Statistical Analysis Plan

TRIAL FULL TITLE	**D-ALBA Front-Line Sequential Treatment of Adult Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Patients with Dasatinib and the Bispecific Monoclonal Antibody Blinatumomab**
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Items Required

Trial Protocol
Trial CRF
P.O. 8.1.1 Raccolta, validazione ed analisi dei dati
I.O.13.3 Disegno dello studio
I.O.13.2 Analisi statistica

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2 Abbreviations and Definitions

AE	Adverse Event
CRF	Case Report Form
IMP	Investigational Medical Product
SAP	Statistical Analysis Plan

3 Introduction

3.1 Preface

Patients who have the Philadelphia (Ph) chromosome and/or the associated *BCR-ABL1* oncogene still have a poorer prognosis than other ALL subtypes. The Ph rearrangement gives rise to the BCR-ABL1 oncogene, whose gene product is a constitutively active tyrosine kinase that is associated with defects in cellular adhesion, apoptosis and DNA repair, as well as growth factor independence. In addition, recent studies have demonstrated that deletions of *IKZF1* (encoding the transcription factor Ikaros) may be an important event in the development of Ph+ ALL; similarly, Src-family kinases (SFKs) may also contribute to the pathogenesis of Ph+ ALL. The frequency of the Ph chromosome increases with age, from approximately 2-5% in children, to about 25% in patients aged 21-50 years, with a progressive increase with age, and to over 40% in patients aged more than 50 years, making it the most common genetic abnormality in adult ALL. Prior to the introduction of tyrosine kinases inhibitors (TKI), the outcome of Ph+ ALL was extremely poor, both in terms of achievement of complete hematologic remission (CHR) and long-term survival, and the only curative option was represented by allogeneic hematopoietic stem cell transplantation (allo-SCT) at the earliest opportunity. Even in the TKI era, this subgroup is still associated to a poor prognosis, because of the high relapse rates and the development of drug resistance. The long-term overall survival (OS) is in the range of 30-50% with current treatments, consisting of TKIs with or without chemotherapy, possibly followed by transplant procedures. Allo-SCT is still considered the only curative treatment for Ph+ ALL; despite treatment-related mortality rates of around 20-30% and significant post-transplant morbidity, long-term benefits are frequently achieved. Currently, many groups administer an induction treatment based on the association of chemotherapy and TKI (first or second generations). Investigators at the M.D. Anderson Cancer Center (MDACC) have studied the efficacy of treatment with Imatinib in association with the hyper-CVAD regimen, obtaining a CHR rate of 93%. The German Multicenter ALL (GMALL) study group tested two strategies in which Imatinib was incorporated either alternatively to or concurrently with chemotherapy, obtaining a CHR rate of 96%. The Japan Adult Leukemia Study Group (JALSG) conducted a phase II study of Imatinib combined with chemotherapy and the CHR rate obtained was 95%. The Northern Italy Leukemia Group (NILG) obtained a CHR of 92% in Ph+ ALL patients at diagnosis treated with chemotherapy plus Imatinib. All these studies have shown that the combination of Imatinib with chemotherapy is effective in improving patients' chances to receive an allo-SCT during first CHR. Also in elderly patients, the use of Imatinib in combination with chemotherapy or alone obtained an increase of CHR. Dasatinib, the second generation TKI, utilized in the MDACC study in association with hyper-CVAD led a CHR rate of 94% even if the combination was accompanied by a high toxicity and side effects. It was later reported that achieving a major molecular response (MMR) at 3, 6, 9, and 12 months significantly impacted on survival. In an another study by the European Working Group on Adult ALL (EWALL), the association between Dasatinib and chemotherapy in elderly patients induced a 95% of CHR. All these trials showed that these approaches are feasible and

capable of inducing high remission rates. However, induction deaths were consistently recorded combining a TKI with chemotherapy.
The GIMEMA experience with the first generation TKI Imatinib in Ph+ ALL is represented by the LAL 0201 protocol. This study included Imatinib for the treatment of Ph+ positive ALL for adult (A study) or elderly (B study) patients. The first report showed a strong activity of an induction treatment based only on a TKI plus steroids and CNS prophylaxis, with a 100% rate of CHR obtained in the elderly patients (>60 years). These results represented the prerequisite starting point for the design of the GIMEMA LAL1205 protocol, based on the use of the second generation TKI Dasatinib alone for 12 weeks as first-line induction treatment for all Ph+ ALL ≥18 years of age (with no upper age limit); the protocol took advantage of the central handling laboratory network operating in Italy over the last 20 years, coordinated by the Hematology Center at the "Sapienza" University in Rome, and aimed at a broad, integrated and uniform characterization of all adult ALL cases entering in the GIMEMA protocols. This allows to identify in all ALL cases the presence of the BCR/ABL1 gene fusion within the 7-day steroid pre-phase, to set up a bank of material and to centrally perform a monitoring of MRD at pre-defined time points during the course of the disease. In this protocol, 53/53 of the evaluable patients (100%) obtained a CHR with an overall good compliance and no deaths (or relapses) during the induction phase. According to the study design, post-induction treatment was left to the investigator's choice. The results of this study have been presented orally twice at ASH, as well as at EHA, and published in Blood. This study showed that remission induction with Dasatinib (12 weeks) is highly effective and safe. Nevertheless, most patients at the end of the induction with Dasatinib were still MRD positive, by means of immunophenotype and/or molecular biology. DFS was significantly better in patients with low MRD levels (cut-off $=10^{-3}$) by day +22. These observations led to the development of the subsequent protocol, the GIMEMA LAL 1509, in which patients not achieving a complete molecular remission (CMR) after Dasatinib induction were further stratified, according to allo-SCT eligibility, to proceed directly to transplant or otherwise to receive one or two consolidation cycles with clofarabine and cyclophosphamide. Also in this setting, a CHR was achieved in all 60 eligible patients by day +57, although the CHR was lost in two cases (both carrying the p210 fusion protein). A CMR with Dasatinib alone was obtained in 19% of cases; OS and DFS at 24 months are of 71.1% and 50.3%. Although not significant, also in this study, a CMR achievement correlated with a better DFS. The first results of the 1509 protocol have been presented orally twice at the ASH meetings. Thus, these latter studies indicate that the administration of dasatinib in induction is capable of inducing sustained molecular responses in a proportion of patients, while most patients remain MRD+, and that a CMR should be regarded as a primary endpoint of induction/consolidation treatment for Ph+ ALL patients, that should be reached as soon as possible, e.g. 3 months, as previously reported, and maintained overtime.

Blinatumomab is bispecific T-cell engager antibody. Blinatumomab was initially used in refractory non-Hodgkin lymphomas, but neurologic side effects were observed. This compound has so far found its largest clinical use in ALL, in both the MRD+ setting, as well as in adults with relapsed/refractory ALL. Thus, the rationale for the current trial relies on the fact that we previously documented that by administering Imatinib or Dasatinib and steroids as induction treatment, virtually all adult patients - including the elderly - can achieve a CHR, without experiencing relevant toxicities and without deaths in induction. However, the majority of patients remain MRD+. If not treated further, MRD+ patients will inevitably relapse. We have shown that the degree of MRD debulking associates with prognosis. Thus, MRD negativity should be the primary endpoint in the management of Ph+ ALL, that can be achieved at early time points (end of induction, 3 months) by Dasatinib administration only in a small fraction of

patients; we hypothesize that following induction with Dasatinib the subsequent administration of Blinatumomab, which has proven particularly effective in a context of MRD positivity, should significantly increase the percentage of cases reaching, and maintaining, a MRD negative status (i.e. BCR/ABL copy number=0) and reduce the incidence of relapses, ultimately leading to a significant improvement in the outcome of adult Ph+ ALL patients, in terms of OS and DFS. Following previous experiences with Blinatumomab, at least 2 cycles of the compound will be administered by CIVI for 28 days followed by a 14-days period wash-out. In order to increase MRD clearance, in patients achieving a CHR Dasatinib will not be discontinued during Blinatumomab administration, as well as following it. Allo-SCT will be offered to eligible patients, according to donor availability and at investigator's discretion. While this approach is valid for all adult patients, it acquires further relevance for the more elderly patients for whom intensive systemic chemotherapy (particularly if associated with a TKI) and/or an allogeneic transplant are often coupled to unacceptable toxicity. It should be further underlined that in patients over the age of 50 the prevalence of the BCR/ABL1 fusion transcript is in the order of 50% of cases.

3.2 Purpose of the analyses

The primary objective of the trial is to evaluate the activity of a combination approach based on Dasatinib and Blinatumomab in obtaining a MRD negativity (complete molecular response: CMR, e.g. BCR-ABL1/ABL1=0) in adult Ph+ ALL.

4 Study Objectives and Endpoints

4.1 Study Objectives

Primary objective

The primary objective of the trial is to evaluate the activity of a combination approach based on Dasatinib and Blinatumomab in obtaining a MRD negativity (complete molecular response: CMR, e.g. BCR-ABL1/ABL1=0) in adult Ph+ ALL.

Secondary objectives

To explore:

- The feasibility of a chemo-free approach, based on Dasatinib and Blinatumomab, in adult Ph+ ALL patients ≥18 years, with no upper age limit
- CMR achievement after induction with Dasatinib
- Capability of Blinatumomab to reduce the MRD levels (an extension of the primary objective)
- CMR duration
- Disease-free survival (DFS)
- Overall survival (OS)
- Cumulative incidence of relapse (CIR)
- Safety profile

- CMR achievement, duration of CMR, OS and DFS according to the clinical, biological and molecular characteristics: clinical and biological assessment at baseline, type of fusion protein (p190 *vs* p210) and presence of additional genomic lesions identified by SNP arrays.

4.2 Endpoints

(ICH E9; 2.2.2)

Primary

The primary endpoint is the rate of patients who achieve MRD negativity (CMR) upon treatment, in particular: the rate of patients in CMR after 2 cycles of Blinatumomab.

Secondary

- Feasibility, calculated on the rate of patients completing the 2 cycles of Blinatumomab treatment and alive in first CHR from day +85 at 12 months
- Rate of patients in CMR at day +22, +45, +57 and +85
- CMR duration
- DFS
- OS
- CIR
- Safety profile in terms of incidence of grade >3 CTC-NCI side effects and toxicities.
- Role of clinical and biological assessment at baseline, type of fusion protein (p190 vs p210) and presence of additional genomic lesions identified by SNP arrays on CMR achievement, duration of CMR, OS and DFS.

4.3 Derived variables

Disease-free survival (DFS): DFS is defined as the time interval between the evaluation of CHR (day +85) and hematologic relapse of the disease or death in first CHR; patients still alive, in first CHR, will be censored at the time of the last follow-up.

Overall survival (OS): OS is defined as the time interval between treatment start and death for any cause; patients still alive will be censored at the time of the last follow-up.

Cumulative incidence of relapse (CIR): the CIR will be calculated from the date of evaluation of CHR until the date of first hematologic relapse of the disease, using the cumulative incidence method considering death in CHR as a competing risk. Patients still alive, without a date of relapse, will be censored at the time of the last follow-up.

5 Study Methods

5.1 General Study Design and Plan

(ICH E3;9)

Study phase Phase 2

Study type Multicenter, prospective, interventional, single arm study

5.2 Equivalence or Non-Inferiority Studies

(ICH E3; 9.2, 9.7.1, 11.4.2.7. ICH E9; 3.3.2)

Na

5.3 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

Inclusion criteria

- Newly diagnosed adult B-precursor Ph+ ALL patients.
- Age greater or equal to 18 years.
- Signed written informed consent according to ICH/EU/GCP and national local laws.
- ECOG Performance Status 0 or 1 and/or WHO performance status less or equal to 2.
- Renal and hepatic function as defined below:
  - AST (GOT), ALT (GPT), and AP <2 x upper limit of normal (ULN).
  - Total bilirubin <1.5 x ULN.
  - Creatinine clearance equal or greater than 50 mL/min.
- Pancreatic function as defined below:
  - Serum amylase less or equal to 1.5 x ULN
  - Serum lipase less or equal to1.5 x ULN.
- Normal cardiac function.
- Negative HIV test, negative HBV DNA and HCV RNA.
- Negative pregnancy test in women of childbearing potential.
- Bone marrow specimen from primary diagnosis available.

Exclusion criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

- Prior systemic chemotherapy for leukemia and/or CD19-directed therapy.
- History of or current relevant CNS pathology (current ≥grade 2 epilepsy, seizure, paresis, aphasia, clinically relevant apoplexia, severe brain injuries, dementia, Parkinson's disease, organic brain syndrome, psychosis).
- Impaired cardiac function, including any one of the following:
  - LVEF (Left Ventricular Ejection Fraction) <45% as determined by MUGA (multigated acquisition) scan or echocardiogram.
  - Complete left bundle branch block.
  - Use of a cardiac pacemaker.
  - ST depression of >1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads.
  - Congenital long QT syndrome.
  - History of or presence of significant ventricular or atrial arrhythmia.
  - Clinically significant resting bradycardia (<50 beats per minute).
  - QTc >450 msec on screening ECG (using the QTcF formula).
  - Right bundle branch block plus left anterior hemiblock, bifascicular block.
  - Myocardial infarction within 3 months prior to starting Dasatinib.
  - Angina pectoris.
- Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
- Impairment of GI function or GI disease that may significantly alter the absorption of Dasatinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- History of or current autoimmune disease.
- Systemic cancer chemotherapy within 2 weeks prior to study.
- Known hypersensitivity to immunoglobulins or to any other component of the study drug formulation.
- Active malignancy other than ALL with the exception of basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix.
- Active infection, any other concurrent disease or medical conditions that are deemed to interfere with the conduct of the study as judged by the investigator.
- Nursing women or women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least 3 months thereafter or male patients not willing to ensure effective contraception during participation in the study and at least three months thereafter.

5.4 Randomisation and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)

Na

5.5 Study Variables

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Data will be collected using e-CRFs managed by a GAMP 5 validated web based Data Management System, installed on a secure IT infrastructure. The system allows for audit trails, logging all user activity and all pages viewed by every user.

GIMEMA is an ECRIN certified high quality data centre. The ECRIN Certification program identifies non-commercial CTUs in Europe demonstrating that they can provide safe, secure, compliant and efficient management of clinical research data.

Only the data requested by the protocol will be gathered.

Assessment at enrolment/baseline (BL)

- Informed consent
- Demography
- General medical history and present medical condition
- Prior and concomitant medications
- Present disease signs and symptoms
- Physical examination and vital signs (height, weight, adenomegaly, spleen and liver size in cm below costal margin, other relevant findings)
- Performance status (WHO)
- ECG & Echocardiogram
- Chest X-RAY
- Abdominal ultrasound
- BM cytomorphology status performed by local investigator
- Blood count and differential, hemoglobin, platelet, total WBC, PMN, blasts including the absolute blasts count (at day -6)
- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and LDH, potassium, calcium
- Coagulation: PT, PTT/INR, fibrinogen; ATIII
- HIV, HBV DNA and HCV RNA test
- Rachicentesis (diagnostic and therapeutic) as soon as possible
- Biological sample centralization procedures (see "**Appendix F**" of the study protocol): BM and PB for cytomorphology, immunophenotype, cytogenetics, molecular studies.

Assessment at the end of pre-treatment phase

- Physical examination and vital signs (height, weight, adenomegaly, spleen and liver size, in cm below costal margin, other relevant findings)
- Performance status (WHO)
- Blood count and differential, hemoglobin, total WBC, PMN, blasts and platelet count
- Response evaluation to steroid pre-treatment (absolute blast count at day 0)
- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and LDH

During induction treatment

- Physical examination/vital signs, Performance status (WHO), hemoglobin, total WBC, PMN, blasts and platelet count:
  - 1st week: daily
  - from 2nd to 5th week: twice a week
  - from the 6th week: weekly
- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), LDH, electrolytes:
  - 1st week: every other day
  - from 2nd to 4th week: twice a week
  - from the 5th week: weekly
- Coagulation: PT, PTT/INR, fibrinogen; ATIII before rachicenteses
- Rachicentesis (diagnostic and therapeutic): days +14, +22, +45, +57, +85
- BM and PB for cytomorphology evaluation of the hematological status performed by the local investigator at least on the following days: +22, +45, +57
- Biological sample (BM and PB) centralization procedures at days +22, +45 and +57 (see "**Appendix F**" of the study protocol) only for patients either in CHR or without evidence of disease in BM and in PB (i.e., no "biological" studies will be performed if disease is still evident by cytomorphology).

End of induction treatment

- Physical examination/vital signs
- Performance status (WHO)
- ECG & Echocardiogram
- Chest X-RAY
- Abdominal ultrasound
- Hemoglobin, total WBC, PMN, blasts and platelet count
- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and LDH
- Rachicentesis (diagnostic and therapeutic) at day +85
- BM and PB for cytomorphology evaluation of the hematological response performed by the local investigator ad day +85.
- Biological sample (BM and PB) centralization procedures at day +85 (see **"Appendix F"** of the study protocol). Patients who have a CMR (i.e. BCR/ABL1 to ABL1 ratio=0) must repeat a centralized confirmatory BM 2 weeks later.
  Subjects found to have grade 1 asymptomatic pleural effusion on day 85 should be closely monitored for the development of symptoms requiring Dasatinib dose interruption and supportive care.

During post-induction treatment (prior to Blinatumomab administration - Cycle 1)

- Physical examination/vital signs
- Performance status (WHO)
- ECG & Echocardiogram
- Chest X-RAY
- Abdominal ultrasound
- Hemoglobin, total WBC, PMN, blasts and platelet count

- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and LDH
- Creatinine Clearance (calculated)
- Diagnostic and medicated rachicentesis, in case of delayed start of Blinatumomab (more than 2 weeks)
- Neurological examination and electroencephalogram (EEG), together with subject's writing test
- BM for cytomorphology to evaluate the persistence of hematologic response (undertaken by the local investigator) and molecular biology in case of delayed start of Blinatumomab (more than 2 weeks)
- Pregnancy test
- IgG
- HIV, HBV DNA and HCV RNA test
- Biological sample (BM and PB) centralization in case of delayed start of Blinatumomab (more than 2 weeks): see time points at the section of translational research and centralization procedures in **"Appendix F"** of the study protocol
- Disease status

During Blinatumomab cycles

- Physical examination, vital signals, neurological examination and performance status (WHO): days +1, +2, +3, +8, +15, +29
- Lumbar puncture (medicated): day +29
- BM aspirate/biopsy for cytomorphology and molecular biology: day +29
- Hemoglobin, total WBC, PMN, blasts and platelet count: days +1, +2, +3, +8, +15, +29
- Biochemistry: BUN, urea, creatinine, uric acid. Albumin, total protein, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT) and LDH: days +1, +2, +3, +8, +15, +29
- IgG: day +29

Chemistry	**Coagulation**	**Urinalysis**	**Hematology**
Sodium	PT	Blood	Hemoglobin
Potassium	PTT	Protein	Hematocrit
Chloride	Fibrinogen	Glucose	Reticulocytes
Total protein	ATIII		Platelets

Albumin			WBC
Calcium			Differential: Neutrophils Eosinophils Basophils Lymphocytes Monocytes Atypical lymphocytes
Magnesium			
Phosphorus			
Glucose			
BUN or Urea			
Creatinine			
Uric acid			
Alk phos			
LDH			
AST (SGOT)			
ALT (SGPT)			
C-reactive Protein			
Amylase			
Lipase Bilirubin			
γGT			

Table 3: Chemistry, coagulation, urinalysis, hematology

8.6 During follow-up after Blinatumomab cycles

All subjects, including subjects who withdraw early, should complete a safety follow-up visit 30 days (±3 days) after the last dose of Blinatumomab, or prior to HSCT/chemotherapy, if applicable. The following procedures will be completed at the visit:

• Physical examination including weight

• Vital signs (eg, systolic/diastolic blood pressure, pulse rate, respirations, and temperature)

• WHO performance status assessment

• Complete neurological examination

• BM aspirate/biopsy for morphological and molecular analysis will be performed every month for the first 6 months and then every 2 months for the first year.

• Local laboratory assessments:

– Hematology with differential

– Chemistry

– Coagulation (includes INR and PTT)

– Immunoglobulins

– Urinalysis via dipstick

– Urine or serum pregnancy test (if indicated)

• Central laboratory assessments including

– Lymphocyte subsets

• Subject writing test

• AEs/SAEs reporting

• Documentation of concomitant medications

6 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)

This study is designed to evaluate the activity of Dasatinib plus Blinatumumab in eradicating MRD in adult Ph+ ALL, in terms of percentage of patients who achieve a CMR after the induction phase based on Dasatinib and steroids only, followed by 2 (up to a maximum of 5) cycles of Blinatumomab to improve the CMR rate from 40% to 60%; this percentage was estimated on the basis of a preliminary analysis of the LAL 1509. The number of patients required to demonstrate this hypothesis with a power of 90% and a Type I error probability of 5%, and considering a 10% drop-out, is 60.

In the proposal, to reject the null hypothesis that $p \leq 0.40$ vs. the alternative hypothesis that $p > 0.60$ with Type I error probability (α) equal to 0.05 and 90% power (1-β), 54 evaluable patients has to be accrued. Considering a 10% rate of non-evaluable patients due to ineligibility, toxicity, medical decision or refusal before treatment starts the estimated total number of patients to include in the study is 60. In the first stage of the study, 29 evaluable patients (32 considering 10% of drop out) will be enrolled and the trial will be terminated if 12 or fewer responses after the completion of the 2 cycles of Blinatumomab will be achieved; otherwise, 25 further evaluable patients (28 considering 10% of drop out) will be enrolled in the second stage. If the total number of responses will be less than or equal to 27, the combination therapy will not be recommended for further studies. If the total number of CMRs is at least 28, the association will be deemed worthy of further investigations. Calculations were implemented in PASS2008 using a Simon two stage (minimax) phase II study design.

7 General Considerations

7.1 Timing of Analyses

The final analysis will be performed when the last subject have completed the last visit or dropped out prior to this visit.

7.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)

All analyses will be analyzed on an Intention-To-Treat basis. Only screen failures and patients who refuse before the treatment start would be excluded according to an Intention-To-Treat basis. In case of relevant non-compliance to the treatment and/or impossibility to evaluate response, a per-protocol analysis and a non-compliance/non-evaluation analysis will also be performed

7.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)

All patient characteristics at baseline will be used to describe the trial population. Relevant subgroup, considered into the analysis, will be the subset of patients in CMR at day+85 and after Blinatumomab treatment.

7.4 Minimum Data Requirement (MDR) before statistical analysis

MDR should include the following clinical data checks:

- All unique key variables in each raw data set are required.

    - Record ID variable is non-missing and unique.
- Confirm minimum and maximum values of selected variables.
    - Hemoglobin, Platelets, age, Wbc, Copies number of p190/ABL x 100, Copies number of p210/ABL x 100
- Display all unique values of selected variables.
    - Sex, ecog, response evaluation (haematological e molecular), BCR/ABL type
- Display values of selected variables to meet primary and secondary endpoints.
    - CMR, OS, DFS, CIR, AEs, SAEs
- Confirm the logic between two variables.
    - Relapse and type of relapse, response evaluation and relapse
- Confirm the consistency among clinical dates.
    - Date of informed consent, date of treatment start, date of treatment end, date of response evaluation, date of off treatment, date of last follow-up
- Check for duplicate records.
- Compare and identify differences of common variables between two data sets.
    - Off treatment due to toxicity, toxicity form is missing
- Evaluate percentage of missing data on critical variables (<5%)
    - Response evaluation: haematological and molecular

In addition to the minimum checks to perform, these additional checks help ensure a more successful clinical study by monitoring important clinical issues:

- Are there any protocol violations that should be excluded from analysis?
    - Main reason for going off protocol treatment
- Are the treatment groups randomly distributed based on safety subset population? NA
- Have lab values been correctly converted from reported units to standard international units? NA
- For each lab, are there major deviations in value from baseline over time? NA
- Are the top 10 adverse events expected? NA
- Are patient follow-up visit windows in compliance with the protocol?
    - Every six months
- For any critical variable, are there any outliers? Wbc, Copies number of p190/ABL x 100, Copies number of p210/ABL x 100

7.5 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

No imputations for missing data will be done

7.6 Interim Analyses

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 "Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics")

Interim analysis will be performed after the first stage according to the Simon design.

7.7 Multi-centre Studies

(ICH E3;9.7.1, 11.4.2.4. ICH E9; 3.2)

Centre effects should be considered exploratory in analyses of studies that have not been explicitly designed with enough power to detect centre effects.

7.8 Multiple Testing

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 2.2.5)

This is a confirmatory trial for the primary endpoint, the choice of sample size will be justified in terms of the power. The primary analysis will be focus only on one primary endpoint.

8 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, subject and by dose level within subject. All summary tables will be structured with a column for each dose level in the order and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

9 Efficacy Analyses

Response achievement will be evaluated in terms of percentage of successful responses over all eligible and evaluable patients enrolled in the study (following an Intention-To-Treat principle). All AEs will be tabulated. All reported toxicities will be correlated with clinical outcome. Patients' characteristics will be summarized by means of cross-tabulations for categorical variables or by means of quantiles for continuous variables. In univariate analysis non-parametric tests will be performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables or response rate, Mann-Whitney and Kruskal-Wallis test in case of continuous variables) and logistic regression will be performed in multivariate analysis to assess the effect of clinical and biologic factors on CMR rate. OS will be defined as the time from treatment start to death from any cause. DFS will be defined as the time from the achievement of CHR to relapse, death, or date of last follow-up for patients alive in first CHR. CMR duration will be defined as the time form the achievement of CMR to molecular relapse, death or date of last follow-up for patients alive in first CMR. The OS, DFS and duration of CMR probabilities will be estimated using the Kaplan-Meier method. CIR will be calculated from the achievement of CHR to relapse or date of last follow-up for patients alive in first CHR, using

the cumulative incidence method and considering death in CHR as competing risk. Subgroups comparisons will be performed for descriptive purposes. Differences in terms of OS, DFS duration of CMR will be evaluated by means of Log-Rank test in univariate analysis and by means of the Cox regression model in multivariate analysis, after assessment of proportionality of hazards. CIR will be estimated by cumulative incidence curves using the proper non-parametric method. The Gray test will be applied for significance tests on cumulative incidence curves. Median follow-up time will be estimated by reversing the codes for the censoring indicator in a Kaplan-Meier analysis. Confidence intervals will be calculated at 95% level and forest plots wil be used to summarize differences among subgroups. All analysis will be performed using the SAS software (release 9.4 or later).

10 Safety Analyses

Analysis of safety data will be conducted on the safety population, which includes all subjects who receive at least 1 dose of study medication. This population will be used for all safety analyses and all analyses of treatment compliance and exposure. All data will be analyzed according to the treatment subjects actually received. The safety variables to be analyzed include AEs, clinical laboratory tests (hematology and chemistry), physical examination results, ECGs, and deaths. Safety variables are to be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

All the analyses of the safety endpoints will be performed on the safety population. CTCAE v4.0 will be used. The safety analyses will be presented at baseline, during the treatment and follow-up period.
AEs will be reported:

- AEs (worst CTC grade of any event and of events by system organ class)
- SAEs (worst CTC grade of any event and of events by system organ class)
- AEs leading to discontinuation of treatment (worst CTC grade of any event and of events by system organ class)
- AEs judged to be related to study treatment (dasatinib and blinatumomab)

No formal toxicity analyses with p-values will be carried out.

11 Pharmacokinetics

Na

12 Other Analyses

Na

13 Figures

Patient characteristics at baseline, primary and secondary analyses, would be considered as candidates for graphical displays.

14 Reporting Conventions

Frequency tables will be tabulated for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment, value of the item and text field contents).

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range.

Other continuous variables (for example age, dose) will be presented using the median and range (minimum, maximum).

If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

15 Summary of Changes to the Protocol

Na

16 References

ICH E9 'Statistical Principles for Clinical Trials'

ICH E8 'General Considerations for Clinical Trials'

ICH E3(1995) 'Structure and Content of Clinical Study Report