kaplan-Meier estimates).
- Comparison of the 3-year EFS rate with that in study COG AALL0031.
- Sensitivity analyses of overall EFS (as described in section 7.5.1): EFS analysis by subgroup or with alternative event definition.

4.2.3 Complete Remission

Complete remission assessed by morphological examination is defined as <5% lymphoblasts in the bone marrow (i.e. M1 bone marrow) and CSF with no evidence of other extramedullary disease. Complete remission will be assessed at the end of Induction IA, end of induction IB and end of HR3.

4.2.4 Minimal Residual Disease (MRD)

At the time of morphologic complete remission, the extent of minimal residual disease (MRD) can vary considerably. In this study, 3 different techniques are used:

- Real-time quantitative PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR).
- Real-time quantitative PCR for BCR-ABL transcript levels.
- Multiparameter flow cytometry.

Each of the 3 methods will be applied for every bone marrow assessment for every subject. The Ig/TCR will be considered as the method of reference. For the first two methods the limit of detection of these assays will be approximately 10^{-4} (0.01%) - 10^{-5} (0.001%). The sample will be declared as MRD negative if the MRD level is undetectable providing the assay lower limit of quantification is at least 0.1%.

4.2.5 BCR-ABL Mutations

A BCR-ABL mutation is defined as the presence of a detectable amino acid substitution in the ABL kinase domain.

4.3 Exploratory Endpoints

[redacted]

[redacted]

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Screening

After diagnosis of acute lymphoblastic leukemia (ALL), subjects will begin standard induction chemotherapy (Block IA). Since the diagnosis of ALL typically requires urgent treatment and it takes up to 10-14 days to determine which patients have Philadelphia chromosome positive (Ph+) ALL, frontline induction chemotherapy (Block IA) will start prior to enrollment in this trial (approximately 2 weeks) and will be based upon the investigator's institutional standard of care. Enrollment on this study will occur prior to day 15 of Induction Block IA. On day 15, dasatinib treatment shall begin and continue without planned interruption until the completion of therapy (102 weeks).

For adverse events, including deaths, and for medications other than study medication, the baseline period ends the day prior to the first day of dasatinib treatment. Otherwise, the latest assessment prior to, or on, the first day of dasatinib will be considered the baseline assessment.

6.1.2 On-Treatment

On-treatment period:

- For evaluations: period after the first day (i.e. as from the 2nd day) of dasatinib, until and including 30 days after the last dose of dasatinib.
- For adverse events, including deaths, and medications other than study medication (concomitant medications): period as from the first dasatinib dosing day until and including 30 days after last dose of dasatinib.

6.1.3 Stem Cell Transplant

Subjects who meet pre-defined MRD criteria prior to the start of the first consolidation block (HR1) or after the completion of the third consolidation block (HR3) of chemotherapy and have a genotype-matched donor (9/10 or 10/10) will receive a hematopoietic stem cell transplant (HSCT) instead of continuing the AIEOP-BFM ALL 2000 regimen. The timing of HSCT would be following the consolidation block 3 (HR3). In practice the HSCT may not follow HR3

directly. For example, if a suitable donor becomes available later. In that case, subjects may continue in Reinduction for a certain time before receiving stem cell transplant. During the HSCT, subjects will not receive dasatinib. Following HSCT, the use of dasatinib is optional at the discretion of the treating investigator. Subjects may receive 12 additional months of post-HSCT dasatinib.

6.1.4 Follow-Up Phase

Subjects who complete or discontinue study treatment will enter the Follow-Up phase. This includes subjects not receiving HSCT, as well as subjects receiving HSCT with or without post-HSCT dasatinib treatment.

6.1.5 Overall Follow-Up

Overall follow-up refers to subject being followed up both on study treatment and off study treatment. For subjects not receiving HSCT and who complete study treatment, the duration of treatment (including chemotherapy and dasatinib) will be approximately 104 weeks (2 years). Subjects will be followed (including time on treatment) for at least 3 years for event-free survival and other secondary endpoints, 5 years for overall survival and 7 years (2 years of treatment + 5 years after completion of treatment) for [redacted] and other exploratory endpoints.

6.2 Treatment Regimens

From the start of induction therapy IB, all subjects will follow the same treatment plan shown in Table 4.3A of the protocol until the end of HR3 where

- Subjects who proceed to HSCT will receive preparatory regimen prior to HSCT and the treatment for the HSCT. After stem cell transplantation dasatinib is allowed in all HSCT recipients, however, is considered optional at the discretion of the treating physician. If dasatinib treatment is given post-HSCT, an initial dose of 48 mg/m^2 daily will be administered provided PTL and WBC counts are satisfactory, with stable neutrophils engraftment (PTL > 50 x 10^9/L; WBC > 1.5 x 10^9/L; neutrophils > 0.5 x 10^9/L for at least 15 days). If the initial dose is deemed tolerable by the treating physician, the dose of dasatinib should be escalated to 60 mg/m^2 within the first month of starting post-HSCT dasatinib. For those subjects that opt for post-HSCT dasatinib, administration is suggested throughout the first year post-transplantation until day +365 from HSCT. The preparative regimen prior to HSCT and the treatment for the HSCT will be according to the institutional standard of care.
- Subjects not receiving HSCT will, after the recovery period following HR3, continue with Reinduction Block 1 (followed by Interim Maintenance, Reinduction Block 2 and Continuation).

6.3 Populations for Analyses

- All Enrolled Subjects Data Set: All subjects with signed informed consent form.

- All Treated Subjects Data Set: All subjects who received at least one dose of dasatinib. Demographic, baseline characteristics, exposure to dasatinib, efficacy, and safety analyses will be performed on all treated subjects.
- Mutation Data Set: All treated subjects who have mutation data available will be included in the mutation data set.

7 STATISTICAL ANALYSES

7.1 General Methods

A complete description of the tables is given in the data presentation plan. By-subject listings will be prepared to support summaries and analyses. Basic principles for table presentation are the following:

- Analyses and summaries will be, except where indicated otherwise, based on the whole target study population, as well as on the following sub-populations:
    - Subjects treated with dasatinib tablets only, and
    - Subjects who at any time received dasatinib in the PFOS (Powder For Oral Solution) formulation.
- Descriptive statistics will be used to summarize demographic characteristics, extent of exposure, safety and laboratory observations (hematology, serum chemistry). Categorical variables will be summarized in frequency tables. In general, continuous and other numeric variables will be summarized by presenting the number of observations, mean, standard deviation, median, interquartile range, minimum and maximum.
- Laboratory results will be classified according to the National Cancer Institute - Common Terminology Criteria (NCI-CTCAE) Version 4.0. Additional laboratory results that are not part of NCI-CTCAE will be presented according to the following categories: below normal limits, within normal limits, and above normal limits. Toxicities will be coded using the most current version at the time of analysis of Medical Dictionary for Regulatory Activities (MedDRA) system organ classes and preferred terms and will be graded using the NCI-CTCAE Version 4.0 criteria.
- Concomitant medications will be coded using the World health Organization (WHO) Drug Dictionary (modified by BMS).

7.2 Study Conduct

7.2.1 Protocol deviations

Relevant protocol deviations as listed in the table below will be tabulated for all treated subjects. In addition, a by-subject listing will be provided.

Table 7.2.1-1: Relevant Protocol Deviations

A. Baseline deviations
I. **Inclusion Criteria**:
1. Diagnosis
Correct identification of the disease, i.e. ALL. This refers to inclusion criterion 2)a).
Documented presence of reciprocal translocation between chromosomes 9 and 22. This refers to inclusion criterion 2)a)i).
Cytogenetic testing or FISH analysis must have been performed or both.
2. Target population
Age at diagnosis must be >1 and <18 years
3. Induction chemotherapy
Subject must have received induction therapy as per institutional standard (At least one record of study medication should be entered for visit B01: Did the subject receive study medication=Yes, and at least one drug name should be provided).
II. Exclusion criteria:
1. Prior treatment with a BCR-ABL inhibitor
BCR-ABL inhibitors include, but may not be limited to, Imatinib, Nilotinib, and Ponatinib. A list of BCR-ABL inhibitors will be provided, and when necessary updated based on clinical input.
2. Biopsy proven Ph+ ALL extramedullary involvement of the testicles
(From Extramedullary Involvement CRF page - extramedullary involvement of the testicles has code #73)
B. On study deviations
1. Concomitant medications known to prolong the QT interval
See section 3.4.1.1 of the protocol for a list of medications associated with QT interval prolongation. "Concomitant" should be interpreted in the strict sense in that these medications are only prohibited on days when also dasatinib is administered.

7.2.2 Enrollment

- Accrual by country will be tabulated for all enrolled subjects. Accrual by site will be tabulated for all treated subjects. Subjects enrolled but not treated will be included in a subject disposition listing.

7.3 Study Population

7.3.1 Subject Disposition

The subject disposition table will include the percentage of treated subjects in the enrolled population and the percentages of subjects off treatment and off study among treated subjects. Subject status will be summarized separately for the following phases: Induction through HR3,

Reinduction through Continuation, HSCT, and Follow-up. Off-treatment and off-study reasons will also be tabulated and listed.

7.3.2 Demographics at baseline

Demographic data, i.e. gender, race, ethnicity, age at disease diagnosis, age at consent, country and site will be summarized and listed. For age at disease diagnosis, in addition to the presentation of sample statistics, frequencies of the following age categories will be presented: >1 to <2; ≥2 to <7; ≥7 to <12; ≥12 to <18.

7.3.3 Medical history

7.3.3.1 General medical history

General Medical History will be summarized by system and listed.

7.3.3.2 Disease history

Disease history will be summarized as follows:

- Time (in days) from initial ALL disease diagnosis to first dasatinib dosing date (Median, Min-Max)

- Immunophenotype disease diagnosis and baseline CNS leukemia disease status

-Philadephia positivity (t(9:22)(q34;q11)) method: Fluorescence in-site hybridisation only, real-time PCR only, both.

-Transcript detected: p190 0r p210 or data not available

- Specific disease history: WBC counts at disease diagnosis will be summarized as continuous data using descriptive statistics and as categorical data after slotting the counts in the following categories:

- < 50,000/μL
- 50,000-100,000/μL
- > 100,000/μL.

7.3.4 Pre-treatment Clinical complaints and findings

Pre-treatment events are those adverse events with an onset date in the baseline period.

Worst CTC grade of any pretreatment events will be summarized by MedDRA system organ classes and preferred terms and also listed. Pre-treatment events will not be included in the on-treatment AE tables.

7.3.5 Baseline evaluations

Baseline evaluations are those collected for treated subjects in the baseline period. For any treated subject, the result included in a baseline summary is the last available measurement or assessment prior to, or on, the first day of dasatinib dosing.

7.3.5.1 Subject Characteristics at baseline

Subject characteristics at baseline (Physical measurements, ECG, Echocardiogram, and site of extramedullary involvement) will be summarized.

7.3.5.2 Physical Examination at baseline

Abnormal physical examination at baseline will be tabulated. A listing for physical examination at baseline will be also provided.

7.3.5.3 Laboratory parameters at baseline

CTC grade of baseline hematology laboratory values (CBC and differential) and serum chemistry baseline results BUN (or urea), serum creatinine, HCO3, ALT, AST, total bilirubin, LDH (high), Na, K, Cl, Mg (low), phosphorus, calcium (low), and uric acid will be tabulated.

7.3.5.4 Risk Groups

High risk and low/standard risk treated subjects will be tabulated and listed.

High risk subjects are those with MRD at end of Induction 1A $\geq$ 0.01%. Low/standard risk subjects are those with MRD at end of Induction 1A of < 0.01%.

The MRD method used to define the risk group for a subject is Ig/TCR. For subjects that do not have informative results of Ig/TCR at Induction 1A, MRD as measured by RQ-PCR for BCR-ABL will be used. If both Ig/TCR and BCR-ABL are uninformative, flow cytometry results will be utilized.

7.4 Extent of Exposure

Extent of exposure will be summarized for dasatinib only (not for chemotherapy). Study therapy, dasatinib and chemotherapy, will be presented in by-subject listings.

7.4.1 Administration of Dasatinib

Duration of therapy (months), the average daily dose (mg/m2/day), and the relative dose intensity (%) will be summarized for:

- All treated subjects, extent of exposure across the study
- All treated subjects, extent of exposure until end of Consolidation
- Treated subjects without HSCT, extent of exposure across the study
- Treated subjects with HSCT, extent of exposure until HSCT
- Treated subjects with HSCT, extent of exposure post-HSCT

In each of these summaries, results will be derived for:

- All treated subjects,
- The subgroup of subjects who received dasatinib exclusively in tablet form, and
- For the subgroup of subjects who received at least 1 dose of dasatinib in PFOS formulation. Duration of treatment will be reported for the whole subgroup and by formulation (PFOS/tablet).

For subjects not receiving HSCT, duration of therapy (in days) will be defined as:

Last dasatinib dose date - first dasatinib dose date + 1

For subjects who did receive HSCT and received dasatinib post-HSCT, the dosing gap around HSCT will be subtracted.

Duration of therapy will be expressed in months by dividing duration of therapy in days by 30.4375.

The average daily dose (in mg/m2/day) will be defined as the cumulative dose (i.e., the sum of daily doses, in mg/m^2, administered during the study) divided by the duration of therapy in days. The daily doses in mg/m^2 are obtained by dividing the dose received in mg by the most recent value of body surface area (BSA). BSA is computed using the following formula[12]: Square root of [Height (cm) x Weight (kg) /3600].

The relative dose intensity will be defined as: average daily dose / 60, and will be expressed as a percentage.

7.4.2 Dose modifications for Dasatinib

Dose modifications (interruption, or reduction to 48 mg/m^2) should be made for adverse events considered related to dasatinib (see protocol section 4.3.2.1 for a complete description of Dasatinib related AEs).

Dasatinib dose modifications (reductions, interruptions and escalations) will be tabulated for the All Treated Subjects dataset for the period through HR3. For the period from start of Reinduction Block 1 through end of Continuation the tabulation will comprise:

- All treated subjects, extent of exposure across the study
- All treated subjects, extent of exposure until end of Consolidation
- Treated subjects without HSCT, extent of exposure across the study
- Treated subjects with HSCT, extent of exposure until HSCT
- Treated subjects with HSCT, extent of exposure post-HSCT

In each of these summaries, results will be derived for:

- All treated subjects,
- The subgroup of subjects who received dasatinib exclusively in tablet form, and
- For the subgroup of subjects who received at least 1 dose of dasatinib in PFOS formulation.

A dose reduction will be defined as an administration at least by 2 consecutive days of a planned dose (in mg/m2) which is lower than both the previous dose and the subject's starting dose (=60 mg/m2/day).

A dose interruption will be defined as a complete omission of actual dosing on 2 consecutive days, provided that the subject resumes his dosing afterwards.

The reason for dose modification will be the first reason reported by the Investigator for the period during which the dose modification was reported.

Time to first reduction/interruption due to hematologic/non-hematologic toxicity will be defined as the time (in days) from the first dasatinib dosing date to the date of first reduction or interruption due to hematologic/non-hematologic toxicity.

The length of first interruption due to hematologic/non-hematologic toxicity will be defined as the time (in days) from the first interruption (i.e. the first date the dosing was omitted) due to hematologic/non-hematologic toxicity to, but not including, the first following date the dosing was resumed (i.e. the first following date dasatinib was administered).

7.4.3 Previous and Concomitant Medications

A previous and concomitant medications listing will be provided.

7.4.4 Duration of Treatment Blocks

The treatment blocks are the following (between brackets are included the target durations):

- Induction IA (4 - 5 weeks)
- Induction IB (4 weeks)

Then follows a recovery period during which dasatinib treatment continues but no chemotherapy is given (2 - 4 weeks)

- 3 successive Consolidation blocks (HR1, HR2, and HR3) (3 x 3 weeks)
- Reinduction Block 1 (9 weeks)
- Interim maintenance (4 weeks)
- Reinduction Block 2 (9 weeks)
- Continuation therapy (62 weeks)

The start of a treatment block is captured as the earliest date of any non-dasatinib medication given during that block. The stop date of a treatment block is captured as the day before the start date of the subsequent block if there is a subsequent block, and the last date of any study treatment if there is no subsequent block.

Treatment block duration will be summarized with descriptive statistics. Subjects who receive HSCT after HR3 (although in individual cases subjects may have already started Consolidation) may restart dasatinib post-HSCT. The duration of that period will be summarized similarly.

7.5 Efficacy

- Efficacy analyses will be based on all treated subjects and will mainly consist of :

- Response rates (3-year EFS rates in primary analysis, complete remission rates, HSCT rates, MRD rates), along with their two-sided, 95% exact (Clopper and Pearson[2]) confidence intervals.
- Kaplan-Meier plots for time to event variables (i.e. EFS in secondary/sensitivity analyses, DFS, OS and time from the MRD assessment until the event) will be provided with number of subjects at risk. A two-sided, 95% confidence interval for the median will be computed using the method of Brookmeyer and Crowley[3].The 3-year and 5-year EFS and DFS rates will be presented with their corresponding 95% CI's using Greenwood's formula for the standard error and based on the log-log transformation. Listings with duration (event free, survival, disease free) will be provided.
-

7.5.1 Event -Free Survival (EFS) Analyses

7.5.1.1 Regulatory Background

Initially the intention for study CA180372 was to be a single-arm study without formal treatment comparisons. The European regulatory authorities (PDCO) during discussions on the PIP required BMS to include formal statistical comparisons with results from external historical control trials. These comparisons would be performed using Kaplan-Meier based analyses utilizing patient level data from all three trials.

A request from BMS for patient level efficacy data from the two external historical control trials (AIEOP-BFM 2000 and Amended EsPhALL) was refused (in May 2013) by the respective study steering committees due to lack of subject consent for data sharing with BMS. However BMS received a confirmation in writing on behalf of the study steering committees that a set of results from each historical control study would be made available to BMS, most importantly the 3-year EFS binomial rates, in which:

- Subjects lost to follow-up prior to the 3-year time point and event-free up until last contact will be considered event-free at the 3-year time point,
- Subjects discontinuing study treatment early but still being followed up will be assessed for 3-year EFS, regardless of the treatment following discontinuation, and
- HSCT is not regarded as an event.

According to the agreement, EFS data will be handled in the same way for study CA180372 and the historical control trials for the primary analyses that are based on differences in the 3-year EFS rates, and also with regard to the calculation of Kaplan-Meier estimates. The binomial rates allow for the formal statistical comparison of the data as required by the PDCO.

As part of the agreement with the steering committees of the historical control trials, the following sensitivity analyses to evaluate the robustness of the primary analysis are also planned:

- The same approach as above, except that subjects lost to follow-up prior to the 3-year time point and event-free up until last contact will be considered as having had an event at the date of last contact.

- The same analysis as above, but in which a subject with HSCT will be considered as having had an event in case the subject discontinued study treatment.

- Finally, the agreement also includes that the following results from the historical control trials will be provided:

- Kaplan-Meier estimates of EFS at 3 and 5 years.
- Complete remission rates at end of Induction (defined as < 5% blasts in bone marrow and no peripheral blasts).

7.5.1.2 Primary analysis

- In the primary analysis the 3-year EFS rate from study CA180372 will be compared with the 3-year EFS rates from two external historical controls (AIEOP-BFM 2000 and Amended EsPhALL) in hierarchical order , so that the overall experiment-wise one-sided type I error rate will be preserved at 0.05.

- The comparisons will be as follows:

  - 1. Superiority over chemotherapy alone of AIEOP-BFM 2000: 3 year EFS rate = 52%.

  - 2. Non-inferiority to continuous imatinib plus chemotherapy of the amended EsPhALL trial: expected 3 year EFS rate = 78%. Non-inferiority margin size of 5%.

  - 3. Superiority over continuous imatinib plus chemotherapy of the amended EsPhALL trial: expected 3 year EFS rate = 78%.

- The trial will be considered positive if at least the first two comparisons are statistically significant.

- The difference with the 3-year EFS rate from the chemotherapy alone control arm will be tested first. If that test is significant in favor of dasatinib, then non-inferiority relative to imatinib plus chemotherapy in the amended EsPhALL trial will be tested. If that test is significant and non-inferiority of dasatinib is declared, then superiority testing of the difference with the 3-year EFS rate in the continuous imatinib added to chemotherapy arm from the amended EsPhALL trial will be tested in third place.

- The comparison will be done after the last subject treated has passed the 3-year follow-up period to ensure all subjects have the opportunity for 3-year EFS assessments (no interim analysis for primary endpoint).

- The differences in 3-year EFS rates will be computed using binomial proportions of subjects who are free of events at 3 years over all treated subjects. **Subjects lost to follow-up at any time without an event will be considered event free in the primary analysis**. All subjects

will have the opportunity to be followed for 3 years prior to the analysis and the denominator will include all treated subjects.

- Event rates will be provided with exact 2-sided 90% Clopper-Pearson CI's. Differences in event rates will be tested at the 0.05 1-sided significance level using a Pearson χ^2 test.

- Non-inferiority testing against the study treatment in the amended EsPhALL trial will be carried out using the corresponding 2-sided 90% CI for the treatment difference (3-year EFS rate in dasatinib+chemo minus 3-year EFS rate in imatinib+chemo) and comparing the lower confidence limit to the non-inferiority margin of -5%. This margin corresponds to 1/4 of the effect size of 18% anticipated in the amended EsPhALL trial over the chemotherapy-only control of the original EsPhALL trial.

- Analyses will be conducted in the treated population. Interim analyses for DMC reports don't include evaluation of EFS rates versus those in the historical external controls. Stopping rules may come into effect only when poor interim EFS results are observed and the Type I error related to the primary analyses is not affected.

- Next to performing the above analyses on all treated subjects, the same analyses will be performed on subjects with uncontested Ph+ ALL diagnosis, meaning that any subject that was considered during treatment not to have Ph+ ALL, but say CML in blast crisis, will be excluded.

7.5.1.3 Secondary analyses

- Secondary analyses related to EFS are:

1. Estimation of EFS at yearly time points (including 3 year and 5 year rates) will be performed utilizing the Kaplan-Meier (KM) Product Limit method.

In this key secondary analysis of estimated EFS, subjects who neither relapse nor die or who are lost to follow-up without an event will be censored on the date of their last bone marrow (BM) assessment, cerebrospinal fluid (CSF) assessment or physical exam, whichever occurs last. For subjects not reaching complete response by end of Consolidation Block 3/start of first Reinduction, the event date will be the date of BM assessment at end of Consolidation Block 3 or the date of the last available valid on-treatment BM assessment after start of dasatinib prior to the end of Consolidation Block 3. Subjects without valid BM results between the start of dasatinib and the last day of Consolidation Block 3 (HR3)/start of Reinduction 1 (no BM done or no evaluable aspirate) will be considered having lack of complete response, and in that case the event date will be set equal to the start date of dasatinib.

2. The difference in 3-year EFS rate with the 3-year EFS rate in study COG AALL0031 will be computed using binomial proportions as a secondary objective.

When comparing with these controls, the definition of event in EFS will be modified in order to align the endpoints for a relevant comparison: for comparison with COG AALL0031, lack of

complete response will be aligned and defined as > 5% bone marrow blasts at the end of induction IB.

Disease relapse/progression will be summarized. Number and percentage of treated subjects with disease relapse/progression will be presented by site (CNS, testicular, bone marrow, other). A by-subject listing will also be provided.

- Next to performing the above analyses on all treated subjects, the same analyses will be performed on subjects with uncontested Ph+ ALL diagnosis, meaning that any subject that was considered during treatment not to have Ph+ ALL, but say CML in blast crisis, will be excluded.

7.5.1.4 Sensitivity and Subgroup analyses

- Additionally, sensitivity analyses will be performed on EFS including :

- 1. HSCT considered as an event if the subject discontinues; i.e. the subject does not continue dasatinib use after HSCT.

- 2. Lost to follow-up considered as an event (at the date of last contact).

- 3. Induction failures considered as an event at time 0. Induction failures are defined as patients who don't achieve a bone marrow Complete Remission (<5% lymphoblasts) by the last day of consolidation block HR3/start of first Reinduction (Protocol II).

4. Resurgence of MRD considered an additional event type, defined by the reason provided to start subsequent systemic cancer therapy being "non protocol-defined relapse".

- 5. Subgroup analyses around HSCT, presenting 3-year EFS rates with 95% CIs:

- Subjects who had HSCT
- Subjects who were eligible to have HSCT but did not undergo this intervention
- Subjects who were ineligible for HSCT
- Subjects who were eligible for HSCT

6. Subgroup analyses of high versus low/standard risk. These risk groups are defined as follows:

- High risk group: subjects with MRD at end of Induction 1A ≥ 0.01%.
- Low/standard risk group: subjects with MRD at end of Induction 1A of < 0.01%.

7. Subgroup analyses based on age group:

- Age below 12 years
- Age at least 12 years

7.5.2 Complete remission rate

Complete remission (CR) rate is defined as the proportion of subjects achieving a complete remission, i.e. < 5% lymphoblasts in bone marrow and in CSF, with no evidence of other extramedullary disease. Complete remission rates at end of Induction 1A, end of Induction 1B, and end of Consolidation will be tabulated. A subject is in Continued Complete Remission (CCR) as long as no relapse occurred since Complete Remission (CR) was achieved. CCR rates will be tabulated for end of Induction IB and end of Consolidation. Achievement of complete remission will be included in a subject listing.

7.5.3 Disease-Free Survival Analysis

- Kaplan-Meier plots and 3-year and 5-year DFS rates will be provided on responders only, i.e. subjects who achieved complete response (M1 bone marrow) by end of HR3 / start of first reinduction block..

7.5.4 Overall Survival Analysis

- Kaplan-Meier plots will be provided on all treated subjects. Subjects will be followed for survival for 5 years after end of treatment.

7.5.5 Minimal Residual Disease (MRD)

The method of reference to estimate MRD levels is the quantitative PCR detection of clone-specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR). The limit of detection of this assay will be approximately 10^{-4} - 10^{-5} or 0.01% - 0.001%.

Quantitative PCR for BCR-ABL will be expressed as a ratio of BCR-ABL transcripts compared to a control gene (eg ABL) with log reduction compared to baseline.

MRD levels from Flow are based on the percent mononuclear cells.

7.5.5.1 MRD Negative Rates

- The rates of MRD negative subjects will be computed for end of Induction 1A (MRD2), end of Induction 1B (MRD3), and end of Consolidation (MRD4). PCR for clone-specific immunoglobulin and T-cell receptor gene rearrangements(Ig/TCR) wil be the method used for deciding a subject MRD-negative or not.

- MRD negative rates will be summarized as:

- The number of MRD negative subjects among all treated subjects. In order to include all treated subjects, those without evaluable Ig/TCR assessment will be considered as MRD positive.
- The number of MRD negative subjects among subjects with an evaluable Ig/TCR assessment.

- Rates will be presented together with exact 2-sided 95% Clopper-Pearson confidence intervals.

7.5.5.2 Correlation between the 3 methods of assessing MRD

To investigate how the 3 MRD methods correlate, concordance between MRD results and concordance between HSCT recommendation will be assessed. These exploratory analyses will be performed based on all MRD data from all treated subjects, ignoring dasatinib formulation.

The three methods are:

- Real-time qPCR for clone specific immunoglobulin and T-cell receptor gene rearrangements (Ig/TCR),
- real-time qPCR for BCR-ABL transcripts (BCR-ABL), and
- multiparameter flow cytometry (Flow)

An MRD result may be positive (a numeric level of positivity is reported), negative, or 'positive but not quantifiable' (in which case no robust level of positivity could be established). Pairwise MRD concordance will be investigated between each 2 out of the 3 methods.

MRD concordance will be summarized and graphically presented for each on-treatment time point (MRD2, MRD3, and MRD4) and for pooled results across time points.

In addition to MRD concordance, also pairwise HSCT recommendation concordance will be tabulated.

7.5.5.3 Prognostic value of MRD on EFS

For the 3 methods of MRD evaluation, Kaplan-Meier plots will be used to estimate the time from the MRD assessment until the event for each category of MRD level. Landmark analyses based on landmark time points MRD2, MRD3, and MRD4 will be performed for the following MRD categories: negative, positive but not quantifiable, and positive.

The medians will be provided with their 2-sided 95% CIs computed using the method of Brookmeyer and Crowley.

7.5.6 HSCT

The rate of subjects who were eligible for HSCT is defined as the number of subjects who were eligible for HSCT divided by the number of treated subjects. The rate of subjects who received hematopoietic stem cell transplant is defined as the number of subjects with HSCT divided by the number of treated subjects.

The numbers of subjects who 1) received HSCT, 2) who were eligible for HSCT but did not receive it, and 3) who were ineligible for HSCT will be tabulated.

Data summarizing HSCT events (such as donor type, transplant source, degree of match and phase of transplant) will be tabulated and listed. Bone marrow blasts and cytogenetic

A bone marrow analysis listing will be provided.

7.5.6.1 Cerebrospinal Fluid (CSF)

A listing with CSF results (cell counts and cytopathology) will be provided.

7.6 Safety

Analyses of safety will be based on the data set of all treated subjects. The latest available MedDRA Dictionary version will be used for the classification of the adverse events. The frequencies of adverse events and other symptoms will be calculated for the on-treatment, i.e. from day 1 of dasatinib treatment through last day of dasatinib treatment + 30 days, and post-treatment period (late toxicities), i.e. IMP-related adverse events with an onset date after the last day of dasatinib treatment + 30 days.

Note: The abbreviation IMP (Investigational Medicinal Product) in this study denotes dasatinib. The AE/SAE forms for this study collect "action taken" and "drug relatedness" for dasatinib specifically, not for study medication generally.

7.6.1 Deaths

The number of deaths will be tabulated by primary reason during induction, during consolidation therapy, and on-treatment post-consolidation. The number of treatment-related deaths will be identified. Death is considered treatment-related if the primary cause of death captured on the death data crf page is 'study drug toxicity'. The number of deaths overall (at any time after start of dasatinib), the number of deaths within 30 days of last dose of dasatinib, as well as the number of deaths in continuous complete remission (CCR) will be tabulated along with the corresponding reason. Subjects are in CCR after a first assessment of Complete Remission (CR), provided that this first CR has been confirmed at the next assessment. A subject is only no longer in CCR if relapse is established. All deaths will be presented in a listing.

7.6.2 Other Serious Adverse Events

On-treatment serious adverse events (SAEs) are defined in section 6.1 of the protocol and consist of adverse events deemed serious by the Investigator.

On-treatment SAEs will be classified by system organ class and by preferred term, and the worst grade per subject will be included in the tabulation. On-treatment SAEs leading to hospitalization and IMP-related on-treatment SAEs will be summarized similarly.

7.6.3 AEs leading to discontinuation

On-treatment AEs leading to discontinuation (AEs with action taken = "Drug was discontinued") will be classified by system organ class and preferred term, and the worst grade per subject will be included in the tabulation. IMP-related adverse events leading to discontinuation will be summarized similarly.

7.6.4 AEs of special interest

Adverse events of special interest are defined within the project (for example pleural effusion/fluid retention, bleeding); the complete list of adverse event of special interest, including any new emerging event, will be detailed in the Data Presentation Plan. On-study adverse events of special interest will be tabulated by any grade versus severe (grade 3-4) and grade 5. IMP-related adverse events of special interest will be summarized similarly.

7.6.5 Overall AES

On- treatment adverse events will be classified by system organ class and by preferred term, and the worst grade per subject will be included in the tabulation. IMP-related on-treatment adverse events will be summarized similarly.

Non-serious adverse events

A table of on-study non-serious adverse events will be provided on the total treated population using a cut-off of 5%.

Adverse events post HSCT

A frequency table of post-HSCT adverse events will be prepared in subjects opting to continue dasatinib after receiving HSCT.

Late toxicities

Late toxicities (IMP-related adverse events reported more than 30 days after last dose of study medication) will be classified by system organ class and preferred term, and the worst grade per subject will be included in the tabulation. A by-subject listing of late toxicities will be prepared.

Analysis of Adverse Event Multiple Occurrences

Several descriptive summaries of adverse events that take into account the number of occurrences that an AE was reported by individual patients will be provided. In order to prepare these summaries, the CRF data will be processed according to standard BMS algorithms to categorize each line of patient data as a new occurrence or a continuation of an existing event. This determination will be based upon onset and resolution dates. Each line of patient data will represent the maximum severity observed as well as the last known assessed relationship to study medication by the investigator.

This data will be presented as the rate per 100 years of patient exposure. Exposure to study medication will be calculated according to approved standard BMS algorithms as well.

As an example, if 5 patients report 7 unique episodes of headache and had a combined cumulative exposure of 20 years to study medication, the incidence rate is reported as 7/20 *(100) or 35 cases per 100 patient years of exposure.

The following summary tables will be provided:

A table showing the total number and rate (exposure adjusted) of occurrences for all AEs occurring in at least 5% of the subjects treated

For events of clinical interest and SAEs that warrant further analysis:

A table showing total number of events and rate (exposure adjusted) by time intervals: 0-6 months, 6-12 months, and annually thereafter

A table showing the number of subjects experiencing an AE once or multiple times

A listing displaying the unique instances of all AEs, i.e., after duplicates have been eliminated and overlapping and contiguous occurrences of the same event have been collapses.

No formal statistical testing will be performed, only summary statistics are provided.

7.6.6 Neoplasms

On-treatment neoplasms, identified from the SAE CRF page (event='cancer'), and neoplasms in follow-up, identified from the follow-up page for new cancer, will be presented in by-subject listings.

7.6.7 Treatment Block Delays

Frequencies of treatment block delay categories (≤ 7 days, 8-14 days, etc.) will be presented for delays in start of HR1 relative to start of dasatinib (for subjects starting HR1), and delays in start of R1 relative to start of HR1 (for subjects starting R1).

7.6.8 Clinical laboratory evaluation

7.6.8.1 Hematology

Worst on-treatment grade for WBC, ANC, platelets and haemoglobin will be tabulated, as well as worst on-treatment grade beyond the end of Induction, and worst on-treatment grade beyond the end of high risk block 3. Analysis will be restricted to treated subjects with at least one on-treatment measurement. Baseline vs. worst on-treatment grade will also be tabulated (grade 0, 1-2 vs. 3-4). Similarly, end of Induction vs. worst post-induction on-treatment grade, and end of consolidation therapy vs. worst post-consolidation therapy on-treatment grade will be tabulated (grade 0, 1-2 vs. 3-4).

7.6.8.2 Serum chemistry

Worst on-treatment grade for BUN (or urea), serum creatinine, HCO3, ALT, AST, total bilirubin, LDH (high), Na, K, Cl, Mg (low), phosphorus, calcium (low), and uric acid will be tabulated. Analysis will be restricted to treated subjects with at least one on-treatment measurement. Baseline vs. worst on-treatment grade will also be tabulated (grade 0, 1-2 vs. 3-4).

7.6.9 Other Safety considerations

7.6.9.1 Electrocardiogram (ECG)

Frequency distribution of maximal QTc(F) intervals on treatment and QTc(F) changes from baseline (<-60, -60-<-30 , -30-<0, 0-30, >30-60, >60) will be tabulated. A listing for ECG parameters will be provided.

7.6.9.2 Echocardiogram / MUGA

Frequencies of abnormal echocardiograms / MUGA findings on treatment will be tabulated. A listing of echocardiogram/MUGA results will be displayed in a by-subject listing.

7.6.9.3 Chest X-Ray

Abnormal chest X-ray findings will be displayed in a listing.

7.6.9.4 Physical measurements and vital signs

By-subject listings will be produced for physical measurements and vital signs.

7.6.9.5 Long-term Growth and Development and Bone Metabolism

Changes from baseline and changes from baseline in z-score, as well as percentile shifts from baseline, will be tabulated for height, weight and BMI. Height, weight, and BMI will be presented in by-subject listings, together with z-scores and percentiles.

The z-scores will be derived using WHO growth standards[13], which are based on a large study (1997 to 2003) on 8500 children from widely different ethnic backgrounds and cultural settings (Brazil, Ghana, India, Norway, Oman, and US). Selection criteria for that study included specific behaviors consistent with current health promotion recommendations (breastfeeding norms, standard pediatric care, non-smoking requirements). The z-scores are dependent on age and gender and correspond to a normal distribution with mean 0 and a standard deviation of 1.

Height, weight, BMI, bone age, free T4, TSH, FSH, LH, IGF-1, IGFbeta-3, urinary N-telopeptide, bone alkaline phosphatase and bone densitometry scan results will be summarized over time using descriptive statistics. Tanner stages will be summarized in shift from baseline tables.

Long-term growth and development assessments and bone mineral content are collected at baseline, annually during treatment, and annually for 5 years after completing dasatinib. In the summary tables, the following periods, relative to start of dasatinib, will be defined: ≤ 1 year, >1 and ≤ 2 years, > 2 and ≤ 3 years, > 3 and ≤ 4 years, > 4 and ≤ 5 years, etc. If a subject has more than 1 assessment in a time interval, the last assessment will be used.

By-subject listings will be prepared for: bone age, Tanner stage, hormone levels (T4, TSH, FSH (for children > 8 years old), LH (for children > 8 years old)) and growth factors (IGF-1/IGFB-3), long-term bone metabolism assessments (Urinary N-Telopeptide, Bone Alkaline Phosphatase), DXA scanning results. DXA scanning will include bone mineral content and density measures in lumbar spine, total body (less head), total hips and femoral neck.

Adverse event (AE) and serious adverse event (SAE) (Grade 2 and above) associated with growth and development disorders and bone mineralization will be listed by subject (the list of events will be specified in the DPP).

7.7 Mutation Analysis

BCR-ABL mutation status will be analyzed at baseline and at disease progression or relapse. The specific type and frequency of mutations in the BCR-ABL kinase domain will be summarized using descriptive statistics.

•

8 CONVENTIONS

- In the instance of a missing day in a date that has the month and year, the day will be imputed as the 15th of the month. In the instance of a missing day and month in a date that has only the year, the day and month will be imputed as July 1.
- For adverse events, missing onset date will be imputed according to the conventions described in the document "Analysis of safety data", supplement to GD SOP 12:0 [5].
- The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.
- Duration (e.g. time from initial ALL disease diagnosis to first dosing date) will be calculated as follows:

$$\text{Duration} = (\text{Last date} - \text{first date} + 1)$$

9 CONTENT OF REPORTS

See DMC charter for tables and listings that have to be produced for DMC review. All the tables and listings described in this SAP will be used for the final CSR.

The list of tables (and figures/listings where indicated) below comprises the set of topline results.

- Subject Accrual
- Relevant Protocol Deviations
- Subject Disposition
- Demographics
- Deaths (summary tables and listing)
- Extent of Exposure to Dasatinib
- Dose Modifications for Dasatinib
- Complete Remission rates
- Primary efficacy analyses
- Kaplan-Meier curve and estimates of EFS
- All On-treatment Adverse Events, Worst CTC Grade
- All On-treatment Drug-Related Adverse Events, Worst CTC Grade
- All On-treatment Serious Adverse Events
- All On-treatment Drug-Related Serious Adverse Events, Worst CTC Grade
- Adverse Events Leading To Discontinuation
- Drug-Related Adverse Events Leading To Discontinuation
- On-treatment Neoplasms
- Height, weight, and BMI z-scores (change from baseline tables and box-plots)

10 REFERENCES

1 Schlieben S, Borkhardt A, Reinisch I, et al. Incidence and clinical outcome of children with BCR/ABL-positive acute lymphoblastic leukemia (ALL). A prospective RT-PCR study based on 673 patients enrolled in the German pediatric multicenter therapy trials ALL-BFM-90 and CoALL-05-92. Leukemia 1996 Jun; 10(6):957-63.

2 Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. Ann Intern Med 1999; 131:207–19.

3 Ottmann OG and Wassmann B. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Hematology (Am Soc Hematol Educ Program). 2005:118–2

4 Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol 2004; 22:4075–86.

5 Fielding AK. Current treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Haematologica 2010; 95:8-12.

6 Arico M, Schrappe M, Hunger SP, et. al. Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J Clin Oncol. 2010 Nov 1;28(31):4755-61.

7 Gruber F, Mustjoki S, Porkka K. Impact of tyrosine kinase inhibitors on patient inhibitors on patient outcomes in Philadelphia chromosome-positive acute lymphoblastic leukaemia. Br J Haematol 2009 Jun; 145(5):581-97. Epub 2009 Apr 15.

8 Conter V, Bartram CR, Valsecchi MG, et. al. Molecular Response to Treatment Redefines All Prognostic Factors in Children and Adolescents with B-cell Precursor Acute Lymphoblastic Leukemia: Results in 3184 Patients of the AIEOP-BFM ALL 2000 Study. Blood. 2010 Apr; 115 (16): 3206-3214.

9 Piccaluga PP, Paolini S, Martinelli G. Tyrosine kinase inhibitors for the treatment of Philadelphia chromosome-positive adult acute lymphoblastic leukemia. Cancer 2007; 110:1178–86.

10 Metha CR and Caine KC. Charts for the early stopping of pilot studies. J Clin Oncol 1984; 2:676-82.

11 Mariani L and Marubini E. Design and analysis of phase II cancer trials: a review of statistical methods and guidelines for medical researchers. International Statistical Review 1996; 64: 61 88.

12 Mosteller RD: Simplified Calculation of Body Surface Area. N Engl J Med 1987 Oct 22;317 (17):1098 (letter)

13 http://www.who.int/childgrowth/en/