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PROTOCOL

A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced-Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Sponsor:	Millennium Pharmaceuticals, Inc (A wholly owned subsidiary of Takeda Pharmaceutical Company Limited) 40 Landsdowne Street Cambridge, MA 02139 USA Note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Sponsor," or "Takeda."		
Study Number:	Ponatinib-3001		
IND Number:	078375	**EudraCT Number:**	2018-000397-30
Compound:	Ponatinib		
Date:	12 March 2018		

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1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site. See the study manual for more information.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints. See the study manual for more information.

Contact Type/Role	North America Contact	EU Contact	Asia Contact	ROW Contact
SAE and pregnancy reporting	See Section 10.0	See Section 10.0	See Section 10.0	See Section 10.0
Medical monitor (medical advice on protocol and compound)	See study manual	See study manual	See study manual	See study manual
Responsible medical officer (carries overall responsibility for the conduct of the study)	See study manual	See study manual	See study manual	See study manual

Abbreviations: EU, European Union; ROW, rest of world; SAE, serious adverse event.

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1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatures can be found on the signature page.

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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** Ponatinib	
Title of Protocol: A Phase 3, Randomized, Open-Label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced-Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)	**IND No.:** 078375	**EudraCT No.:** 2018-000397-30
Study Number: Ponatinib-3001	**Phase:** 3	

Study Design: This phase 3 study is designed as an open-label, multicenter, randomized comparison of the tyrosine kinase inhibitors (TKIs) ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously until patients have completed the study, experience progressive disease, have an unacceptable toxicity, withdraw consent, proceed to hematopoietic stem cell transplant (HSCT), or the sponsor terminates the study. Patients who do not achieve the primary endpoint of minimal residual disease (MRD)-negative complete remission (CR) at the end of induction will be discontinued from study drug, after which the patient's treating physician should consider alternative chemotherapy options (see Table 13.a for definitions).

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib once daily (QD), which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Section 8.4.1). Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for central nervous system (CNS) disease prophylaxis. Patients who achieve the primary endpoint at the end of induction will continue in the consolidation phase and the maintenance phase. At the end of the 20 cycles, patients will remain on ponatinib or imatinib (administered as a single agent).

The primary endpoint of this study is MRD-negative CR at the end of induction (defined in Table 13.a). As CR must have been maintained for at least 4 weeks, patients who do not achieve CR by the end of Cycle 2 will be considered as having failed to achieve the primary endpoint.

MRD status will be measured using quantitative polymerase chain reaction–based tests validated for the ability to detect breakpoint cluster region-Abelson (BCR-ABL1)/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as ≤0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale with traceability to the World Health Organization first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported. To ensure uniformity of analysis, all samples will be tested in the same central laboratory. Assessment of the primary endpoint at the end of induction will be based on analysis of bone marrow (BM) samples. To minimize the number and volume of BM aspirates required, and in keeping with available recommendations [1] and evidence of general concordance between results [2], assessment of BCR-ABL1/ABL1 levels at other time points may use peripheral blood samples. Both sample types will be collected at a subset of time points to allow the levels of concordance between sample types to be broadly assessed.

The key secondary endpoint for this study is the rate of event-free survival (EFS). Other secondary endpoints will include rates of CR and incomplete CR (CRi) at the end of Cycle 1, Cycle 2, and the end of induction; rates of MR3,

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MRD negativity (MR4, BCR-ABL1/ABL1 ≤0.01%), and MR4.5 (BCR-ABL1/ABL1 ≤0.0032%) at the end of Cycle 1, the end of Cycle 2, and the end of induction; rates of primary induction failure (PIF) and overall response rate (ORR) at the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; rates of MR4.5 at multiple intervals after the end of induction, including best response; duration of MR4.5 in patients who achieved MR4.5; subgroup analyses for on-study patients with and without HSCT (including rates of overall survival [OS] and relapse from CR), and OS. (See Table 13.a for endpoint definitions.)

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all adverse events (AEs), serious adverse events (SAEs), arterial occlusive events (AOEs), and venous thrombotic/embolic events (VTEs); rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

Exploratory endpoints will include change from baseline in patient-reported quality-of-life and medical resource utilization (MRU) assessments; time to start of alternative chemotherapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

Primary Objectives:

To compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction.

Key Secondary Objectives:

- To compare the rates of EFS between the 2 cohorts

Other Secondary Objectives:

- To compare the rates of CR and CRi between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- To compare the rates of MR3, MRD negativity (MR4), and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- To compare the rates of PIF and ORR between the 2 cohorts, at the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To compare the rate of MR4.5 between the 2 cohorts, at multiple intervals after the end of induction, including best response.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare the rates of OS between the 2 cohorts.
- To characterize the incidence of AEs, SAEs, AOEs, VTEs, and other safety outcomes of interest in each of the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.
- To collect plasma concentration-time data to contribute to population pharmacokinetic and exposure-response analyses of ponatinib

Subject Population: Male and female patients with newly diagnosed Ph+ ALL, aged 18 years and older

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Number of Subjects:	**Number of Sites:**
Ponatinib treatment group: 214 Imatinib treatment group (active comparator): 106 Estimated total randomized: 320	Estimated total: Approximately 80 sites in up to 35 countries globally
Dose Level(s): Ponatinib: 30 mg QD Imatinib: 600 mg QD	**Route of Administration:** Both ponatinib and imatinib are administered by mouth.
Duration of Treatment: All patients will remain on study drug until they are deceased, have failed to achieve the primary endpoint, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.	**Period of Evaluation:** Study data will be evaluated up to 5 years after enrollment of the last patient.

Main Criteria for Inclusion:

1. Male or female patients aged 18 years or older.
2. Newly diagnosed Ph+ or BCR-ABL1 positive ALL, as defined by the 2017 National Comprehensive Cancer Network guidelines.
3. Molecular assessment of BCR-ABL1 must demonstrate the presence of a p190 (ie, e1a2) or p210 (ie, e13a2 or e14a2 [also known as b2a2 or b3a2]) transcript type.
4. Eastern Cooperative Oncology Group performance status ≤2.
5. Clinical laboratory values as follows, within 30 days before randomization:
   a) Total serum bilirubin ≤1.5× the upper limit of normal (ULN).
   b) Alanine aminotransferase or aspartate aminotransferase ≤2.5× the ULN.
   c) Serum creatinine ≤1.5× the ULN and estimated creatinine clearance ≥40 mL/minute (Cockcroft-Gault formula).
   d) Serum lipase and amylase <1.5× the ULN.
6. Normal QT interval corrected per Fridericia method (QTcF) on screening electrocardiogram, defined as QTcF of ≤450 ms in males or ≤470 ms in females.
7. Female patients who:
   a) Are postmenopausal for at least 1 year before the screening visit, *or*
   b) Are surgically sterile, *or*
   c) If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 1 month after the last dose of study drug, *or*
   d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
8. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, *or*
   b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male

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condoms should not be used together.)

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Willingness and ability to comply with scheduled visits and study procedures.

Main Criteria for Exclusion:

1. Patients with a history or current diagnosis of chronic phase, accelerated phase, or blast phase chronic myeloid leukemia.
2. Prior/current treatment with any systemic anticancer therapy (including but not limited to any TKI) and/or radiotherapy for cancer, with the exception of an optional prephase therapy, which should be discussed with the sponsor's medical monitor/designee.
3. Treatment with any investigational products within 30 days before randomization or 6 half-lives of the agent, whichever is longer.
4. Currently taking drugs that are known to have a risk of causing prolonged QTc or torsades de pointes (unless these can be changed to acceptable alternatives or discontinued) (Appendix E).
5. Taking any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 3A4 within at least 14 days before the first dose of study drug.
6. Active serious infection requiring antibiotics within 14 days before the first dose of study drug.
7. Major surgery within 28 days before randomization (minor surgical procedures such as catheter placement or BM biopsy are not exclusionary criteria).
8. Ongoing or active systemic infection, known seropositive HIV, or known active hepatitis B or C infection.
9. History of acute pancreatitis within 1 year of study screening or history of chronic pancreatitis.
10. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
11. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are excluded if they have not undergone complete resection.
12. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
13. Active ALL in the CNS (confirmed by cerebrospinal fluid analysis).
14. Autoimmune disease with potential CNS involvement.
15. Known significant neuropathy of Grade ≥2 severity.
16. Clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease, including, but not restricted to:
    a) Complete left bundle branch block.
    b) Right bundle branch block plus left anterior hemiblock, or bifascicular block.
    c) History of or presence of clinically significant ventricular or atrial tachyarrhythmias.
    d) Clinically significant resting bradycardia (<50 beats per minute).
    e) Uncontrolled hypertension (HTN; systolic blood pressure [BP] ≥150 mmHg and/or diastolic BP ≥90 mmHg). Patients with Stage 2 HTN (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) should be under treatment at study entry per the current American Heart Association guidelines to ensure BP control. Patients requiring 3 or more antihypertensive medications should have controlled HTN for the past 6 months.
    f) Any history of myocardial infarction, unstable angina, coronary artery disease, cerebrovascular accident, ischemic stroke, or transient ischemic attack.
    g) History of congestive heart failure (New York Heart Association class III or IV) or left ventricular ejection

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fraction <40%, within 6 months before randomization.

h) Symptomatic peripheral vascular disease or history of infarction, including visceral infarction.

i) History of any revascularization procedure, including the placement of a stent.

j) History of pleural or pericardial effusions.

k) Any history of venous thromboembolism, including but not limited to deep venous thrombosis or pulmonary embolism within 6 months before randomization.

17. Poorly controlled diabetes, defined as glycosylated hemoglobin values of >7.5%. Patients with preexisting, well-controlled diabetes are not excluded.
18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.
19. Ongoing uncontrolled nausea or vomiting of any severity.
20. Diarrhea of Grade >1, based on the National Cancer Institute Common Terminology Criteria for Adverse Events categorization.
21. History of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease.
22. Have a significant bleeding disorder unrelated to ALL.
23. Life-threatening illness unrelated to cancer, such as severe CNS, pulmonary, renal, or hepatic disease unrelated to cancer.
24. Female patients who are lactating or breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug is administered.
25. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
26. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Main Criteria for Evaluation and Analyses:

Primary efficacy endpoint: MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 13.a)

Key secondary efficacy endpoint:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve MRD-negative CR by the end of induction.
  - Relapse from CR.

Other secondary endpoints (defined in Table 13.a)

- Rates of CR and CRi at the end of Cycle 1, Cycle 2, and the end of induction.
- Rates of MR3, MRD negativity (MR4), and MR4.5 at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- Rates of PIF and ORR at the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Rates of MR4.5 at multiple intervals after the end of induction, including best response.
- Duration of MR4.5 in patients who achieved MR4.5.
- Subgroup analyses for on-study patients with and without HSCT (including rates of OS and relapse from CR).

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- OS.

Safety and tolerability endpoints:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

Exploratory endpoints:

- Change from baseline in patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]).
- Change from baseline in MRU assessments.
- Time to start of alternative chemotherapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

Statistical Considerations:

Stratification and Test for MRD-negative CR Primary Endpoint

To adjust for the known confounding factors in the trial, patients' randomization assignments will be stratified dependent on the following factors:

1. Ages: 18 through <45 years; ≥45 through <60 years; and ≥60 years.
2. Transcript 190 versus 210.

Adaptive Design Considerations

The conditional power based sample size re-estimation adaptive design proposed in Mehta et al is used in determining the sample size and power of the trial [3,4].

Assuming an optimistic effect size of 28% (48% and 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of 230 patients (153 vs 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 83% power at interim analysis (IA). IA will be performed after the end of induction phase data have been collected for 150 patients. If the enrollment is not terminated after IA (for futility) the conditional power will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the pre-planned sample size for final analysis (FA) of MRD-negative CR will remain unchanged at 230 patients. If the conditional power falls in the promising zone, the sample size will be determined according to a prespecified sample size adaptation rule, with a cap of approximately 320 patients, by which the overall study power will be 82.6% if the actual effect size is 17% (40% and 23% MRD-negative CR rates for the active and control arms, respectively).

The sample size adaptation rule is a prespecified stepwise function to avoid the possibility of back calculation of the trial IA outcome, as one sample size recommendation will correspond to multiple IA results: either barely promising or highly promising. The sample size adaptation rule (including the definitions for the unfavorable, favorable, and promising zones) will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the head of biostatistics will be involved in the study conduct.

The adaptation rules will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the independent data monitoring committee (IDMC), and the statistics representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

The overall 2-sided type 1 error is controlled at the 0.05 level. The O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significance and futility boundaries for the primary endpoint at IA

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and FA. With 65% information available at IA, the efficacy boundary will be 0.011 and 0.046 at IA and FA, respectively, for the primary endpoint.

Inference for the key secondary endpoint of EFS will be conducted at $\alpha = 5\%$ level only if the primary endpoint is met either at IA or FA for the MRD-negative CR (Figure 13.a). The EFS endpoint will be analyzed via a time-to-event analysis method. Based on 3-year EFS data observed from various phase 2 trials [5,6], effect size is assumed as 67% vs 46% for EFS at year 3 for the active and control arms, respectively, or hazard ratio (HR) = 0.516. Under this assumption, at least 120 events need to be accumulated so that the power will be at least 80% for the EFS endpoint. If the MRD-negative CR result is positive at IA, the plan is to reach a stable enrollment rate of 10 or more patients per month after IA to accumulate a sufficient number of patients to power the EFS endpoint analysis at >80% level.

It is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT before loss of MRD-negative CR. Since the HR is different for patients with or without HSCT [7-9], depending on how patients who proceed to HSCT are handled in the EFS analysis, the number of events needed to power the EFS analysis may change. Thus, the final number of events will be specified in the statistical analysis plan based on simulation results before the database lock for the IA on the MRD-negative CR.

Interim Analyses:

There will be 1 IA performed when end-of-induction phase data have been collected on 150 patients. Final analysis, if needed, will be conducted based on the number of patients decided by conditional power at IA.

The IA for MRD-negative CR will be carried out by an independent statistical team in a manner that maintains the blinding of the study results to the team. Based on the results from the IA, by applying the prespecified promising zone adaptive approach rules, the IDMC may recommend stopping the trial for efficacy or futility, or recommend continuing the trial with or without sample size modification. The sponsor's executive committee will make final decisions based on the IDMC recommendations.

Dosing Regimen:

Upon enrollment, patients will be randomized in a 2:1 ratio (ponatinib:imatinib) to receive either 30 mg of oral ponatinib (QD) or 600 mg of oral imatinib (QD), to be taken throughout the study, beginning on Cycle 1 Day 1. All patients will receive reduced-intensity chemotherapy, with an initial induction phase (3 cycles). Patients who achieve the primary endpoint at the end of induction will continue in a consolidation phase (6 cycles) and a maintenance phase (11 cycles), for a possible total of 20 cycles of reduced-intensity chemotherapy. At the end of the 20 cycles, patients will remain on ponatinib or imatinib (administered as a single agent).

Dose modifications for ponatinib will be performed as per dose modification guidelines (defined in detail in the protocol Section 8.3 and Section 8.4). After completing the maintenance phase, patients will continue to receive only ponatinib or imatinib as long-term therapy. Patients in each cohort will remain on study drug until they are deceased, have failed to achieve the primary endpoint, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.

Note: Dose modification guidelines are detailed in the protocol Section 8.3 and Section 8.4 for ponatinib; investigators should refer to local product labels for all other therapies included in the study. Patients who proceed to HSCT will be discontinued from study drug but will be followed per the on-study data collection schedule as specified in the Schedule of Events (Table 2) for posttransplantation data collection, including rates of OS and relapse from CR.

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The following table outlines the study dosing regimens.

Induction Phase Treatment (Three 28-Day Cycles) [a,b]	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)
Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14	Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14
Ponatinib: [c] Starting dose: 30 mg QD, starting on Cycle 1 Day 1.	Imatinib: [c] Starting dose: 600 mg QD, starting on Cycle 1 Day 1.
Consolidation Phase Treatment (Six 28-Day Cycles) [a,b]	
Cohort A	**Cohort B**
Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation Cycles 1, 3, and 5): – Patients aged ≤60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged >60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation Cycles 2, 4, and 6): – Patients aged ≤60 years: 1000 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion. – Patients aged >60 years: 250 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).	Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation Cycles 1, 3, and 5): – Patients aged ≤60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged >60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation Cycles 2, 4, and 6): – Patients aged ≤60 years: 1000 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion. – Patients aged >60 years: 250 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).
Ponatinib: [c] Start with the last induction phase dose; modify the dose based on MRD-negative CR results from the end of induction (see Section 8.3).	Imatinib: [c] Start with the last induction phase dose.
Maintenance Phase Treatment (Eleven 28-Day Cycles)	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)
Prednisone: Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5	Prednisone: Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5
Ponatinib: [c] Start with the last consolidation phase dose.	Imatinib: [c] Start with the last consolidation phase dose.

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Post–Cycle 20 Therapy	
Ponatinib monotherapy: Patients will continue on the last maintenance phase dose until they are deceased, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.	Imatinib monotherapy: Patients will continue on the last maintenance phase dose until they are deceased, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.

Abbreviations: CNS, central nervous system; CR, complete remission; CrCl, creatinine clearance; HSCT, hematopoietic stem cell transplant; IV, intravenously; PO, by mouth; q, every; QD, once daily.

[a] Lumbar punctures will be performed to test cerebrospinal fluid for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples).

[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.

[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list or equivalent. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

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3.3 List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
ALL	chromosome-positive acute lymphoblastic leukemia
AP	accelerated phase
AOE	arterial occlusive event
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BM	bone marrow
BMI	body mass index
BP	blood pressure
CAD	coronary artery disease
CHF	congestive heart failure
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
CNS	central nervous system
CP	chronic phase
CP-CML	chronic phase chronic myeloid leukemia
CR	complete remission (complete response)
CRi	incomplete complete remission
CrCl	creatinine clearance
CRO	contract research organization
CSF	cerebrospinal fluid
CV	cardiovascular
CVA	cerebrovascular accident
CVEAC	cardiovascular endpoint adjudication committee
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EOT	end of treatment
ESMO	European Society for Medical Oncology
FA	final analysis
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio

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HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HLT	High Level Term
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
IA	interim analysis
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IS	International Scale
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
K-M	Kaplan-Meier
LVEF	left ventricular ejection fraction
MaHR	major hematologic response
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MR3	molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%)
MR4	molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%)
MR4.5	molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%)
MRD	minimal residual disease
MRU	medical resource utilization
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Ph+ ALL	Philadelphia chromosome–positive acute lymphoblastic leukemia
PIF	primary induction failure
PK	pharmacokinetic
PP	per-protocol
PO	by mouth (orally)
PT	Preferred Term
PTE	pretreatment event

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QD	once daily
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected per Fridericia method
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOE	Schedule of Events
SUSARs	suspected unexpected serious adverse reactions
TdP	torsades de pointes
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
VTE	venous thrombotic/embolic event
WHO	World Health Organization

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millenium Pharmaceuticals, Inc; TDC Japan; TDC Asia; TDC Europe and/or TDC Americas; as applicable

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4.0 INTRODUCTION

4.1 Background

4.1.1 Disease State Background

4.1.1.1 Ph+ ALL

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) is a rare malignancy of the blood and bone marrow (BM), constituting approximately 20% to 30% of adult ALL [10,11]. ALL occurs at an age-adjusted incidence in the United States (US) of 1.58 per 100,000 individuals per year. In 2014, the estimated prevalence of Ph+ ALL was approximately 16,367 to 24,551 (20% to 30% of total ALL prevalence in 2014). In 2017, the estimated incidence of Ph+ ALL is 5970 new cases and 1440 deaths [11] (seer.cancer.gov/statfacts/html/alyl.html, Accessed 29 Nov 2017). Ph+ ALL is mainly a disease of adults, accounting for only approximately 3% of pediatric cases of ALL [10,11].

Ph+ ALL results from a translocation of chromosomes 9 and 22, referred to as the Philadelphia chromosome, which leads to the fusion of the breakpoint cluster region (BCR) coding sequence with the tyrosine kinase coding region of Abelson1 (ABL1). The consequence is expression of a BCR-ABL1 fusion oncoprotein with constitutive activation of ABL1 tyrosine kinase activity, which in turn activates cell signaling pathways promoting cell proliferation and survival. The constitutive ABL1 kinase activity is both necessary and sufficient for induction of both Ph+ ALL and chronic myeloid leukemia (CML) [12].

4.1.1.2 Treatment for Ph+ ALL

Ph+ ALL has been historically associated with very poor prognosis [13]. Before the introduction of tyrosine kinase inhibitors (TKIs), the outcome of treatment for patients with Ph+ ALL was poor. While treatment with chemotherapy alone (in the absence of a TKI) resulted in complete remission (CR) in many patients initially (45% to 90%), the median duration of CR was short (approximately 10 months), and most patients later relapsed, leading to few long-term survivors [14-16].

The National Comprehensive Cancer Network (NCCN) guidelines [11] contain widely accepted recommendations for the treatment of Ph+ ALL in the US. NCCN guidelines first recommend treatment of Ph+ ALL patients in a clinical trial. If that is not possible, the guidelines then generally recommend first-line treatment of Ph+ ALL with a TKI, along with chemotherapy (which usually includes vincristine, and may also include doxorubicin or daunorubicin and/or cyclophosphamide) and/or a steroid (generally dexamethasone or prednisone). Similarly, the European Society for Medical Oncology (ESMO) has published clinical practice guidelines for treating Ph+ ALL in adults with TKIs; ESMO recommends that a TKI should be administered continuously and should be combined with chemotherapy in front-line therapy [17]. Central nervous system (CNS) prophylaxis is also recommended to be administered throughout treatment. Hematopoietic stem cell transplantation (HSCT) is performed in some patients, depending on factors such as availability of a suitable donor and the suitability of the patient to withstand the

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procedure. HSCT, however, may have some limitations, as it is an option for only a limited number of patients (particularly younger patients) and is associated with significant rates of both mortality and relapse [16].

4.1.1.3 Use of TKIs and Unmet Medical Need

All regimens recommended by NCCN guidelines [11] include a TKI; however, in the US, no TKI has yet received regulatory approval for newly diagnosed Ph+ ALL in adult patients. In the US, imatinib (a first-generation BCR-ABL1 TKI) is approved for pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy and for relapsed or refractory Ph+ ALL in adult patients; dasatinib (a second-generation BCR-ABL1 TKI) is approved for adults with Ph+ ALL with resistance or intolerance to prior therapy; and ponatinib (a third-generation BCR-ABL1 TKI) is approved for adult patients with Ph+ ALL for whom no other TKI therapy is indicated or who are T315I–mutation-positive.

First-line use of first- or second-generation TKIs in combination with chemotherapy results in 3- and 5-year overall survival (OS) rates of approximately 46% to 56% and 43%, respectively [6,18,19]. These relatively modest OS rates are generally due to relapse after achievement of an initial CR by hematologic criteria and create opportunity for considerable improvement in the treatment of Ph+ ALL. Relapse in Ph+ ALL is generally associated with TKI resistance, which can occur by multiple mechanisms. The most common mechanism of resistance to the first- and second-generation TKIs is single mutations in the ABL1 kinase domain [10,20,21]. While the second-generation TKIs are more potent inhibitors of BCR-ABL1 compared with imatinib and have inhibitory activity against most imatinib-resistant mutations, several mutations such as T315I, V299L, and F317L are also resistant to dasatinib [11]. Of these, the T315I mutation is the most common mutation associated with resistance to both imatinib and dasatinib [20,21]. In one study with dasatinib, the T315I mutation was observed in 75% of relapsed patients on whom mutation analysis by Sanger sequencing was performed [21].

Rationale therefore exists that there is an unmet medical need for a more potent TKI that can suppress the development of mutations and is also active against the single mutations associated with resistance to the early generation TKIs. This more potent TKI could result in deeper and more durable responses in the first-line treatment of Ph+ ALL compared with the earlier generation TKIs.

There also remains an unmet medical need for effective treatment regimens in older patients with Ph+ ALL and in patients who are unable to tolerate intensive chemotherapy regimens. Increasing age is a risk factor for the development of Ph+ ALL, and generally the older the patient, the worse the prognosis [11,20,22]. In older patients (aged ≥65 years), NCCN guidelines recommend either reduced-intensity chemotherapy or no chemotherapy (steroid only) in combination with a TKI. Even among younger adults, the use of a TKI along with reduced-intensity chemotherapy may have a more favorable benefit-risk profile compared with more intensive regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD). The combination of a more potent TKI (ponatinib) with a chemotherapy regimen that is more intensive than steroids but less intensive than chemotherapy such as hyper-CVAD,

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may be a good option for the first-line treatment of Ph+ ALL and warrants further investigation in a broad Ph+ ALL patient population.

In summary, the increased potency of ponatinib compared with the early generation TKIs, along with ponatinib's activity toward the single mutations associated with resistance to the early generation TKIs and its ability to suppress the development of resistance mutations, forms the rationale for the use of ponatinib in combination with less-intensive chemotherapy in the treatment of first-line Ph+ ALL in this phase 3 study.

4.1.2 Ponatinib Design and Mechanism of Action

Ponatinib is the product of a computational and structure-based approach to the design of a small-molecule TKI [23]. Ponatinib was designed to optimally inhibit native BCR-ABL1 and mutant forms of the protein that cause resistance to other TKIs, including the T315I gatekeeper mutation that confers resistance to all approved BCR-ABL1 inhibitors other than ponatinib (ie, imatinib, nilotinib, dasatinib, and bosutinib).

A critical feature of ponatinib's design is the incorporation of multiple contact points with the ABL1 kinase domain, which balances and distributes overall binding affinity [24]. This leads not only to high-affinity binding to ABL1, but also renders binding less susceptible to disruption by any single amino acid mutation. A second critical structural feature is a carbon-carbon triple bond linkage that allows ponatinib to make a productive hydrophobic contact with the bulky isoleucine residue present in the T315I mutation rather than being sterically hindered by it.

Through direct inhibition of native BCR-ABL1 and its variants, ponatinib inhibits aberrant downstream signaling by reducing phosphorylated CRKL (pCRKL), thereby promoting apoptosis and cell death in BCR-ABL1–positive cells [23].

4.1.3 Ponatinib: Nonclinical to Clinical

Nonclinical studies have demonstrated that ponatinib potently inhibits native BCR-ABL1, and all single-mutation variants, at clinically relevant concentrations [23,25]. In a cell line expressing native BCR-ABL1, ponatinib inhibited viability with a half-maximal inhibitory concentration (IC_{50}) <1 nM, which is more than 200-fold lower than that of imatinib. Ponatinib also potently inhibited viability (with IC_{50}s <40 nM) of cell lines expressing 14 major clinically observed imatinib-resistant BCR-ABL1 mutations, including T315I. Ponatinib exhibited potent in vivo activity in 2 mouse tumor models expressing the T315I mutation of BCR-ABL1. Using an in vitro mutagenesis screen approach that has successfully predicted mutations that confer clinical resistance to imatinib and nilotinib and dasatinib [26], a concentration between 20 nM and 40 nM of ponatinib was found to suppress the emergence of any resistant BCR-ABL1 mutation [23].

While nonclinical studies have shown that no single BCR-ABL1 mutation can cause resistance to ponatinib, it has been shown that certain compound mutations (2 mutations in the same BCR-ABL1 protein) can confer resistance [23,27]. For example, the presence of a T315I mutation on the same allele with Y253H or E255K can confer nonclinical resistance to ponatinib, though ponatinib is able to inhibit each of those mutants individually. Development of compound mutations is a risk associated with sequential use of BCR-ABL1 TKIs [28], whereby expansion of

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a leukemic progenitor cell that has a single resistance mutation provides a template on which a second mutation can develop.

The association between ponatinib efficacy and BCR-ABL1 mutation status in patients has been studied most extensively in the phase 2 PACE study (Study AP24534-10-201), the pivotal study upon which full marketing approval was granted by the US Food and Drug Administration (FDA) for the indications described in the current Iclusig label. The PACE study enrolled 449 heavily pretreated patients, including 267 patients with chronic phase CML (CP-CML) and 32 patients with Ph+ ALL [29]. All patients previously had been treated with at least 1 approved BCR-ABL1 inhibitor, with the majority having been treated with 3 or more. A starting dose of 45 mg was used, which was the recommended dose established in the phase 1 study (Study AP24534-07-101) [30].

Though response rates were high in heavily pretreated patients with CP-CML or Ph+ ALL, long-term outcomes differed substantially [29]. Among patients with CP-CML, 56% of patients achieved the primary endpoint of a major cytogenetic response (MCyR), and these responses were durable: The estimated rate of a sustained MCyR for at least 12 months was 91%. Among patients with Ph+ ALL, 41% achieved the primary endpoint of a major hematologic response (MaHR); however, these responses were not durable: The estimated rate of a sustained MaHR of at least 12 months was 8%. It is important to note that short- and long-term outcomes in patients with CP-CML and Ph+ ALL could be rationalized based on the relationship between BCR-ABL1 mutation status and ponatinib efficacy, as assessed in these patients.

First, analysis of efficacy based on baseline mutation status demonstrated that high response rates were observed in patients regardless of BCR-ABL1 mutation status (ie, in patients with or without BCR-ABL1 mutations), and responses were observed for each of the 15 mutations present in more than 1 patient with CP-CML at baseline. Thus, high initial response rates observed in patients with CP-CML and Ph+ ALL are likely explained by the ability of ponatinib to potently inhibit native and single mutation variants of BCR-ABL1 that exist before ponatinib therapy and which constitute most of the leukemic cell population.

Second, analysis of BCR-ABL1 mutation status at the end of ponatinib treatment revealed that the acquisition of compound mutations was rare in patients with CP-CML but common in patients with Ph+ ALL treated with ponatinib [29,31]. Among 130 patients with CP-CML, 19 patients (15%) were found to have acquired any mutation at the end of treatment (EOT) that was not detected at baseline, and 4 patients (3%) were found to have acquired a compound mutation. In contrast, among 20 patients with Ph+ ALL, 13 patients (65%) were found to have acquired any mutation, and 12 patients (60%) were found to have acquired a compound mutation. In all the patients who acquired a compound mutation, 1 of the mutations was detected at baseline.

In summary, nonclinical and clinical data consistently indicate that ponatinib is a highly potent and a “pan” BCR-ABL1 inhibitor, defined as having the ability to inhibit all single BCR-ABL1 mutations. This likely explains the high degree of efficacy initially observed in patients with CP-CML and Ph+ ALL, even if they had been heavily pretreated. However, certain compound mutations, which emerge during prior treatment with a non–pan-BCR-ABL1 inhibitor, can confer resistance to ponatinib. Development of compound mutations is common in Ph+ ALL but not in

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CP-CML, likely explaining the durable response induced by ponatinib in heavily pretreated patients with CP-CML but not in patients with Ph+ ALL.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for Ponatinib in Newly Diagnosed Ph+ ALL

As described previously (Section 4.1.1.3), in newly diagnosed patients with Ph+ ALL treated with first- or second-generation TKIs, the development of secondary resistance mutations in BCR-ABL1 is strongly associated with disease progression. When these patients with relapsed or refractory Ph+ ALL are then treated with ponatinib, many have developed a second (compound) mutation in BCR-ABL1. Some of these compound mutations may be resistant to ponatinib and to the first- and second-generation TKIs. Options for further treatment with TKIs are then exhausted.

The rationale for use of ponatinib in the first-line treatment of Ph+ ALL is that, by suppressing all single BCR-ABL1 resistance mutations, the predominant mechanism by which a leukemic cell is expected to develop a BCR-ABL1-mediated mechanism of resistance to ponatinib would be to develop 2 independent mutations simultaneously. The decreased likelihood of this occurring in patients only treated with ponatinib, compared with patients treated with a first- or second-generation TKI and then ponatinib, leads to the hypothesis of more durable responses in patients with newly diagnosed Ph+ ALL treated with ponatinib compared with sequential treatment with first- or second-generation TKIs followed by ponatinib.

On the basis of this rationale, the data summarized in Section 4.1.3, and the greater potency of ponatinib compared with the earlier-generation TKIs, the sponsor hypothesizes that ponatinib treatment in patients with newly diagnosed Ph+ ALL will lead to superior outcomes compared with those treated with first- or second-generation TKIs. In contrast to heavily pretreated patients with Ph+ ALL, where long-term outcomes were limited by development of compound resistance mutations, this is not expected to be the case in newly diagnosed patients. Preliminary clinical data are consistent with this hypothesis.

Ph+ ALL is a fast and aggressive disease for which the long-term prognosis remains poor, even when treated with the first- and second-generation TKIs. An improvement in long-term outcome may justify the risk of using a more potent TKI (ponatinib) in patients with newly diagnosed Ph+ ALL. Furthermore, if clinical data suggest that a more potent TKI could allow for the use of less intensive chemotherapy, the first-line use of ponatinib in adult patients with newly diagnosed Ph+ ALL may be additionally justified.

4.2.2 Ponatinib Dose Rationale

Clinical information on the safety and efficacy of different doses of ponatinib comes from multiple sources which, taken together, led to the selection of 30 mg as the starting dose for this protocol, with a dose reduction to 15 mg upon achievement of minimal residual disease (MRD)-negative CR and re-escalation to 30 mg if response is lost, as permitted by safety and tolerability in individual patients. Although a starting dose of 45 mg is recommended in the current prescribing information for ponatinib, it is acknowledged that the optimal dose of ponatinib remains to be defined; this is

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the objective of an ongoing, phase 2, dose-ranging trial (Study AP24534-14-203) evaluating the efficacy and safety of starting doses of 15 mg, 30 mg, or 45 mg once daily (QD) in patients with resistant CP-CML. The proposed starting dose of 30 mg QD for the current protocol is based upon consideration of the expected superior benefit-risk balance at 30 mg versus 45 mg, informed by previously conducted dose intensity-response analyses of data from the completed Studies AP24534-07-101 and AP24534-10-201.

Logistic regression analyses of dose intensity-adverse event (AE) relationships in patients with CP-CML in the phase 2 Study AP24534-10-201 indicated a dose-dependent increase in AEs, and notably in arterial occlusive event (AOE) rates, which are of specific importance for ponatinib. Dose intensity was a statistically significant predictor of AOE rates in that multivariate analysis after adjustment for known cardiovascular (CV) risk factors, leading to the expectation that the 30 mg QD dose will have a superior safety profile compared with 45 mg QD, thus supporting 30 mg QD selection as the starting dose.

In addition, a dose intensity-efficacy logistic regression analyses in Study AP24534-10-201 demonstrated a statistically significant relationship between dose intensity and the probability of achieving MCyR at 12 months. These analyses clearly indicated that 30 mg (vs 15 mg) is within the dynamic range of the inferred dose-response relationship, with the estimated probability of MCyR by 12 months at 30 mg (~60%) being meaningfully greater than at 15 mg (~25%), and both the 30 mg and 15 mg doses are likely to be biologically active on the basis of data that demonstrated average plasma concentrations exceeding the IC_{50} for all BCR-ABL1 mutations at the 30 mg dose, and for most BCR-ABL1 mutations at the 15 mg dose. Although a direct translation of exposure-efficacy relationships in a resistant CP-CML population to a previously untreated Ph+ ALL population is not possible, the estimated dose intensity-efficacy relationship in Study AP24534-10-201 nevertheless provides valuable prior information regarding expectations of dose-response relationships for efficacy of ponatinib in BCR-ABL1–driven hematologic malignancies. Accordingly, the results of these analyses provide the supporting rationale for selecting the 30 mg QD starting dose for this phase 3 protocol.

4.2.3 Rationale for Selection of MRD-Negative CR as Primary Endpoint

Treatment guidelines for patients with ALL [11] recommend an initial minimal threshold for response to be the achievement of a CR (also referred to as *complete response*), with no recurrence for 4 weeks, by the end of the induction phase.

More important, the absence of MRD has been found to have strong long-term prognostic power in patients with ALL, with a large body of evidence demonstrating a strong correlation between MRD negativity and improved event-free survival (EFS) and OS [11,32]. Consistent with most studies, NCCN guidelines recommend that MRD be assessed upon completion of the initial induction [11]. MRD assessment relies on accurate and sensitive detection of the relative proportion of leukemic cells, with an assay sensitivity of at least 0.01% (ie, the ability to detect 1 ALL cell among at least 10,000 normal cells) generally being required to consider a sample to be MRD-negative [11,33].

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In Ph+ ALL, MRD status can be assessed by detecting the specific genetic abnormality that defines the leukemic cells (ie, the presence of the BCR-ABL1 fusion gene transcript). In this approach, quantitative polymerase chain reaction (qPCR) is used to measure BCR-ABL1 levels (present in leukemic cells) relative to ABL1 levels (present in normal cells and leukemic cells) to assess disease levels.

In a meta-analysis that included 5 studies conducted in adult Ph+ ALL patients, MRD negativity at the end of induction was associated with significantly improved EFS and OS [32]. In the study most pertinent to the phase 3 trial described here, Short performed a retrospective analysis to test the association between achievement of MRD negativity and long-term outcomes in 85 patients with newly diagnosed Ph+ ALL treated with 1 of 3 TKIs (imatinib [N = 23], dasatinib [N = 39], or ponatinib [N = 23]) and a hyper-CVAD chemotherapy backbone, who did not undergo allogeneic stem cell transplantation. In this study, achievement of MRD negativity at 3 months, which was defined as absence of detectable BCR-ABL1 transcripts with a sensitivity of 0.01%, was associated with significantly longer OS and relapse-free survival. Importantly, though rates of MRD negativity were different according to the TKI (eg, 39% and 87% for patients receiving imatinib and ponatinib, respectively), among patients who achieved MRD negativity at 3 months, there was no impact on either OS or relapse-free survival according to the TKI received [5].

Given the reliance of this test on assessment of the genetic abnormality underlying Ph+ ALL, the assay used to assess BCR-ABL1 levels must be able to quantify the variants present in most patients with Ph+ ALL. More specifically, differences in the location of the BCR breakpoint result in 2 major variants of the BCR-ABL1 fusion transcript [34], which require separate polymerase chain reaction (PCR) primers for detection. In the variant present in the majority (~75%) of adult patients with Ph+ ALL, the first exon of the BCR gene is fused to the second exon of the ABL1 gene, resulting in a fusion transcript that encodes a 190 kDa oncoprotein. These are referred to as the e1a2 or p190 variants. In the second most common variant (~25% of patients), exons 13 or 14 (also known as exons b2 or b3) of the BCR gene are fused to the second exon of the ABL1 gene, resulting in a fusion transcript that encodes a 210 kDa oncoprotein. These are referred to as the e13a2 (or b2a2), e14a2 (or b3a2), or p210 variants. Thus, assessment of BCR-ABL1 levels in patients with Ph+ ALL requires use of 2 separate assays able to quantitatively measure levels of p190 and p210 variants, with a minimal sensitivity of at least 0.01%.

In summary, current treatment guidelines and multiple retrospective analyses support assessment of MRD negativity at the end of the induction phase of treatment as a meaningful surrogate for long-term efficacy (coupled with achievement of CR for at least 4 weeks). These studies also support defining MRD negativity as BCR-ABL1/ABL1 levels ≤0.01% (also referred to as molecular response 4-log reduction [MR4]) and measuring MRD negativity with appropriately qualified assays. Assessment of alternate residual disease thresholds, including BCR-ABL1/ABL1 levels ≤0.1% (molecular response 3-log reduction [MR3]) and ≤0.0032% (molecular response 4.5-log reduction [MR4.5]), at multiple timepoints, may further inform response milestones that may help guide future optimization of treatment regimens.

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective of the study is to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction (see Table 13.a for the definitions of MRD negativity and CR).

5.1.2 Secondary Objectives

The key secondary objective is to compare the rates of EFS between the 2 cohorts.

Other secondary objectives are:

- To compare the rates of CR and incomplete CR (CRi) between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- To compare the rates of MR3, MRD negativity (MR4), and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- To compare the rates of primary induction failure (PIF) and overall response rate (ORR) between the 2 cohorts, at the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To compare the rate of MR4.5 between the 2 cohorts, at multiple intervals after the end of induction, including best response.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare the rates of OS between the 2 cohorts.

5.1.3 Safety Objectives

The safety objectives are:

- To characterize the rates of AEs/SAEs, AOEs, venous thrombotic/embolic events (VTEs), and other safety outcomes of interest in the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

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5.1.4 Exploratory Objectives

The exploratory objectives are:

- To compare patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]) results between the 2 cohorts.
- To compare medical resource utilization (MRU) results between the 2 cohorts.
- To compare the time to start of alternative chemotherapy between the 2 cohorts.
- To compare the time to HSCT between the 2 cohorts.
- To explore biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoint is MRD-negative CR at the end of induction (see Table 13.a for the definitions of MRD negativity and CR).

5.2.2 Secondary Endpoints

5.2.2.1 Key Secondary Endpoints

The key secondary endpoint is:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve MRD-negative CR by the end of induction (CR and BCR-ABL1/ABL1 ≤0.01%).
  - Relapse from CR.

5.2.2.2 Other Secondary Endpoints

Other secondary endpoints (defined in Table 13.a) are:

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- Rates of PIF and ORR at the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.

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- Rates of MR4.5 at multiple intervals after the end of induction, including best response.
- Duration of MR4.5 in patients who achieved MR4.5.
- Subgroup analysis for on-study patients with and without HSCT (including rates of OS and relapse from CR).
- OS.

5.2.3 Safety Endpoints

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic blood pressure [BP] and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

5.2.4 Pharmacokinetic Endpoint

The pharmacokinetic (PK) endpoint is plasma concentration-time data to contribute to population PK and exposure-response analyses of ponatinib.

5.2.5 Exploratory Endpoints

The exploratory endpoints are (see Table 13.a for the definitions):

- Change from baseline in patient-reported quality of life (FACT-Leu and EQ-5D-5L).
- Change from baseline in MRU assessments.
- Time to start of alternative chemotherapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

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6.0 STUDY DESIGN

6.1 Overview of Study Design

This phase 3 study is designed as an open-label, multicenter, randomized comparison of the TKIs ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced-intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously. Patients will remain on study treatment until they are deceased, have failed to achieve the primary endpoint, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first. Patients who do not achieve the primary endpoint of MRD-negative CR at the end of induction will be discontinued from study drug, after which the patient's treating physician should consider alternative chemotherapy options (see Table 13.a for definitions).

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib, to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib QD, which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Section 8.4.1). Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for CNS disease prophylaxis. Patients who achieve the primary endpoint at the end of induction will continue in the consolidation phase and the maintenance phase. At the end of the 20 cycles, patients will remain on ponatinib or imatinib (administered as a single agent).

The primary endpoint of this study is MRD-negative CR at the end of induction (defined in Table 13.a). As CR must have been maintained for at least 4 weeks, patients who do not achieve CR by the end of Cycle 2 will be considered as having failed to achieve the primary endpoint.

MRD status will be measured using qPCR-based tests validated for the ability to detect BCR-ABL1/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as ≤0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale (IS) with traceability to the World Health Organization (WHO) first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported. To ensure uniformity of analysis, all samples will be tested in the same central laboratory. Assessment of the primary endpoint at the end of induction will be based on analysis of BM samples. To minimize the number and volume of BM aspirates required, and in keeping with available recommendations [1] and

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evidence of general concordance between results [2], assessment of BCR-ABL1/ABL1 levels at other time points may use peripheral blood samples. Both sample types will be collected at a subset of time points to allow the levels of concordance between sample types to be broadly assessed.

The key secondary endpoint for this study is the rate of EFS. Other secondary endpoints will include rates of CR and CRi at the end of Cycle 1, Cycle 2, and the end of induction; rates of MR3, MRD negativity (MR4), and MR4.5 at the end of Cycle 1, the end of Cycle 2, and the end of induction; rates of PIF and ORR at the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; rates of MR4.5 at multiple intervals after the end of induction, including best response; duration of MR4.5 in patients who achieved MR4.5; subgroup analyses for on-study patients with and without HSCT (including rates of OS and relapse from CR), and OS. (See Table 13.a for endpoint definitions.)

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all AEs, SAEs, AOEs, and VTEs; rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

Exploratory endpoints will include change from baseline in patient-reported quality-of-life and MRU assessments; time to start of alternative chemotherapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

6.2 Number of Patients

Up to 320 patients will be enrolled in this study from approximately 80 study centers globally. Enrollment is defined as randomized to study drug.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients, including those who achieve a clinical response, may receive study drug until they are deceased, have failed to achieve the primary endpoint, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.

After disease progression, all patients will be contacted every 3 months for survival follow-up. Patients will be followed until completion of the study or until the patient's death has been reported.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be considered completed when the death of all patients has been recorded or when the study has been terminated by the sponsor.

Study results will be reported in a clinical study report.

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6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Table 6.a provides disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: MRD-negative CR	BCR-ABL1/ABL1 ratio ≤0.01% and meeting criteria for CR (see Table 13.a)	The end of induction, ie, approximately 3 months
Key Secondary: EFS	The dates of randomization until: • Death due to any cause. • Failure to achieve MRD-negative CR by the end of induction. • Relapse from CR.	Approximately 3 years; EFS is event-driven, exact time period to be specified in statistical analysis plan
Secondary: CR and CRi	See Table 13.a	At approximately 1 month, 2 months, and 3 months
Secondary: Molecular response rates (MR3, MR4, and MR4.5)	MR3 is defined as molecular response 3-log reduction (≤0.1% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts; MR4 is defined as molecular response 4-log reduction (≤0.01% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts; MR4.5 is defined as molecular response 4.5-log reduction (≤0.0032% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.	At approximately 1 month, 2 months, and 3 months
Secondary: PIF and ORR	See Table 13.a for definition of PIF. ORR is defined as CR + CRi.	At approximately 3 months
Secondary: Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.	Up to 5 years
Secondary: Duration of CR	The interval between the first assessment at which the criteria for CR are met until the earliest date at which relapse from CR occurs.	Up to 5 years
Secondary: Time to treatment failure	Time to being off study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to both safety and/or loss of efficacy benefit reasons.	Updated annually after year 3, up to 5 years
Secondary: MR4.5, including best response	MR4.5 is defined as ≤0.0032% BCR-ABL1.	Up to 5 years

Footntotes are on last table page.

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Table 6.a Primary and Secondary Endpoints for Disclosures (continued)

Endpoint	Definition	Maximum Time Frame
Secondary: Duration of MR4.5 in patients who achieved MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.	Up to 5 years
Secondary: Subgroup analysis for on-study patients with and without HSCT (including rates of OS and relapse from CR)	Relapse from CR: Reappearance of blasts in the blood or BM (>5%) or in any extramedullary site after a CR. OS: The interval between the first dose date of study drug and death due to any cause, censored at the last contact date when the patient was alive.	Updated annually after year 3, up to 5 years
Secondary: OS	The interval between the first dose date of study drug and death due to any cause, censored at the last contact date when the patient was alive.	Up to 5 years

Abbreviations: AEs, adverse events; BCR-ABL, breakpoint cluster region-Abelson; cDNA, complementary DNA; CR, complete remission; CRi, incomplete CR; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction; MR4.5, molecular response 4.5-log reduction; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PIF, primary induction failure.

6.3.4 Total Study Duration

The duration of the study will be approximately 6 to 8 years, including 12 to 36 months for enrollment and at least 60 months (5 years) of follow-up from the date that the last patient enrolled.

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7.0 STUDY POPULATION

The study population will include male and female adult patients aged 18 years and older who have newly diagnosed Ph+ ALL.

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study and randomized to treatment:

1. Male or female patients aged 18 years or older.
2. Newly diagnosed Ph+ or BCR-ABL1-positive ALL, as defined by the 2017 NCCN guidelines.
3. Molecular assessment of BCR-ABL1 must demonstrate the presence of a p190 (ie, e1a2) or p210 (ie, e13a2 or e14a2 [also known as b2a2 or b3a2]) transcript type.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
5. Clinical laboratory values as follows, within 30 days before randomization:
   a) Total serum bilirubin ≤1.5× the upper limit of normal (ULN).
   b) Alanine aminotransferase or aspartate aminotransferase (AST) ≤2.5× the ULN.
   c) Serum creatinine ≤1.5× the ULN and estimated creatinine clearance (CrCl) ≥40 mL/minute (Cockcroft-Gault formula).
   d) Serum lipase and amylase <1.5× the ULN.
6. Normal QT interval corrected per Fridericia method (QTcF) on screening electrocardiogram (ECG), defined as QTcF of ≤450 ms in males or ≤470 ms in females.
7. Female patients who:
   a) Are postmenopausal for at least 1 year before the screening visit, *or*
   b) Are surgically sterile, *or*
   c) If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 1 month after the last dose of study drug, *or*
   d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
8. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, *or*

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b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
10. Willingness and ability to comply with scheduled visits and study procedures.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study or randomized to treatment.

1. Patients with a history or current diagnosis of chronic phase, accelerated phase, or blast phase CML.
2. Prior/current treatment with any systemic anticancer therapy (including but not limited to any TKI) and/or radiotherapy for cancer, with the exception of an optional prephase therapy, which should be discussed with the sponsor's medical monitor/designee.
3. Treatment with any investigational products within 30 days before randomization or 6 half-lives of the agent, whichever is longer.
4. Currently taking drugs that are known to have a risk of causing prolonged QTc or torsades de pointes (TdP) (unless these can be changed to acceptable alternatives or discontinued) (Appendix E).
5. Taking any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 (CYP)3A4 within at least 14 days before the first dose of study drug (Appendix F).
6. Active serious infection requiring antibiotics within 14 days before the first dose of study drug.
7. Major surgery within 28 days before randomization (minor surgical procedures such as catheter placement or BM biopsy are not exclusionary criteria).
8. Ongoing or active systemic infection, known seropositive HIV, known active hepatitis B or C infection.
9. History of acute pancreatitis within 1 year of study screening or history of chronic pancreatitis.
10. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
11. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are excluded if they have not undergone complete resection.
12. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.

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13. Active ALL in the CNS (confirmed by cerebrospinal fluid [CSF] analysis).
14. Autoimmune disease with potential CNS involvement.
15. Known significant neuropathy of Grade ≥2 severity.
16. Clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease, including, but not restricted to:
    a) Complete left bundle branch block.
    b) Right bundle branch block plus left anterior hemiblock, or bifascicular block.
    c) History of or presence of clinically significant ventricular or atrial tachyarrhythmias.
    d) Clinically significant resting bradycardia (<50 beats per minute).
    e) Uncontrolled hypertension (HTN); systolic BP ≥150 mmHg and/or diastolic BP ≥90 mmHg). Patients with Stage 2 HTN (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg should be under treatment at study entry per the current American Heart Association guidelines to ensure BP control. Patients requiring 3 or more antihypertensive medications should have controlled HTN for the past 6 months.
    f) Any history of myocardial infarction (MI), unstable angina, coronary artery disease (CAD), cerebrovascular accident (CVA), ischemic stroke, or transient ischemic attack (TIA).
    g) History of congestive heart failure (CHF) (New York Heart Association class III or IV) or left ventricular ejection fraction (LVEF) <40%, within 6 months before randomization.
    h) Symptomatic peripheral vascular disease or history of infarction, including visceral infarction.
    i) History of any revascularization procedure, including the placement of a stent.
    j) History of pleural or pericardial effusions.
    k) Any history of venous thromboembolism, including but not limited to deep venous thrombosis (DVT) or pulmonary embolism within 6 months before randomization.
17. Poorly controlled diabetes, defined as glycosylated hemoglobin (HbA1c) values of >7.5%. Patients with preexisting, well-controlled diabetes are not excluded.
18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.
19. Ongoing uncontrolled nausea or vomiting of any severity.
20. Diarrhea of Grade >1, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) categorization.
21. History of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease.

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22. Have a significant bleeding disorder unrelated to ALL.
23. Life-threatening illness unrelated to cancer, such as severe CNS, pulmonary, renal, or hepatic disease unrelated to cancer.
24. Female patients who are lactating or breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug is administered.
25. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
26. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

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8.0 STUDY DRUG

8.1 Study Drug Administration

8.1.1 Investigational Therapy: Ponatinib

Ponatinib will be supplied by the sponsor as 10 mg, 15 mg, and 30 mg round, white, film-coated tablets. All protocol-specific criteria for administration of ponatinib must be met and documented before ponatinib administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Ponatinib will be self-administered by the patient on a daily schedule at a starting dose of 30 mg by mouth (PO) QD. Each 28-day dosing period is referred to as 1 Cycle. Patients should be instructed to take the prescribed number of tablets with water, with or without food, at approximately the same time each day, continuously throughout the study, and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will be provided a diary or equivalent where the date and time of administration will be recorded; complete instructions will be provided with the study manual.

Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (eg, clinic chart) and in the electronic case report form (eCRF).

If severe emesis or mucositis prevents the patient from taking a ponatinib dose, that dose will be skipped. Under no circumstance should a patient repeat a dose or double-up doses.

8.1.2 Induction Phase (Cycles 1 Through 3)

The induction phase will begin on Day 1 of the study (Cycle 1 Day 1) and will comprise three 28-day cycles, including ponatinib (Cohort A; study drug; 30 mg QD), imatinib (Cohort B; active comparator; 600 mg QD), and reduced-intensity chemotherapy (Table 8.a).

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Table 8.a Induction Phase Treatment

Induction Phase Treatment (Three 28-Day Cycles) [a,b]	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)
Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14	Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14
Ponatinib: [c] Starting dose: 30 mg QD, starting on Cycle 1 Day 1	Imatinib: [c] Starting dose: 600 mg QD, starting on Cycle 1 Day 1

Abbreviations: IV, intravenous; PO, by mouth; QD, once daily.
Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to product labels for all other therapies included in this protocol.
[a] Lumbar punctures will be performed to test CSF for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples).
[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.
[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

8.1.3 Consolidation Phase (Cycles 4 Through 9)

The consolidation phase will begin after Cycle 3 of the induction phase is complete and will comprise six 28-day cycles, including ponatinib or imatinib and alternating cytarabine (even-numbered cycles) and methotrexate (odd-numbered cycles) (Table 8.b).

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Table 8.b Consolidation Phase Treatment

Consolidation Phase Treatment (Six 28-Day Cycles) [a,b]	
Cohort A	**Cohort B**
Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation Cycles 1, 3, and 5): – Patients aged ≤60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged >60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation Cycles 2, 4, and 6): – Patients aged ≤60 years: 1000 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion. – Patients aged >60 years: 250 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).	Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation Cycles 1, 3, and 5): – Patients aged ≤60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged >60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation Cycles 2, 4, and 6): – Patients aged ≤60 years: 1000 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion. – Patients aged >60 years: 250 mg/m^2/q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).
Ponatinib: [c] Start with the last induction phase dose; modify the dose based on MRD-negative CR results from the end of induction (see Section 8.3).	Imatinib: [c] Start with the last induction phase dose.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; PO, by mouth; q, every; QD, once daily.
Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to product labels for all other therapies included in this protocol.
[a] Lumbar punctures will be performed to test CSF for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples).
[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the first 3 consolidation phase cycles (total with the induction phase administration: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.
[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

8.1.4 Maintenance Phase (Cycles 10 Through 20)

The maintenance phase will begin after Cycle 9 of the consolidation phase is complete and will comprise eleven 28-day cycles, including the following (Table 8.c):

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Table 8.c Maintenance Phase Treatment

Maintenance Phase Treatment (Eleven 28-Day Cycles)	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)
Prednisone: Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5	Prednisone: Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5
Ponatinib: [a] Start with the last consolidation phase dose.	Imatinib: [a] Start with the last consolidation phase dose.

Abbreviations: IV, intravenous; PO, by mouth; QD, once daily.
Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to product labels for all other therapies included in this protocol.
[a] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

8.1.5 Postcycle 20 Therapy

Patients will continue on the last maintenance phase dose of TKI alone until they are deceased, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first. Patients who proceed to HSCT will be discontinued from study drug but will be followed per the on-study data collection schedule as specified in the Schedule of Events (SOE) for posttransplantation data collection, including rates of OS and relapse from CR. During this single-agent therapy phase study drug will be dispensed at each visit (ie, every 3 months).

8.2 Reference/Control Therapy: Imatinib

The active comparator in this study is imatinib, to be administered at 600 mg PO QD continuously during the study. Imatinib was chosen primarily because it is currently the most widely used standard of care throughout the world in the first-line treatment of adult patients with Ph+ ALL. The use of imatinib in combination with the reduced-intensity chemotherapy proposed in this phase 3 study is consistent with the recommended NCCN treatments for both adolescent and young adults and adult patients [11].

Patients will be provided a diary or equivalent where the date and time of administration will be recorded; complete instructions will be provided with the study manual.

Investigators should refer to the current local prescribing information for details on imatinib therapy.

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8.3 Dose Modification Guidelines for Efficacy

8.3.1 Mandatory Dose Reduction for Response

The primary endpoint of this study will be achievement of MRD-negative CR at the end of induction (as defined in Section 13.1.3.4). Ponatinib dose reductions to 15 mg QD will be implemented if patients achieve MRD-negative CR after completion of the induction phase. No dose reductions for response will be implemented for patients in the imatinib cohort.

Patients who do not achieve MRD-negative CR at the end of induction will be discontinued from study drug (both ponatinib and imatinib), after which the patient's treating physician should consider alternative treatment options.

8.3.2 Loss of Response After Dose Reduction for MRD-Negative CR

Patients in the ponatinib cohort who achieve MRD-negative status (defined in Table 13.a) at the end of induction, undergo dose reduction, and subsequently lose MRD-negative status at a single time point, can have dose re-escalation to 30 mg upon review and agreement with the sponsor's medical monitor/designee and in the absence of AEs requiring dose modification.

8.4 Dose Modification Guidelines for Adverse Drug Reactions

Dose modification guidelines detailed in this section are for patients receiving ponatinib only. Investigators should refer to local prescribing information for all other therapies included in this study. In instances where local prescribing information is not available, the sponsor will provide dose modification guidelines to the sites.

8.4.1 Dose Reduction Guidelines for Ponatinib

Dose reduction guidelines for ponatinib are summarized in Table 8.d and Table 8.e, and AEs should be graded according to NCI CTCAE, version 5.0 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, NCI Division of Cancer Treatment & Diagnosis, Accessed 05 December 2017). These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation can also be based on the clinical circumstance. Variation from these guidelines should be discussed with the sponsor's medical monitor/designee and resulting agreements should be recorded in source documents. When the observed toxicity has resolved to Grade ≤1 or returned to baseline, the investigator may resume dosing if clinically indicated. Guidance for re-escalation after resolution of adverse drug reactions is provided in Section 8.4.3.

Grade 4 nonhematologic toxicities (considered related to treatment) will, in general, require that treatment with study drug be permanently discontinued. If, in the opinion of the investigator and the sponsor's medical monitor or designee, it is in the patient's best interest to continue treatment with study drug, then the dose of study drug will be reduced by at least 1 dose level in subsequent cycles of treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

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Dose reduction below 10 mg QD is not permitted (see Table 8.d, Table 8.e, Table 8.f, and Table 8.g). Doses may be interrupted for study drug–related toxicities for up to 28 days; longer interruptions need to be discussed with the sponsor's medical monitor/designee.

See Section 8.4.3 for dose re-escalation guidelines after the resolution of adverse drug reactions.

Table 8.d Dose Modifications for Nonhematologic Adverse Drug Reactions: Ponatinib

General Toxicities	**Modification**
Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days with optimal care	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg Discontinue ponatinib
Grade 3 or 4	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib
Pancreatitis and Elevation of Lipase	**Modification**
Asymptomatic Grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
Asymptomatic Grade 3 or 4 elevation of lipase (>2× the ULN) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib

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Table 8.d Dose Modifications for Nonhematologic Adverse Drug Reactions: Ponatinib (continued)

Pancreatitis and Elevation of Lipase (continued)	**Modification**
Symptomatic Grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [eg, analgesia, nutritional support])	Occurrence [a] at 30 mg: Hold until complete resolution of symptoms and after recovery of lipase elevation to Grade ≤1 Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib
Grade 4 pancreatitis	Discontinue ponatinib
Hepatic Toxicity	**Modification**
Elevation of liver transaminase >3 × ULN (Grade 2 or higher)	Occurrence [a] at 30 mg: Hold ponatinib and monitor hepatic function until event is Grade ≤1 (≤3× the ULN) or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Elevation of AST or ALT >3× the ULN concurrent with an elevation of bilirubin >2× the ULN and ALP <2× the ULN	Discontinue ponatinib
LVEF/CHF [c]	**Modification**
Grade 1	No dose adjustment
Grade 2	Monitor by ECHO First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib

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Table 8.d Dose Modifications for Nonhematologic Adverse Drug Reactions: Ponatinib (continued)

LVEF/CHF [c] (continued)	**Modification**
Grade 3	Monitor by ECHO Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib
Skin Rash	**Modification**
Grade 1	No intervention
Grade 2 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is Grade ≤ 1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 3 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is Grade ≤ 1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; ECHO, echocardiogram; LVEF, left ventricular ejection fraction; ULN, upper limit of normal.

[a] "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

[b] "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

[c] For Grade 2: LVEF <50%-40%, Grade 3: LVEF <39-20%, Grade 4: refractory CHF or LVEF <20%.

Note: NCI CTCAE, version 5.0, 2018 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, NCI Division of Cancer Treatment & Diagnosis, Accessed 05 December 2017) criteria should be used to interrupt or discontinue study drug for Grades 2, 3, or 4 events considered to be study drug–related.

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Table 8.e Dose Modifications for Hematologic Adverse Drug Reactions: Ponatinib

Drug-Related ANC/Platelets	Modification
Grade 1 or 2	No dose adjustment
Grade 3 or 4	First occurrence[a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level
	Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg
	Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg
	Recurrence [b] at 10 mg: Discontinue ponatinib

Abbreviation: ANC, absolute neutrophil count.
NCI CTCAE, v5.0, 2018 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, NCI Division of Cancer Treatment & Diagnosis, Accessed 05 December 2017) criteria should be used to interrupt or discontinue study drug for Grades 2, 3, or 4 events considered to be study drug–related.
[a] "Occurrence" means the first time an AE is encountered by a patient at a given dose level.
[b] "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

8.4.2 Dose Modifications for AOEs and VTEs: Ponatinib

If a serious AOE or VTE occurs, treatment should be interrupted. Ponatinib should not be re-administered to patients with arterial or venous occlusive events unless the investigator assesses that the potential benefit outweighs the risk of continued therapy.

AOEs and VTEs include a broad range of nonspecific terms that could meet the criteria for diagnosis of this type of event. Investigators should use their clinical judgment and medical knowledge of the specific terms in describing these AOEs and VTEs.

Investigator discretion should be used to judge the event as a vascular pathology when applying these dose-modifying schemes.

8.4.2.1 AOEs

In patients suspected of developing any AOE, ponatinib should be immediately interrupted.

Patients should be discontinued from ponatinib in the event of MI, unstable angina, CVA, TIA, or revascularization procedures. For all other AOEs, dose modification guidelines are outlined in Table 8.f.

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Table 8.f Dose Modifications for AOEs: Ponatinib

Arterial Occlusion: Other Cardiovascular and Cerebrovascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Discontinue study drug Recurrence [b] at 15 mg: Discontinue study drug Recurrence [b] at 10 mg: Discontinue study drug
Grade 3 and 4	Discontinue ponatinib.
Other Arterial Occlusions, including Peripheral Vascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [c] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib Any recurrence [b] at any dose level: discontinue ponatinib
Grade 4	Discontinue ponatinib

Abbreviations: AOE, arterial occlusive event; CVA, cerebrovascular accident; MI, myocardial infarction; TIA, transient ischemic attack.
Patients should be discontinued from ponatinib in the event of MI, unstable angina, CVA or TIA, or revascularization procedures.
[a] "Occurrence" means the first time an AOE is encountered by a patient at a given dose level.
[b] "Recurrence" means the second time any AOE is encountered by a patient at a given dose level, not necessarily recurrence of the same AOE.

8.4.2.2 Venous Thrombotic/Embolic Events

Patients should be discontinued from study drug in the event of life-threatening pulmonary embolism or retinal vein thrombosis.

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For all other VTEs, dose modification guidelines are outlined in Table 8.g.

Table 8.g Dose Modifications for Venous Thrombotic/Embolic Events: Ponatinib

Venous Thrombotic/Embolic Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.

Abbreviation: VTE, venous thrombotic/embolic event.
[a] "Occurrence" means the first time a VTE is encountered by a patient at a given dose level.
[b] "Recurrence" means the second time any VTE is encountered by a patient at a given dose level, not necessarily recurrence of the same VTE.

8.4.3 Dose Re-Escalation after Resolution of Adverse Drug Reactions: Ponatinib

After dose reductions for toxicity, the dose of ponatinib can be re-escalated from the reduced dose level to the previously administered dose level if either of the following criteria is met:

- All Grade ≥2 nonhematologic toxicities have recovered to Grade ≤1 for at least 1 month, or
- All Grade ≥3 hematologic and nonhematologic toxicities have recovered to Grade ≤2 and are manageable with supportive therapy.

Patients may receive step-wise dose escalations (eg, 10 mg QD to 15 mg QD to 30 mg QD) up to the starting dose if the above criteria continue to be met. In no circumstances should a patient receive a ponatinib dose higher than 30 mg QD.

Note: Patients with Grade ≥3 left ventricular dysfunction, CHF, or arterial occlusion are not eligible for dose re-escalation after resolution of their symptoms.

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8.5 Excluded Concomitant Medications and Procedures

The following concurrent medications and treatments are prohibited:

- Other anticancer therapies.
- Other investigational drugs or devices.
- Herbal preparations or related over-the-counter preparations containing herbal ingredients.
- Elective surgery requiring inpatient care that cannot be postponed until study completion.

The following concurrent medications should be avoided but are not wholly excluded:

- Medications that are strong inhibitors or inducers of CYP3A4 should be avoided, but are not prohibited (Appendix F) in patients assigned to the ponatinib arm. Consider alternatives to strong CYP3A4 inhibitors or inducers. If coadministration of ponatinib with strong inhibitors of CYP3A4 is unavoidable, a dose reduction is recommended; the ponatinib dose is to be lowered by 1 dose level from the current dose (that is, 15 mg for a patient receiving 30 mg, or 10 mg for a patient receiving 15 mg).
- Medications with a known risk of TdP (see Appendix E):
  Medications that are associated with the prolongation of the QT interval may interact with ponatinib as well. Some medications associated with QT prolongation also interact with CYP3A4.
  Medications that prolong the QT interval, but are not associated with a known risk of TdP, should be avoided, but are not prohibited. If such medications are necessary and used while a patient is on study, additional ECG monitoring should be performed as clinically indicated.

8.6 Permitted Concomitant Medications and Procedures

All treatments/therapy received within 30 days before the first dose of study drug will be recorded as prior treatments.

All concomitant medications administered from the time of informed consent signature through the EOT visit (either the last dose of study drug or the investigator/patient decision to discontinue, whichever occurs later) are to be reported on the appropriate eCRF for each patient.

All routine and appropriate supportive care (including blood products, and hematopoietic growth factors) will be allowed during this study, as clinically indicated, and in accordance with standard-of-care practices. Clinical judgment should be exercised in the treatment of any AE experienced by an individual patient.

Information on all concomitant medications, administered blood products, and interventions occurring during the study must be recorded on each patient's eCRF. Among other treatments for concurrent illnesses, the following therapies are allowed:

- Medical or surgical treatment necessary for the patient's well-being.
- Where appropriate, treatment with hematopoietic growth factors.

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- Antiplatelet agents and anticoagulants are permitted with caution in patients who may be at risk of bleeding events.

8.7 Precautions and Restrictions

In order to participate in this study, female and male patients must qualify for the study per the inclusion and exclusion criteria (Section 7.1 and Section 7.2, respectively).

It is not known what effects the study therapies have on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment. Lactating females should be advised not to breast feed. All patients must meet the inclusion criteria for female and male patients as outlined in Section 7.1.

8.8 Management of Clinical Events for Ponatinib

Refer to the local ponatinib prescribing information for details on management of patients who have or who develop the following conditions: AOEs; VTEs; HTN; neuropathy; hepatotoxicity; CHF or left ventricular dysfunction; serious ocular toxicities; pancreatitis or lipase/amylase elevations; ocular toxicity, bleeding events; fluid retention/edema; cardiac arrhythmias; myelosuppression; tumor lysis syndrome; posterior reversible encephalopathy syndrome; compromised wound healing; or GI perforation.

For all other therapies to be administered per this protocol, investigators should refer to the local prescribing information for specific drugs for management of clinical events.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agent

8.10.1 Ponatinib

Ponatinib investigational drug product is supplied as white, round, film-coated tablets for oral administration. Each tablet contains 10 mg, 15 mg, or 30 mg of active ingredient. Other ingredients are typical pharmaceutical excipients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and a tablet coating comprised of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

8.10.2 Imatinib

Imatinib is dispensed as film-coated tablets, as described in the local prescribing information.

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8.11 Preparation, Reconstitution, and Dispensation

8.11.1 Ponatinib

Ponatinib tablets should be swallowed whole with water and should not be crushed or dissolved in liquid [35].

8.11.2 Imatinib

Imatinib is dispensed as film-coated tablets, as described in the local prescribing information.

8.12 Packaging and Labeling

8.12.1 Ponatinib

Ponatinib tablets will be supplied as follows:

- 10 mg tablets: 30 count in white high-density polyethylene (HDPE) bottles with foil induction seal and cap.
- 15 mg tablets: 30 count in white HDPE bottles with foil induction seal and cap.
- 30 mg tablets: 30 count in white HDPE bottles with foil induction seal and cap.

Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

8.12.2 Imatinib

Imatinib will either be dispensed from local supplies or provided by Takeda according to country regulatory requirements. If provided by Takeda, imatinib will be supplied as 100 mg and 400 mg film-coated tablets in appropriate packaging.

8.13 Storage, Handling, and Accountability

8.13.1 Storage

8.13.1.1 Ponatinib

Store Iclusig tablets at 20°C to 25°C (68°F-77°F); excursions permitted to 15°C to 30°C (59°F-86°F). Keep away from children.

8.13.1.2 Imatinib

Imatinib should be stored as described in the local prescribing information.

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8.13.2 Handling and Accountability

8.13.2.1 Ponatinib

The study pharmacist or designee at the investigative site will be responsible for handling and dispensing study drug and completing associated documentary paperwork.

Ponatinib supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. Supply shipping will be managed by interactive response technology (IRT). The site must use either an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute. Each time study medication is dispensed for a patient, the following information is recommended to be recorded: the patient's initials, the patient's study number, tablet strength, the number of tablets dispensed (with the corresponding lot number), and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study, and will be periodically verified by a representative of the sponsor. The investigator is responsible for ensuring that the patient diary and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

8.13.2.2 Imatinib

The study pharmacist or designee at the investigative site will be responsible for handling and dispensing study drug and completing associated documentary paperwork.

The site must use either an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute. Each time study medication is dispensed for a patient, the following information is recommended to be recorded: the patient's initials, the patient's study number, tablet strength, the number of tablets dispensed (with the corresponding lot number), and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study, and will be periodically verified by a representative of the sponsor. The investigator is responsible for ensuring that the patient diary and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

8.13.3 Disposition of Used and Unused Study Drug

No other use of ponatinib in this study is authorized by the sponsor. The principal investigator or designee will be responsible for the appropriate handling and disposition of residual study drug.

During the trial and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be redispensed.

Periodically throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the trial, a final study drug accountability review will be conducted, and any discrepancies must be investigated. All used and unused bottles or packs of study drug must be destroyed in an appropriate manner according to the

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standard practice at each study center (ie, destroyed at the site or returned to the local distribution center). Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

8.14 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this study, unless otherwise required by national local law or regulations.

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9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor's medical monitor for this study, the central laboratory, any additional clinical laboratories, the coordinating investigator, and any other vendors may be found in the study manual. For 24-hour contact information, please refer to the study manual or equivalent.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC) and Takeda (or designee).

It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

The randomization scheme will be generated by an independent statistician at Takeda. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by IRT.

9.4 Study Procedures

Refer to the Schedule of Events (Appendix A, Table 1 and Table 2) for timing of assessments. Additional details are provided as necessary in the sections that follow and in the SOE footnotes.

Tests and procedures should be performed on schedule, but occasional changes may be allowed for holidays, vacation, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed before dosing.

9.4.1 Screening Period Procedures

Screening tests and procedures are used to establish eligibility of the patient for the trial. If any given procedure or laboratory test is repeated before randomization, patients must continue to maintain laboratory values within eligibility parameters. See Appendix A, Table 1 for all screening procedures.

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9.4.2 Informed Consent

Each patient must provide written informed consent by signing and dating an IRB/IEC-approved informed consent form (ICF) before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision.

9.4.3 Enrollment and Randomization

Enrollment is defined as randomization to a treatment cohort. See Appendix A, Table 1 for enrollment procedures. Specific instructions for randomization will be supplied in the study manual. Randomization procedures should be performed following complete eligibility assessments and just before the initiation of the assigned dose cohort.

Patients will be randomized in a 2:1 ratio to receive oral ponatinib or imatinib (Cohort A and Cohort B, respectively) QD throughout the study. Study drug administration is detailed in Section 8.1. Each cycle of therapy will comprise 28 days of treatment, regardless of dose.

This study is open-label; patients, investigators, and the sponsor will know the identity of each patient's study drug.

9.4.4 Medical/Surgical History and Demographics

During the screening period, demographic data and a complete medical and surgical history will be compiled for each patient. Details of the data to be collected are specified in the SOE footnotes (Appendix A, Table 1).

9.4.5 Initial Leukemia Diagnosis

The initial leukemia diagnosis must be recorded during the screening period. Only patients who are newly diagnosed with Ph+ ALL or BCR-ABL1-positive ALL are eligible for this study.

9.4.6 Pregnancy Test

The pregnancy test must be a serum beta-human chorionic gonadotropin test and must be performed as specified in the SOE (Appendix A, Table 1 and Table 2). Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

9.4.7 Physical Examination and ECOG Performance Status

Complete physical examinations (including weight) will be completed as specified in the SOE (Appendix A, Table 1 and Table 2). Sites should calculate body mass index (BMI) from the weight and height measured at baseline, and the additional weight assessments will be documented in the eCRF without the need to calculate the BMI. Height will be measured at screening only.

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The ECOG performance status should be evaluated during each complete physical examination, as specified in the SOE (Appendix A, Table 1 and Table 2). Patients must have an ECOG performance status ≤2 to be eligible for this study. Additional details on assessing ECOG status are provided in the study manual.

9.4.8 Eye Examinations

A detailed eye history and eye examinations must be performed as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.9 Vital Signs

Vital sign measurements will include systolic and diastolic BP, heart rate, respiratory rate, and oral body temperature. Vital sign measurements will be assessed as specified in the SOE (Appendix A, Table 1 and Table 2) and the SOE footnotes.

9.4.10 CV Risk Assessments

9.4.10.1 Framingham Score

The Framingham risk score (Appendix G) estimates the risk of various CV disease outcomes, and will be performed as specified in the SOE (Appendix A, Table 1 and Table 2). Details of assessing the Framingham risk scores are provided in the study manual.

9.4.10.2 Ankle-Brachial Index

An assessment of the ankle-brachial index (ABI) will be performed to assess patients for the risk of peripheral arterial disease, as specified in the SOE (Appendix A, Table 1 and Table 2). Additional details on assessing the ABI are provided in the study manual.

9.4.10.3 12-Lead ECG

All ECGs must be 12-lead ECGs, performed as specified in the SOE (Appendix A, Table 1 and Table 2). If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

If the timing of a PK blood sample or other blood draw coincides with the timing of an ECG, the ECG should be performed first, followed by the blood draw.

9.4.11 Echocardiogram

An echocardiogram for assessment of LVEF must be performed as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.12 Prior and Concomitant Medications and Procedures

All medications/therapies and therapeutic procedures used/completed by the patient within 30 days before the first dose of study drug will be recorded as prior medication in the eCRF. All medications/therapies and therapeutic procedures used/completed by the patients from the signing

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of the ICF until the EOT visit (30 days after the last dose) will be recorded in the eCRF as concomitant medications, as specified in the SOE (Appendix A, Table 1 and Table 2). See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.4.13 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study, starting on the date of signed ICF, and continuing until the 30-day EOT visit, as specified in the SOE (Appendix A, Table 1 and Table 2). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

It is expected that new and updated AEs and concomitant medications will be reported within the treatment period; ongoing AEs thought to be at least possibly study drug–related; and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, version 5.0, Grade ≤1), stabilize, or are considered to be chronic/irreversible.

9.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as specified in the SOE (Appendix A, Table 1 and Table 2). Laboratory test results should be assessed before dosing. Handling and shipment of clinical laboratory samples will be outlined in the laboratory manual.

9.4.14.1 Hematology

Blood samples for complete blood count with differential will be obtained as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

9.4.14.2 Serum Analysis

a) **Chemistry**
The full chemistry panel must be obtained as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

If CrCl is to be estimated, the Cockroft-Gault formula will be employed as follows:

Estimated CrCl = [(140 - Age) * Mass(kg)] / [72 * serum creatinine(mg/dL)]
For female patients, the result of the formula above should be multiplied by 0.85.

b) **Fasting Glucose, Cholesterol, Lipids, and HbA1c**
Fasting glucose, HbA1c, and serum lipid panel (total, high-density lipoprotein, and low-density lipoprotein), including triglycerides, must be collected during screening and at subsequent time as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

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c) **C-Reactive Protein, and Cardiac Troponin-I**
C-reactive protein and cardiac troponin I assessments must be performed as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

d) **Hepatitis B Serology**
At the time of screening, blood serum must be tested for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum, as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.15 Disease Assessment

9.4.15.1 BM Aspirate

BM samples needed to assess the MRD-negative CR rate at the end of induction and other efficacy endpoints will be collected as specified in the SOE (Appendix A, Table 1 and Table 2). The optimal sample for MRD assessment is the first pull or early pull of the BM aspirate. Additional details regarding handling, shipping, and analysis of BM aspirates are provided in the laboratory manual.

Note: The BM aspirate on Cycle 3 Day 1 is only required in patients who have not achieved CR at Cycle 2 Day 1 (see Table 13.a for the definition of CR). Patients who have not achieved CR at Cycle 3 Day 1 should be discontinued from the study, after discussion with the sponsor's medical monitor.

Quantitative assessment of BCR-ABL1/ABL1 levels will be performed by a central molecular diagnostics laboratory, and the results will be reported to the participating investigator. For patients with the p190 BCR-ABL1 variant, the absolute ratio of BCR-ABL1 to ABL1 transcripts will be reported. For patients with the p210 BCR-ABL1 variant, the ratio of BCR-ABL1 to ABL1 transcripts will be reported on the IS (see Table 13.a for the definition of MRD negativity).

A portion of the BM aspirate sample may also be used for exploratory biomarker assessments as described in Section 9.4.15.2.

BM aspirates may be performed at other times when clinically indicated. Results of any BM aspirate, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

9.4.15.2 Peripheral Blood Samples for Molecular Response and Exploratory Biomarker Assessments

Peripheral blood samples needed to assess molecular response and exploratory biomarkers will be collected as specified in the SOE (Appendix A, Table 1 and Table 2). Details of handling, shipping, and analysis of peripheral blood samples are provided in the laboratory manual.

Quantitative assessment of BCR-ABL1 levels (ie, molecular response assessments) will be performed by a central molecular diagnostics laboratory, and the results will be reported to the participating investigator. For patients with the p190 BCR-ABL1 variant, the absolute ratio of BCR-ABL1 to ABL1 transcripts will be reported. For patients with the p210 BCR-ABL1 variant, the ratio of BCR-ABL1 to ABL1 transcripts will be reported on the IS.

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Exploratory biomarker assessments will include analysis of molecular determinants of response or resistance to ponatinib and imatinib, including those present at the initiation of study drug or those that develop during study treatment. This testing will include, but may not be limited to, analysis of BCR-ABL1 mutation status.

9.4.15.3 Extramedullary Disease

Extramedullary disease assessments will include lumbar punctures to test CSF for CNS disease as specified in the SOEs (Appendix A, Table 1 and Table 2) and as clinically indicated. Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should be performed as clinically indicated throughout the study.

9.4.16 Quality of Life and Health Outcomes Measures

Both the EQ-5D-5L and the FACT-Leu forms are validated and self-administered forms. The EQ-5D-5L is a general questionnaire of health-related quality of life (HRQOL) issues, developed by the EuroQOL Group. The FACT-Leu questionnaire was developed specifically for patients with leukemia by the Functional Assessment of Chronic Illness Therapy Measurement System (www.facit.org) which manages administration, scoring and interpretation of a questionnaires that measure HRQOL for people with chronic illnesses. Patients for whom a validated translation exists in a language in which they are fluent will complete the EQ-5D-5L and the FACT-Leu during study visits, as specified in the SOE (Appendix A, Table 1 and Table 2) [36-39]. Details on administration of the EQ-5D-5L are provided in the study manual.

9.4.17 Medical Resource Utilization Data Collection

All medical care encounters will be collected for all patients until study closure, as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.18 PK Measurements: Ponatinib

Blood samples for plasma PK assessments will be collected as specified in the SOE (Appendix A, Table 1 and Table 2) in patients assigned to the ponatinib cohort. Details on sample collection times are provided in the SOE footnotes. Details of collection and handling of plasma PK samples are provided in the laboratory manual. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples should be recorded in the eCRF.

9.5 Completion of Study Treatment (for Individual Patients)

All patients will be considered to have completed study treatment when they are deceased, have failed to achieve the primary endpoint, have experienced relapse from CR, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT, or until the sponsor terminates the study, whichever occurs first.

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9.6 Completion of Study (for Individual Patients)

The study will be completed for individual patients when death occurs or the study has been terminated by the sponsor.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Discontinuation of treatment with study drug is to be reviewed and confirmed by the sponsor's medical monitor or designee.

Study drug must be permanently discontinued for patients who become pregnant.

Treatment with study drug may also be discontinued for any of the following reasons:

- Adverse event.
- Protocol deviation.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other.

Patients who discontinue study drug will not be replaced.

Ensure that patients discontinuing treatment or assessments early have adequate follow-up, as described in Section 9.10.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Table 2). The primary reason for study drug discontinuation will be recorded on the eCRF.

Investigators should refer to the current local prescribing information for details on criteria for discontinuing imatinib therapy.

9.8 Withdrawal of Patients From Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or sponsor by the terminating party.

A patient may be withdrawn from the study for any of the following reasons; the reason for withdrawal from the study must be documented in the eCRF:

- Death.
- Study terminated by sponsor.
- Withdrawal by subject.

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- Lost to follow-up.
- Other.

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. (See also Section 8.13.2 and Section 8.13.3.) Patients will be provided a diary or equivalent where the date and time of ponatinib and imatinib administration will be recorded; complete instructions will be provided with the study manual.

9.10 Posttreatment Follow-up Assessments

Patients who stop study drug due to failure to achieve the primary endpoint, withdrawal of informed consent, having relapse from CR, proceeding to HSCT, study termination by the sponsor, or until the patient's death will be followed for OS. Survival data will be collected every 3 months◦±◦14◦days, starting after the last dose of study drug or the investigator/patient decision to discontinue treatment (whichever occurs later).

Patients who discontinue study drug due to HSCT will be followed per the on-study data collection schedule as specified in the SOE for posttransplantation data collection, including OS and relapse from CR.

Survival, HSCT, and the start of alternative chemotherapy data may be collected by methods that include, but are not limited to, telephone, email, mail, and retrieval from online social security indexes and other public records as permitted by local regulations. The EOS eCRF page is to be completed at the time the patient discontinues from the survival follow-up period. See the SOE for appropriate assessments during follow-up.

Note: Related SAEs occurring during the posttreatment period must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the posttreatment follow-up period. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

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10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

Pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

Adverse event means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

Serious adverse event means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the

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development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, 2018 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, NCI Division of Cancer Treatment & Diagnosis, Accessed 05 December 2017). Clarification should be made between an SAE and an AE that is considered severe in intensity (Grades 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grades 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 AEs of Special Interest Definitions

AOEs and VTEs have been identified as AEs of special interest (AESIs) for ponatinib. These include arterial and venous thrombotic and occlusive AEs that meet the criteria for SAEs, as defined in Section 10.1.3, as well as those AEs that do not meet the SAE criteria.

AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the sponsor. All AESIs, whether they are SAEs or not, must be reported immediately (within 24 hours) to the sponsor. The sponsor has determined that the events in the following list (whether considered serious or nonserious by investigators) should be considered AESIs, and should therefore be reported within 24 hours (see Section 10.2):

- MI: The Third Universal Definition of Myocardial Infarction [40] is used for the following definitions of MI:
  - Angina (newly diagnosed or worsening of existing or unstable angina).
  - CAD (newly diagnosed or worsening of existing CAD) or symptoms that may reflect CV disease [40].
- Cerebrovascular ischemic disease, including ischemic or hemorrhagic stroke, vascular stenosis, TIA, cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease [41].
- New onset or worsening of peripheral artery occlusive disease (eg, of the renal artery, mesenteric artery, or femoral artery) or symptoms that may reflect peripheral vascular disease.
- Retinal vascular thrombosis, both venous and arterial.

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- Venous thromboembolism that could result in significant compromise of organ function or other significant consequences (eg, pulmonary embolism, portal vein thrombosis, or renal vein thrombosis), or symptoms that may reflect venous thrombosis.

AOEs and VTEs will be documented in both cohorts for comparison.

10.2 Procedures for Recording and Reporting AEs, SAEs, and AESIs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs, AESIs, and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the SAE report or form must be consistent with the data provided on the eCRF. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

All SAEs and AESIs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

SAE Reporting Contact Information

PPD

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

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For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 5.0, 2018 (ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm, NCI Division of Cancer Treatment & Diagnosis, Accessed 05 December 2017). The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?"

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of the ICF through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs should be monitored until they are resolved or return to baseline or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es); the exception is peripheral neuropathy, which will be followed monthly until (1) resolution of peripheral neuropathy, (2) the start of a second-line alternative antineoplastic treatment, or (3) 6 months after PD has occurred, whichever occurs first.
- SAEs.
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The Pregnancy Form may be faxed or scanned and e-mailed. The pregnancy must be followed for the final pregnancy outcome.

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If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses as follows:

Product	Call Center	Phone Number	Email	Fax
PPD				

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported (refer to Section 10.2). Medication errors should also be documented accurately in the patient diary.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

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11.0 STUDY-SPECIFIC COMMITTEES

11.1 Steering Committee

The steering committee will comprise medical experts involved in the study, the sponsor, and an independent statistician. The steering committee will remain blinded to treatment assignments throughout the conduct of the study. The steering committee will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality, and making any necessary modifications to the protocol. The Steering Committee Charter will define the responsibilities of the committee.

11.2 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) supported by an independent statistician will review safety and efficacy data at the planned primary analysis and at regular intervals outlined in the charter. The IDMC will review the outcomes at the interim analysis (IA) and make recommendations on study conduct if needed.

The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. If the study is terminated early based on the IDMC recommendation, Takeda will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter.

Study accrual will not be interrupted because of the scheduled safety reviews. The IDMC or study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, subject incidence rates of AEs (including all SAEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study drug) will be tabulated by System Organ Class (SOC), Preferred Term, and severity grade. Listings and/or narratives of on-study deaths and other serious and significant AEs, including any early withdrawals because of AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Takeda.

Details of the IDMC will be captured in a charter before the start of the study. Further details will be provided in the IDMC charter.

11.3 Cardiovascular Endpoint Adjudication Committee

The cardiovascular endpoint adjudication committee (CVEAC) will comprise independent experts with experience and training appropriate for reviews of the CV AOE and VTE endpoints. They will review all CV events defined as AOEs and VTEs reported by the sites (ie, initial diagnoses, laboratory values, results of procedures, hospital discharge summaries) to determine the occurrence of CV endpoints. The adjudication of these events will be performed based on the CVEAC adjudication charter, which will document details for performing adjudication, to be written before the start of the trial. The CVEAC's assessment of each potential CV endpoint will be documented in the clinical database and will be used in the endpoint analysis. The process will

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be coordinated by the contract research organization (CRO), and the CVEAC charter will define the endpoints and the responsibilities of the committee.

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12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Guideline, Section 4.9.5, requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years

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after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

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13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

Further details regarding the definition of analysis variables and analysis methodology to address all study objectives will be provided in the statistical analysis plan (SAP).

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided CIs for time-to-event data. In case survival distributions cannot be summarized appropriately, alternative approaches will be defined in the SAP.

The SAP will be written by Takeda and will be finalized before the planned IA. Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; any further modifications will be noted in the final clinical study report.

13.1.1 Analysis Sets

13.1.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

13.1.1.2 Per-Protocol Population

The per-protocol (PP) population is a subset of the ITT population. The PP population consists of all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the sponsor's medical monitor. All decisions to exclude patients from the PP population will be made before the database lock for the analyses.

13.1.1.3 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but received the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but received the regimen in the active arm will be included in the active arm for safety analyses.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions and summary statistics based on the primary efficacy data set for each treatment cohort and for all patients combined.

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13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy Endpoint Assessment

The primary endpoint is achievement of MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 13.a for endpoint definitions). The analysis of the primary efficacy endpoint will test for differences comparing the proportion of patients who achieve the primary endpoint at the end of induction in the ponatinib arm versus the imatinib arm. The analysis of the primary endpoint will be based on the ITT population. If the MRD-negative CR data are missing at the end of the induction phase, it will be treated as failure for the primary endpoint.

If the 2-sided p-value is greater than the alpha spending cut-off at IA, or if the enrollment is not terminated after IA for futility, the conditional power for the primary endpoint analysis will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the pre-planned sample size for final analysis (FA) of MRD-negative CR will remain unchanged at 230 patients. If the conditional power falls in the promising zone, the sample size will be determined according to a prespecified sample size adaptation rule, with a cap of approximately 320 patients.

At IA, the primary analysis for the primary endpoint will be conducted by comparing the MRD-negative CR rates at the end of the induction phase between treatment arms using a Cochran-Mantel-Haenszel (CMH) chi-square test at significance level ($\alpha_1 = 0.011$) designated by the alpha spending assigned by the group sequential procedure, with stratification according to the stratification factors. The CMH chi-square p-value and the relative risk along with its $(1 - \alpha_1)$% 2-sided CI will be provided. Besides the relative risk summary, the absolute treatment difference will be provided along with the $(1 - \alpha_1)$% 2-sided CI.

If the FA will be conducted and conditional power is less than 50% at IA, then at FA, the Cui-Hung-Wang test, a weighted statistic based on CMH test results at IA and FA, will be used in analyzing the primary endpoint [42]. Level of the test at FA for the primary endpoint will be designated by the alpha spending assigned by the group sequential procedure ($\alpha_2 = 0.046$).

Sensitivity analyses for the primary endpoint will include:

1. MRD-negative CR will be analyzed in the PP population.
2. MRD-negative CR will be analyzed with nonmissing observed cases.

Subgroup analyses will be performed for the primary endpoint relative to baseline stratification factors, demographic data such as sex and race, and disease characteristics. In addition, the absolute treatment difference will be provided along with the 95% 2-sided CI estimate.

Further details on the analyses of primary endpoint will be discussed in the SAP.

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13.1.3.2 Key Secondary Efficacy Endpoint Assessment

The key secondary endpoint is EFS.

EFS will be tested only if the primary endpoint comparison is significant, in which case the EFS endpoint will be tested at 5% level, per the closed sequential testing procedure, to maintain the family-wise type I error rate at 5% level. The analysis of the key secondary endpoint, EFS, will be based on the ITT population.

As discussed in the adaptive design Section 13.3, power for the EFS analysis is estimated based on 3-year EFS data observed from various phase 2 trials [5,6]. EFS will be analyzed when a sufficient number of EFS events have accumulated after patients have been followed for 3 years. The primary analysis for EFS will be based on time-to-event analysis. Since it is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT, the number of events needed for EFS analysis may change depending on how HSCT cases are handled in the EFS; the exact analysis method will be specified in the SAP.

Sensitivity analyses for EFS will include:

1. EFS will be analyzed in the PP population.
2. A different approach will be used in dealing with HSCT cases from the one used in the primary analysis for the EFS endpoint.
3. Inverse Probability of Censoring Weighted analysis of the EFS endpoint will be used, adjusting for possible confounding caused by informative censoring from imbalance in the proportion of HSCT events between the 2 cohorts.

Since more than one approach can be used in handing HSCT cases differently in the EFS analysis, once one of them is designated as the primary EFS analysis method in the SAP, the rest will be used as sensitivity analysis methods.

Subgroup analyses will be performed for EFS relative to baseline stratification factors, demographic data such as sex, race, and disease characteristics.

Further details on the key secondary endpoint analyses will be discussed in the SAP.

13.1.3.3 Other Secondary Efficacy Endpoint Assessments

The following other secondary endpoints will be analyzed (see Table 13.a for endpoint definitions):

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5), at the end of Cycle 1, the end of Cycle 2, and the end of induction.
- Rates of PIF and ORR at the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.

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- Time to treatment failure.
- Rate of MR4.5 at multiple intervals after the end of induction, including best response.
- Duration of MR4.5 in patients who achieved MR4.5.
- Subgroup analysis for on-study patients with and without HSCT (including rates of OS and relapse from CR).
- OS.

The other secondary efficacy endpoints will be tested at $\alpha = 0.05$ level in a nonhierarchical fashion without adjustments for multiplicity.

For analysis of time-to-event endpoints (eg, time to treatment failure, OS, duration of MR4.5), 2-sided, stratified log-rank tests will be used to compare the treatment groups with respect to the endpoints. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio (HR) and its 95% CIs for the treatment effect using the stratification factors. Kaplan-Meier (K-M) survival curves and K-M medians (if appropriate and estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

Per the trial design, if a patient has been discontinued from study drug, death data will be collected for up to 5 years. Therefore, OS results are expected to be confounded by alternative therapies after patients discontinue from the study assigned drug. Thus, various sensitivity analyses will be outlined in the SAP for time-to-OS analysis adjusting for time depending on confounding factors occurring due to taking alternative therapies.

The primary analysis for duration of MRD-negative CR will be based on time-to-event analysis. Since more than one approach can be used in handing HSCT cases differently in the analyses for duration MRD-negative CR, once one of them is designated as the primary analysis method in the SAP, the rest will be used as sensitivity analysis methods.

The proportion-based other secondary endpoints (eg, CR, and CRi rates) will be analyzed in the same fashion as the primary endpoint. The CMH chi-square p-value and the relative risk, along with its 95% 2-sided CI, will be provided. In addition, the absolute treatment difference in proportion will be provided along with the 95% 2-sided CI estimate.

Further details on the analyses of other secondary endpoints will be discussed in the SAP.

13.1.3.4 Definitions of Response Criteria

Definitions of response criteria for the purpose of efficacy analyses are provided in Table 13.a.

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Table 13.a Definitions of Efficacy Response Criteria

Term	Definition
CNS-1	CNS-1: No lymphoblasts in the CSF regardless of WBC count
CNS-2	WBC count <5 leukocytes/µl in the CSF with the presence of blasts
CNS-3	WBC count of ≥5 leukocytes/µl with the presence of blasts
CNS disease remission	No lymphoblasts in CSF regardless of WBC count in a patient with CNS-2 or CNS-3 at diagnosis
CNS relapse	Development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome)
CR	Complete remission; meeting all of the following for at least 4 weeks (ie, no recurrence): • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass). • ANC >1000/µl (or >1.0 × 10^9/L). • Platelets >100,000/µl (or >100 × 10^9/L).
CRi	Hematologic complete remission with incomplete hematologic recovery. Meets all criteria for CR except platelet count and/or ANC.
Duration of CR	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.
Duration of MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.
Duration of MRD negativity (MR4)	The interval between the first assessment at which the criteria for MRD negativity are met until the earliest date at which loss of MRD negativity occurs or relapse from CR occurs.
Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.
EFS	Event-free survival (EFS), defined as the dates of randomization until: • Death due to any cause. • Failure to achieve MRD-negative CR by end of induction. • Relapse from CR.
Loss of MR3	An increase to >0.1% BCR-ABL1/ABL1.
Loss of MR4.5	An increase to >0.0032% BCR-ABL1/ABL1. This result must be confirmed at the subsequent visit, unless it is associated with loss of MR4.5 or relapse from CR.
Loss of MRD negativity	An increase to >0.01% BCR-ABL1/ABL1. This result must be confirmed within 4 weeks with either a BM aspirate (optional) or peripheral blood, unless it is associated with loss of MR3 or relapse from CR.

Footnotes are on last table page.

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Table 13.a Definitions of Efficacy Response Criteria (continued)

Term	Definition
MR3	Molecular response 3-log reduction (≤0.1% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts.
MR4.5	Molecular response 4.5-log reduction (≤0.0032% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.
MRD-negative CR	Meeting the criteria for both MRD negativity and CR.
MRD negativity (MR4)	≤0.01% BCR-ABL1/ABL1, or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. Also referred to as MR4.
ORR	Overall response rate: CR + CRi.
OS	Overall survival. The interval between the first dose date of study drug and death due to any cause.
PD	Progressive disease. Increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease.
PIF	Primary induction failure: Patients who received treatment for ALL but never achieved CR or CRi by the end of induction. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi.
Relapse from CR	Reappearance of blasts in the blood or BM (>5%) or in any extramedullary site after a CR.
Time to treatment failure	Time to being off study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to both safety and/or loss of efficacy benefit reasons.

Abbreviations: ANC, absolute neutrophil count; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; CR, complete remission; CRi, incomplete blood count recovery; CSF, cerebrospinal fluid; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MR4, molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%); MR4.5, molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%); MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; WBC, white blood cell.

13.1.4 Safety Endpoints

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP, and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

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13.1.5 Exploratory Endpoints

The exploratory endpoints are:

- Change from baseline in patient-reported HRQOL (FACT-Leu and EQ-5D-5L).
- Change from baseline in MRU assessments.
- Time to start of alternative chemotherapy.
- Time to HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

Further details on the exploratory endpoint analyses will be discussed in the SAP.

13.1.5.1 Time-to-Next-Treatment and Time-to-HSCT Analyses

Time to subsequent antineoplastic therapy will be defined as the time from randomization to the date of first documentation of subsequent antineoplastic therapy or the last contact date for subjects who never received subsequent antineoplastic therapy.

Likewise, time to HSCT will be defined as the time from randomization to the date of first documentation of HSCT or the last contact date for subjects who did not receive an HSCT.

A Cox regression model with treatment as explanatory variable will be used for the time-to-event analyses. Median follow-up will be calculated by K-M method.

13.1.5.2 Patient-Reported Outcomes Analysis

Quality of life and health outcomes measures are being collected using the EQ-5D-5L and FACT-Leu instruments. Means and medians of scores of these questionnaires will be summarized for each cohort by time point, overall, and for each domain. Assessments based on the FACT-Leu will be analyzed to determine if treatments affect all domains.

Analyses of HRQOL scores, including global health status, will be performed using longitudinal models for scores and change from baseline scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point.

Initially, the manuals published for FACT-Leu will be used for scoring and handling missing data. Further investigation of missing patterns and details of imputation will be discussed in the SAP.

EQ-5D-5L scores will be summarized in descriptive statistics for treatment groups. Both utility scores and change from baseline scores will be assessed across time using longitudinal models.

13.1.5.3 Health Economics Analysis Using Medical Resource Utilization

Medical resource utilization data will be summarized in descriptive statistics for hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities, by patient and caregiver, and by treatment group.

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13.1.5.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib

The mutation status of BCR-ABL1 and other genes implicated in tumor biology and/or drug metabolism will be determined through analyses of tumor cells collected at study entry, on study, and/or at EOT. Analysis methodologies include, but are not limited to, DNA sequencing, digital PCR, and mass spectrometry.

13.1.6 PK Analysis (Ponatinib)

The PK data collected in this study are intended to contribute to future population PK analyses of ponatinib. These population PK analyses may additionally include data collected in other ponatinib clinical studies. The analysis plan for the population PK analysis will be defined separately and the results of these analyses will be reported separately.

13.1.7 Safety Analysis

The safety analysis will be carried out at interim and final analyses. In addition, an extended safety analysis for the study will be carried out at study completion.

Safety evaluations will be based on incidence, severity, and type of AEs; clinically significant changes or abnormalities in the patient's physical or neurological examinations; vital signs; and clinical laboratory test results.

Descriptive statistics will be calculated. Treatment-emergent adverse events (TEAEs) will be tabulated by primary SOC, High Level Term (HLT), and PT. MedDRA will be used for coding AEs. A TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

To summarize the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each SOC, HLT, and PT. Events that are considered related to treatment will also be tabulated. AEs will also be summarized by intensity. Deaths, AEs, SAEs, AOEs, VTEs, and events resulting in study discontinuation, if present, will be presented in separate data listings.

13.2 IA and Criteria for Early Termination

There will be 1 IA and possibly an FA in the study for the MRD-negative CR primary endpoint. If the outcome from the IA or FA for the primary endpoint is positive, there will be an FA for the EFS and other long-term endpoints.

The IA for MRD-negative CR will be carried out by an independent statistical team in a manner that maintains the blinding of the study results to the team. Based on the results from the IA, by applying the prespecified promising zone adaptive approach rules, the IDMC may recommend stopping the trial for efficacy or futility, or recommend continuing the trial with or without sample size modification. The sponsor's executive committee will make final decisions based on the IDMC recommendations.

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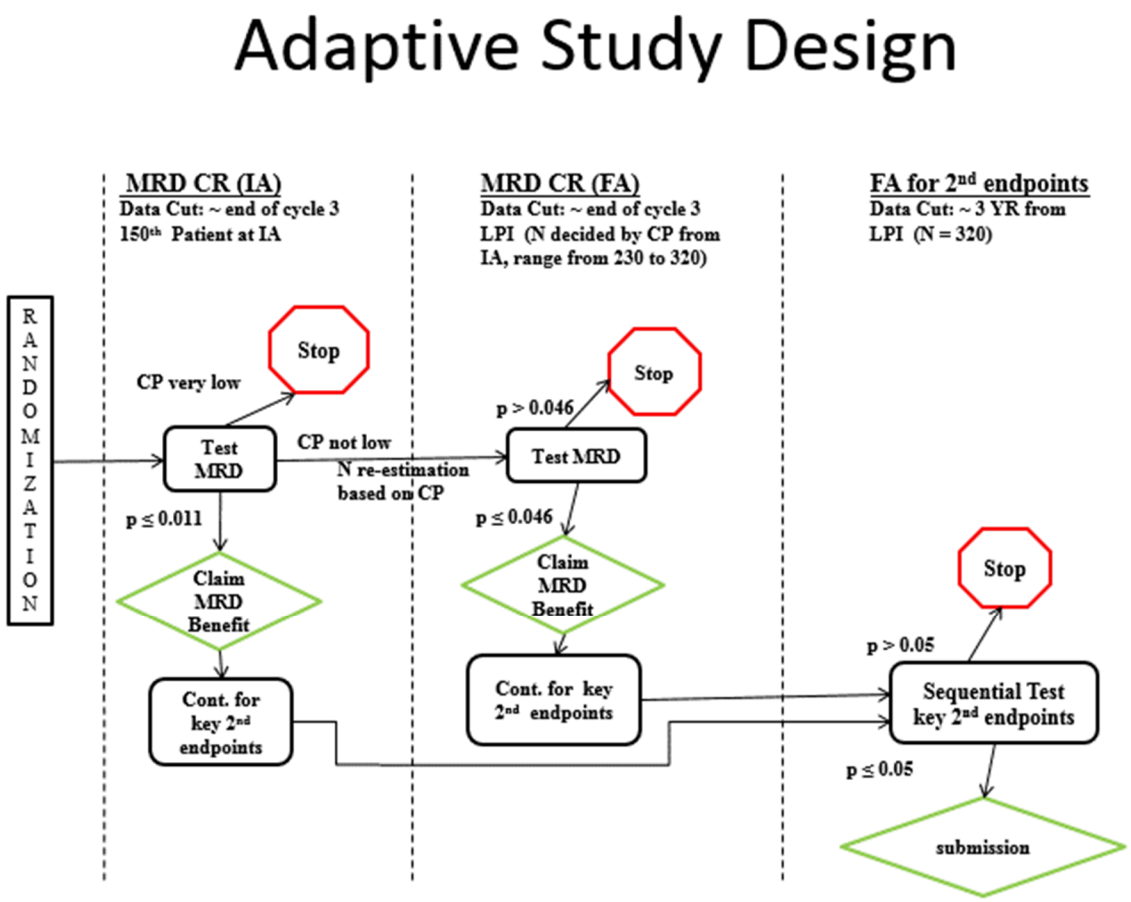
13.3 Determination of Sample Size and Adaptive Design

The conditional power based sample size re-estimation adaptive design proposed in Mehta et al is used in determining the sample size and power of the trial [3,4].

Figure 13.a Statistical Design: Alpha Spending Plan



Abbreviations: Cont., continue; CP, conditional probability;CR, complete response; FA, final analysis; IA, interim analysis; LPI, last patient in; MRD, minimal residual disease.

Assuming an optimistic effect size of 28% (48% and 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of 230 patients (153 vs 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 83% power at IA. IA will be performed after the end of induction phase data have been collected for 150 patients. If the enrollment is not terminated after IA (for futility) the conditional power will be calculated. If the conditional power falls in the favorable zone or unfavorable zone, the preplanned sample size for FA of MRD-negative CR will remain unchanged at 230 patients. If the conditional power falls in the promising zone, the sample size will be determined according to a prespecified sample size adaptation rule, with a cap of approximately 320 patients, by which the overall study

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power will be 82.6% if the actual effect size is 17% (40% and 23% MRD-negative CR rates for the active and control arms, respectively).

The sample size adaptation rule is a prespecified stepwise function to avoid the possibility of back calculation of the trial IA outcome, as 1 sample size recommendation will correspond to multiple IA results: either barely promising or highly promising. The sample size adaptation rule (including the definitions for the unfavorable, favorable, and promising zones) will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the head of biostatistics will be involved in the study conduct.

The adaptation rules will be outlined in a separate document and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the IDMC, and the statistics representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

The overall 2-sided type 1 error is controlled at the 0.05 level. The O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to calculate the significance and futility boundaries for the primary endpoint at IA and FA. With 65% information available at IA, the efficacy boundary will be 0.011 and 0.046 at IA and FA, respectively, for the primary endpoint.

Inference for the key secondary endpoint of EFS will be conducted at $\alpha = 5\%$ level only if the primary endpoint is met either at IA or FA for the MRD-negative CR (Figure 13.a). The EFS endpoint will be analyzed via a time-to-event analysis method. Based on 3-year EFS data observed from various phase 2 trials [5,6], effect size is assumed as 67% vs 46% for EFS at year 3 for the active and control arms, respectively, or HR = 0.516. Under this assumption, at least 120 events need to be accumulated so that the power will be at least 80% for the EFS endpoint. If the MRD-negative CR result is positive at IA, the plan is to reach a stable enrollment rate of 10 or more patients per month after IA to accumulate a sufficient number of patients to power the EFS endpoint analysis at >80% level.

It is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT before loss of MRD-negative CR. Since the HR is different for patients with or without HSCT [7-9], depending on how to handle HSCT patients in the EFS analysis, the number of events needed to power the EFS analysis may change. Thus, the final number of events will be specified in the SAP based on simulation results before the database lock for the IA on the MRD-negative CR.

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14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified

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immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

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15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH E6 Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal-Wide Assurance Number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug and notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

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15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH E6 Guideline for GCP and will be in accordance with all applicable laws and regulations. The ICF describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF. The ICF must be approved by both the IRB or IEC and the sponsor before use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copy of the signed and dated ICF shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date

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of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest

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to their homes by providing the investigator name, address, and phone number via e-mail/phone or other methods callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases

Study Procedures	**Screening / Baseline**	**Induction Phase**						**Consolidation Phase**											
28-Day Cycles		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7**		**Cycle 8**		**Cycle 9**	
Cycle Days	**-28 to -1**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**
Window (days) [a]	**N/A**	**±2**																	
Informed consent [b]	X																		
Enrollment [b]	X																		
Med/Surg history and demographics [c]	X																		
Pregnancy test [d]	X	X																	
Leukemia diagnosis	X																		
Prior medications [e]	X																		
Vital signs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exams [g]	X	X	**X**	X	**X**	X	**X**	X	X	X	X	X	X	X	X	X	X	X	X
ECOG [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABI [h]	X	Additional Assessments as Clinically Indicated																	
Framingham score [i]	X																		
12-Lead ECG [j]	X							X						X					
ECHO [k]	X	Additional Assessments as Clinically Indicated																	

Footnotes are on last table page.

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Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases (continued)

Study Procedures	**Screening / Baseline**	**Induction Phase**						**Consolidation Phase**											
28-Day Cycles		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7**		**Cycle 8**		**Cycle 9**	
Cycle Days	**-28 to -1**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**
Window (days) [a]	**N/A**	**±2**																	
Eye exams [l]	X	Additional Assessments as Clinically Indicated																	
PROs [m]	X	X						X						X					
MRU [n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CNS prophylaxis [o]		X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]						
AE monitoring	Recorded at every visit from the signing of ICF through 30 days after last dose of study drug (See Section 10.0)																		
Concomitant medications [p]		Recorded at every visit from Cycle 1 Day 1 through 30 days after last dose of study drug																	
Alternative chemo and/or HSCT [q]		Documented Per Occurrence																	
Clinical Laboratory Sampling																			
Hep B serology [r]	X	Additional Assessments as Clinically Indicated																	
CNS prophylaxis [o]		X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]						
Plasma samples for PK (Cohort A)		X [s]	X [t]	X [s]	X [t]	X [s]		X [s]				X [s]						X [s]	
CBC with diff [u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes are on last table page.

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Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases (continued)

Study Procedures	**Screening / Baseline**	**Induction Phase**						**Consolidation Phase**											
28-Day Cycles		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7**		**Cycle 8**		**Cycle 9**	
Cycle Days	**-28 to -1**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**
Window (days) [a]	**N/A**	**±2**																	
Chemistry [v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose, cholesterol, lipids, and HbA1c [w]	X	X						X						X					
CRP and cTnI [x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bone marrow aspirate [y,z,aa]	X [y]	X [y]		X		X [aa]		X				X				X			
Peripheral blood sample [bb]	X [bb]	X [bb]		X		X		X				X				X			
Extramedullary assessments [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	Additional Assessments as Clinically Indicated					

Abbreviations: β-HCG, beta-human chorionic gonadotropin; ABI, ankle-brachial index; AE, adverse event; ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCR-ABL, breakpoint cluster region-Abelson; BP, blood pressure; BM, bone marrow; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CBC with Diff, complete blood count with differential; CNS, central nervous system; CR, complete remission; CRP, C-reactive protein; cTnI, cardiac troponin-I; CSF, cerebrospinal fluid; CV, cardiovascular; CVA, cerebrovascular accident; DVT, deep venous thrombosis; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; ECG, electrocardiogram; ECHO, echocardiogram; EOT, end of treatment; EQ-5D-5L, EuroQOL-5 dimension-5 level (patient-reported outcome tool); FACT-Leu, Functional Assessment of Cancer Therapy – Leukemia; F/U, follow-up; HbA1c, glycosylated hemoglobin; Hep, hepatitis; HSCT, hematopoietic stem cell transplant; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; IRT, interactive response technology; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; Med/Surg, medical and surgical; MI, myocardial infarction; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MRD, minimum residual disease; MRU, medical resource utilization; N/A, not applicable; PK, pharmacokinetic; PROs, patient-reported outcomes; QTcF, QT interval corrected per Fridericia method; TIA, transient ischemic attack; TKI, tyrosine kinase inhibitor; Tx, therapy; WBC, white blood cell.

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[a] Visit windows: Tests and procedures should be performed on schedule, but occasional changes are allowable within a window (±2 days) for holidays, vacations, and other administrative reasons. See Table 2 for acceptable visit window at the 30-day follow-up visit and for survival follow-up.
[b] Enrollment: Screening and randomization procedures should be performed within the 28-day screening period. Central laboratory results will be used for determination of eligibility criteria. Local laboratory results may be used for the BCR-ABL testing (see inclusion criterion 3); however, samples must still be sent to the central laboratory in parallel. The ICF may be signed more than 28 days before Cycle 1 Day 1. Confirmation of patient eligibility by the sponsor's medical monitor or designee is required before randomization and first dose administration. Cycle 1 Day 1 should be no later than 7 days after the date of enrollment call in IRT. Specific instructions for randomization will be supplied in the study manual.
[c] Medical and surgical history and demographic information will include all diagnoses, therapies, and medical and surgical treatments.
Special attention should be paid to documenting risk factors for cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolic disease, including but not limited to any history of ischemic heart disease (eg, angina, MI, acute coronary syndrome); valvular heart disease; congestive heart failure; arrhythmias; myocarditis; peripheral arterial occlusive disease (eg, claudication, distal extremity amputation, angioplasty); or stroke (eg, TIAs, cerebral atherosclerosis). Any type of revascularization procedures (eg, stent, arterial bypass grafts) must also be recorded.
In addition, diabetes mellitus; hypertension; hypercholesterolemia; hyperlipidemia; DVT; pulmonary embolism; any other coagulopathy (for example, protein S or protein C deficiency or anticardiolipin antibody); physical activity status; obesity; and history of and current smoking status.
Family medical history will be collected, and should include any history of CAD, early death from MI or CVA, sudden death, or bleeding or clotting diatheses in first-degree relatives.
Demographic information will include the patient's date of birth (outside European Economic Area) or age (European Economic Area), sex, race, and ethnicity (optional depending on country), to be recorded during screening (as allowed by local law and regulations).
[d] Pregnancy test must be a serum β-HCG test, performed for patients of childbearing potential during screening and again at Cycle 1 Day 1 before the first dose of study drug, if the screening test was performed >4 days before the visit. The results must be negative within 4 days before the first dose of study drug is administered (ie, within the 4 days before Cycle 1 Day 1), or as otherwise required by local regulations. Women who are not of childbearing potential (status posthysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.
[e] Prior medication data collection should include those listed in the exclusion criteria to determine the patient's eligibility for the study, as well as all other medications/therapies received within 30 days before the first dose of study drug. Prior medications that are ongoing as of the first dose of study drug will then be recorded as concomitant medications.
[f] Vital signs will be performed at every visit before dosing and will include systolic and diastolic BP, heart rate, respiratory rate, and oral temperature. On Cycle 1 Day 1 only, vital signs should be performed before dosing, as well as at 1, 3, and 8 hours (±15 minutes) postdose. BP measurements should be assessed in a seated position after the patient has been sitting quietly for 5 minutes, performed 3 times with 2-minute intervals between BP assessments. BP can be measured manually or with an automated device, but must be done using a consistent method for all patients at a given site.
[g] Physical examinations will include a complete physical (including weight) performed at screening and at every visit before dosing during the induction and consolidation phases. The examination at Cycle 1 Day 1 should be performed before the first administration of study drug, but is not required if the screening physical examination was conducted and medical history obtained within 2 days before administration of the first dose of study drug. Sites should calculate BMI from the weight and height measured at baseline, and the additional weight assessments will be documented in the eCRF without the need to calculate the BMI. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. All physical examinations should address the presence or absence of hepatomegaly and splenomegaly, and all findings should be recorded in the eCRF. ECOG performance status should be evaluated during

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each physical examination. Height measurement is required at screening only.
[h] ABI will be performed at screening and as clinically indicated to assess patients for the risk of peripheral arterial disease (see also Table 2). In a supine position, the patient's BP will be assessed in both arms and again in both ankles. A hand-held Doppler ultrasound may be used to confirm the diastolic pressure in the ankles. Instructions for scoring the ABI will be provided in the study manual.
[i] Framingham Score will be done at screening to assess patients who may be at risk for cardiovascular events (see also Table 2).
[j] ECGs must all be 12-lead ECGs, performed at screening and before dosing on Day 1 after every 3 cycles (ie, Cycles 4 and 7) (see also Table 2 for assessments continuing with the maintenance phase). ECGs may be performed at other times as clinically indicated. All ECGs are to be interpreted and signed by a local cardiologist. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated. If the timing of a PK blood sample or other blood draw coincides with the timing of an ECG measurement, the ECG measurement should be taken first, followed by the blood draw.
[k] ECHO for assessment of LVEF must be performed at screening; additional ECHOs need only be performed if clinically indicated.
[l] Eye examinations must be performed at screening (including a detailed history) and as clinically indicated. The eye examinations should test visual acuity, refraction, pupillary function, ocular motility, and intraocular pressure. Perform a retinal examination, particularly noting the appearance of the retinal vasculature. Describe any signs of serious vascular occlusion (both venous and arterial) in the retina. Also, clinically evaluate for photophobia, conjunctival disease, uveitis, and cataracts.
[m] PROs include both the EQ-5D-5L instrument from the EuroQOL group and the FACT-Leu instrument, used to collect patient-assessed quality-of-life and health outcomes measures, respectively. The instruments will be implemented at screening; at Cycle 1 Day 1, and at Day 1 of Cycles 4 and 7 (see Table 2 for assessments continuing with the maintenance phase). All instruments will be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures. Patients are required to complete the instruments if there is a validated translation available in a language in which they are fluent.
[n] MRU: All medical care encounters will be collected each time an AE or unscheduled physician visit occurs. Examples of data to be collected are the number of medical care encounters, such as hospital admissions or major diagnostic procedures.
[o] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase Cycles 1, 2, and 3 and the first 3 consolidation phase Cycles 4, 5, and 6 (total: 6 cycles, 12 intrathecal injections). CNS prophylaxis will comprise a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center.
[p] Concomitant medications include all medications/therapies that are ongoing as of or started on Cycle 1 Day 1.
[q] Alternative chemotherapy and/or proceeding to HSCT will be documented if applicable. Patients who proceed to alternative chemotherapy and/or HSCT will be discontinued from study drug but will continue in the study to be followed additionally every 3 months for survival follow-up and for transplant-related parameters. The date that the patient starts alternative chemotherapy and/or HSCT should be noted.
[r] Hepatitis B serology will be performed during screening and as clinically indicated for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum. Note: Patients who are chronic carriers of hepatitis B virus and receive a BCR-ABL1 TKI therapy may have a reactivation of hepatitis B. For patients with evidence of prior or current hepatitis B infection, please refer to the investigator's brochure.
[s] Pre- and postdose ponatinib plasma sample for PK: Patients should be instructed to not take their dose of ponatinib on the days of predose PK sampling, ie, at Day 1 of Cycles 1, 2, 3, 4, 6, 9, and 12 (see also Table 2). Patients will be administered ponatinib at the site on those days no later than 1 hour after the predose sample is obtained. Additional plasma samples for PK will be obtained postdose during Cycle 2 Day 1 only, at 1 hour (±15 minutes), and at 4 and 6 hours (±30 minutes) postdose. Note: An unscheduled trough (predose) sample will be collected at the first scheduled visit following a dose reduction of at least 7 days duration before the

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visit. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples, should be recorded in the eCRF.

[t] Postdose ponatinib plasma sample for PK: Ponatinib should be taken early in the morning at home on the days of postdose PK sampling, ie, on Day 14 of Cycle 1 and Cycle 2, and sites should obtain the first postdose PK sample before initiating the vincristine infusion. An additional PK sample will be obtained on these days (Day 14 of Cycles 1 and 2) after the vincristine infusion is completed and immediately before leaving the clinic. Note: A distribution of visit times during the day is recommended for these visits in order to provide a range of PK blood sampling times relative to the timing of early morning at-home dosing of ponatinib. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples, should be recorded in the eCRF.

[u] CBC with differential testing will be performed at screening and at every visit throughout the induction and consolidation phase, and additionally as clinically indicated. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Laboratory testing to confirm dosing decisions may be based on local laboratory results; however, samples should still be sent to the central laboratory in parallel. CBC with differential is defined as peripheral blood total WBC count, hemoglobin, hematocrit, platelet count, ANC, and WBC differential, reported individually for each cell type. Cell types required for diagnosis and response assessment (including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present) must be quantified.

[v] Serum chemistry testing will be performed at screening and at every visit throughout the induction and consolidation phase, and additionally as clinically indicated. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Laboratory testing to confirm dosing decisions may be based on local laboratory results; however, samples should still be sent to the central laboratory in parallel. Serum chemistry testing consists of a peripheral blood draw with the following assessments: sodium, potassium, chloride, bicarbonate (or CO_2), BUN (urea), albumin, creatinine, total bilirubin (direct and indirect), AST, ALT, ALP, LDH, magnesium, phosphorous, calcium, amylase, and lipase.

[w] Fasting glucose, cholesterol, lipids, and HbA1c must be performed at screening, at Cycle 1 Day 1, and on Day 1 of every third cycle thereafter (ie, Cycle 4, Cycle 7, Cycle 10, etc), or more frequently as clinically indicated. Tests performed within 3 days before Cycle 1 Day 1 need not be repeated at that visit.

[x] CRP and cTnI assessments must be included with every blood draw to assess CV risks, or more frequently as clinically indicated.

[y] BM aspirate must occur within 28 days before randomization. BM aspirates will be obtained at screening and within ±7 days before Day 1 of Cycles 1, 2, 3, 4, 6, and 8 (see Table 2 for assessment schedule during the remainder of the study). Cycle 1 Day 1 assessments need not be repeated if the screening assessment was within 7 days before Cycle 1 Day 1. BM aspirates may be performed at other times when clinically indicated. Results of any BM aspirate, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

[z] Confirmation of loss of MRD negativity: For assessments beyond Cycle 4, in the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[aa] BM aspirate on Cycle 3 Day 1: This sample is only required in patients who have not achieved CR at Cycle 2 Day 1.

[bb] Peripheral blood sample collection for assessment of molecular response and exploratory biomarkers must occur at screening and within ±7 days before Day 1 of Cycles 1, 2, 3, 4, 6, and 8 (see Table 2 for assessment schedule during the remainder of the study). Quantitative assessment of BCR-ABL1 levels will be performed by a central molecular diagnostics laboratory and the results will be reported to the participating investigator. A portion of the sample collected for molecular response assessment may also be used for exploratory biomarker assessment; which will include analysis of molecular determinants of response or resistance to ponatinib or imatinib, including BCR-ABL1 mutation analysis. Specific instructions for collection of peripheral blood for molecular response and exploratory assessments will be provided in the laboratory manual. For assessments beyond Cycle 4, in the event that a patient had achieved MRD negativity at the previous

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assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[cc] Extramedullary assessments will include lumbar punctures to test CSF for CNS disease at screening, on Day 1 and Day 14 of Cycles 1, 2, 3, 4, 5, and 6, and as clinically indicated thereafter. Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should be performed as clinically indicated throughout the study. When imaging studies have been used to assess extramedullary involvement, the same imaging methods should be used consistently throughout the study for individual patients.

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Table 2 Schedule of Events: Maintenance Phase, Single-Agent Therapy, End-of-Treatment, and Follow-up

Study Procedures	**Maintenance Phase**												**Single Agent Tx [a]**	**EOT 30 Days After Last Dose or D/C [b]**	**Follow-up Q3 mo after D/C [c,d,e]**
28-Day Cycles	**Cycle 10**		**Cycle 11**	**Cycle 12**	**Cycle 13**	**Cycle 14**	**Cycle 15**	**Cycle 16**	**Cycle 17**	**Cycle 18**	**Cycle 19**	**Cycle 20**			
Days	**1**	**7**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1, Q3 mo**		
Window [f]	**±2**														**±14**
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X	X	X [g]	X	
Physical exams [h]	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X	
ECOG [h]	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X	
12-lead ECGs [i]	X				X			X			X		X [i]	X	
PROs [j]	X				X			X			X		X [j]	X	X [j]
MRU [k]	X		X	X	X	X	X	X	X	X	X	X	X [k]	X	
Diary review [l]	X		X	X	X	X	X	X	X	X	X	X	X [l]	X	
AEs	Recorded at every visit through the 30-day EOT visit or longer														
Concomitant medications [m]	Recorded at every visit through the 30-day EOT visit or longer														
Pregnancy test [n]	Additional testing as Clinically Indicated													X	
ABI [o]	Additional Assessments as Clinically Indicated													X	
Framingham score [p]														X	
ECHOs [q]	Additional Assessments as Clinically Indicated													X	
Eye exams [r]	Additional Assessments as Clinically Indicated													X	

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Table 2 Schedule of Events: Maintenance Phase, Single-Agent Therapy, End-of-Treatment, and Follow-up (continued)

Study Procedures	**Maintenance Phase'**												**Single Agent Tx [a]**	**EOT 30 Days After Last Dose or D/C [b]**	**Follow-up q3 mo after D/C [c,d,e]**
28-Day Cycles	**Cycle 10**		**Cycle 11**	**Cycle 12**	**Cycle 13**	**Cycle 14**	**Cycle 15**	**Cycle 16**	**Cycle 17**	**Cycle 18**	**Cycle 19**	**Cycle 20**			
Days	**1**	**7**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1, Q3 mo**		
Window [d]	**±2**														**±14**
Clinical Laboratory Sampling															
Plasma samples for PK [s]				X											
CBC with diff [t]	X	X	X	X	X	X	X	X	X	X	X	X	X [t]	X	
Chemistry [u]	X	X	X	X	X	X	X	X	X	X	X	X	X [u]	X	
Fasting glucose, cholesterol, lipids, and HbA1c [v]	X				X			X			X		X [v]	X	
CRP and cTnI [w]	X		X	X	X	X	X	X	X	X	X	X	X [w]	X	
Bone marrow aspirate [x,y]	X				X			X			X		X [x,y]	X	
Peripheral blood sample [z]	X				X			X			X		X [z]	X	
Hep B serology [aa]	Additional assessments as Clinically Indicated														
Extramedullary assessments [bb]	Additional Assessments as Clinically Indicated													X [bb]	

Footnotes on the next page.

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Abbreviations: β-HCG, beta-human chorionic gonadotropin; ABI, ankle-brachial index; AE, adverse event; ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AOE, arterial occlusive event; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CBC with Diff, complete blood count with differential; chemo, chemotherapy; CNS, central nervous system; CR, complete remission; CRP, C-reactive protein; CSF, cerebrospinal fluid; cTnI, cardiac troponin-I; CV, cardiovascular; D/C, discontinuation; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; eCRF, electronic case report form; EOT, end of treatment; EQ-5D-5L, EuroQOL-5 dimension-5 level (patient-reported outcome tool); FACT-Leu, Functional Assessment of Cancer Therapy – Leukemia; F/U, follow-up; HbA1c, glycosylated hemoglobin; Hep, hepatitis; HSCT, hematopoietic stem cell transplant; IEC, independent ethics committee; IRB, institutional review board; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; Med/Surg, medical and surgical; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MRD, minimum residual disease; MRU, medical resource utilization; PD, progressive disease; PROs, patient-reported outcomes (EQ-5D-5L and FACT-Leu); Q3 mo, every 3 months; QTcF, QT interval corrected per Fridericia method; SAE, serious adverse event; TKI, tyrosine kinase inhibitor; Tx, therapy; VTE, venous thrombotic/embolic event; ; WBC, white blood cell.

[a] Single-Agent Therapy: After the end of Cycle 20, patients will receive single-agent TKIs (ponatinib or imatinib) continuously until they have experienced PD, have an unacceptable toxicity, withdraw consent, proceed to HSCT, have completed the study, or until the sponsor terminates the study, whichever occurs first.
Note: Efficacy and safety data (as indicated on the table) will be collected Q3 months after the end of Cycle 20 (ie, at the end of Cycle 23, 26, 29, etc).

[b] EOT visit should occur within 30 days of the last dose or the decision to discontinue treatment, whichever occurs first.

[c] Survival follow-up: Patients who have been discontinued from study drug will be contacted every 3 months (±14 days) until the patient's death has been reported. Delayed treatment-related SAEs, AOEs, and VTEs will be followed until resolution or the start of subsequent alternative anticancer therapy. The EOS eCRF page is to be completed at the time the patient discontinues from the survival follow-up period.

[d] Alternative chemotherapy: The start of alternative chemotherapy will be documented.

[e] Transplant follow-up: Patients who proceed to HSCT will be discontinued from study drug but will continue in the study for collection of transplant-related parameters, including response assessments for CR.

[f] Visit windows: Tests and procedures should be performed on schedule, but occasional changes are allowable within a window (±2 days) for holidays, vacations, and other administrative reasons.

[g] Vital signs will be performed at every visit before dosing, including during the single-agent therapy phase and EOT, and will include systolic and diastolic BP, heart rate, respiratory rate, and oral temperature. BP measurements should be assessed after the patient has been sitting quietly for 5 minutes, performed 3 times with 2-minute intervals between BP assessments. BP can be measured manually or with an automated device, but must be done using a consistent method for all patients at a given site.

[h] Physical examinations will include a complete physical (including weight) performed before dosing on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle in the single-agent therapy phase, and at the EOT Visit. The weight assessments will be documented in the electronic case report form without the need to calculate the BMI. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. All physical examinations should address the presence or absence of hepatomegaly and splenomegaly, and all findings should be recorded in the eCRF. ECOG performance status should be evaluated during each physical examination. Height measurement is not required.

[i] ECGs must all be 12-lead ECGs, performed before dosing on Day 1 of every third cycle after Cycle 7 (ie, Cycles 10, 13, 16, 19, 22, 25, etc), and at the EOT visit; ECGs may be performed at other times as clinically indicated. All ECGs are to be interpreted and signed by a local cardiologist. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

[j] PROs include both the EQ-5D-5L instrument from the EuroQOL group and the FACT-Leu instrument, used to collect patient-assessed quality-of-life and health

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outcomes measures, respectively. The instruments will be implemented at Day 1 every third cycle after Cycle 7 (ie, Cycles 10, 13, 16, 19, 22, 25, etc). All instruments will be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures. Patients are required to complete the instruments if there is a validated translation available in a language in which they are fluent. At the survival follow-up assessments, only the EQ-5D-5L should be administered, via telephone contact.

[k] MRU: All medical care encounters will be collected each time an AE or unscheduled physician visit occurs. Examples of data to be collected are the number of medical care encounters, such as hospital admissions or major diagnostic procedures.

[l] Diary review will continue at every visit, including during the single-agent therapy phase and at the EOT visit.

[m] Concomitant medications include all medications/therapies that are ongoing as of or started on Cycle 10 Day 1.

[n] Pregnancy test must be a serum β-HCG test. If the pregnancy test was deemed necessary at screening, it must be performed again at the EOT visit. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

[o] ABI will be repeated at the EOT visit and as clinically indicated to assess patients for the risk of peripheral arterial disease. In a supine position, the patient's BP will be assessed in both arms and again in both ankles. A hand-held Doppler ultrasound may be used to confirm the diastolic pressure in the ankles. Instructions for scoring the ABI will be provided in the study manual.

[p] Framingham Score will be done at the EOT visit to assess patients who may be at risk for cardiovascular events.

[q] ECHO for assessment of LVEF should be performed at the EOT and need only be repeated if clinically indicated.

[r] Eye examinations should be repeated at the EOT visit and as clinically indicated. The eye examinations should test visual acuity, refraction, pupillary function, ocular motility, and intraocular pressure. Perform a retinal examination, particularly noting the appearance of the retinal vasculature. Describe any signs of serious vascular occlusion (both venous and arterial) in the retina. Also, clinically evaluate for photophobia, conjunctival disease, uveitis, and cataracts.

[s] Predose plasma sample for PK: Patients should be instructed to <u>not</u> take their dose of ponatinib on Cycle 12 Day 1. Patients will be administered ponatinib at the site that day within 1 hour after the predose sample is obtained. Note: An unscheduled trough (predose) sample will be collected at the first scheduled visit following a dose reduction of at least 7 days duration before the visit. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples should be recorded in the eCRF.

[t] CBC with differential assessments will continue on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle during single-agent therapy, and at the EOT visit. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Laboratory testing to confirm dosing decisions may be based on local laboratory results; however, samples should also be sent to the central laboratory in parallel. CBC with differential is defined as peripheral blood total WBC count, hemoglobin, hematocrit, platelet count, ANC, and WBC differential, reported individually for each cell type. Cell types required for diagnosis and response assessment (including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present) must be quantified.

[u] Serum chemistry assessments will continue on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle during single-agent therapy, and at the EOT visit. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Laboratory testing to confirm dosing decisions may be based on local laboratory results; however, samples should also be sent to the central laboratory in parallel. Serum chemistry consists of a peripheral blood draw with the following assessments: sodium, potassium, chloride, bicarbonate (or total CO_2), BUN (or urea), albumin, creatinine, total bilirubin (direct and indirect), AST, ALT, ALP, LDH, magnesium, phosphorous, calcium, amylase, and lipase.

[v] Fasting glucose, cholesterol, lipids, and HbA1c should be included on Day 1 of every third cycle starting with Cycle 10 (eg, Cycle 10, Cycle 13, Cycle 16), including during single-agent therapy and at the EOT visit, or more frequently as clinically indicated.

[w] CRP and cTnI assessments must be included with every blood draw (except Cycle 10, Day 7) to assess CV risks or more frequently as clinically indicated.

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[x] BM aspirate must occur within ±7 days of the scheduled assessments. BM aspirates will continue on Day 1 of every third cycle starting with Cycle 10 (eg, Cycles 13, 16, 19). During the single-agent therapy phase, sampling will start on Day 1 of Cycle 21 (eg, Cycles 21, 24, 27) to be consistent with the visit schedule. BM aspirates may be performed at other times when clinically indicated. Results of any BM aspirate, whether scheduled or unscheduled, must be recorded in the patient's electronic case report form.

[y] Confirmation of loss of MRD negativity: In the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[z] Peripheral blood samples for molecular response assessment must occur within 7 days of the scheduled assessments. Samples will be obtained on Day 1 of every third cycle starting with Cycle 10 (eg, Cycles 10, 13, 16, 19). During the single-agent therapy phase, sampling will start on Day 1 of Cycle 21 (eg, Cycles 21, 24, 27) to be consistent with the visit schedule. Quantitative assessment of BCR-ABL1 levels will be performed by a central molecular diagnostics laboratory and the results will be reported to the participating investigator. A portion of the sample collected for molecular response assessment may also be used for exploratory biomarker assessment; which will include analysis of molecular determinants of response or resistance to ponatinib or imatinib, including BCR-ABL1 mutation analysis. Specific instructions for collection of peripheral blood for molecular response and exploratory assessments will be provided in the laboratory manual. In the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood.

[aa] Hepatitis B serology will be performed as clinically indicated for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum. Note: Patients who are chronic carriers of hepatitis B virus and receive a BCR-ABL1 TKI therapy may have a reactivation of hepatitis B. For patients with evidence of prior or current hepatitis B infection, refer to the investigator's brochure.

[bb] Extramedullary assessments will include lumbar punctures to test CSF for CNS disease at the EOT visit and as clinically indicated during the maintenance phase and the single-agent therapy phase. Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should be performed as clinically indicated throughout the study. When imaging studies have been used to assess extramedullary involvement, the same imaging methods should be used consistently throughout the study for individual patients.

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Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study-related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56 ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

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11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

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Appendix D Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.

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Appendix E Drugs With a Risk of TdP

Four categories of QT-prolonging drugs that may be used as a guide for this protocol can be accessed at crediblemeds.org/everyone/composite-list-all-qtdrugs/: drugs with known risk of TdP, drugs with possible risk of TdP, drugs with conditional risk of TdP (ie, can cause TdP under certain conditions), and drugs to be avoided by congenital long QT patients (accessed 18 December 2017). The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

Drugs that are often used to treat patients with cancer and are currently listed as having a known risk, a possible risk, and a conditional risk of TdP are listed in Appendix D; drugs with a known risk are presented in bold font and are the only category of QT-prolonging drugs that are prohibited in this study.

Note: The website and table are only to be used as a guideline and are not comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as causing TdP.

Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class
Arsenic trioxide [a]	**Trisenox**	**Anticancer**
Amitriptyline [b]	Triavil, Duo-Vil, Etrafon, Etrafon Forte	Antidepressant
Aripiprazole [c]	Abilify, Abilify Maintena, Aristada, Abilify Discmelt	Antidepressant
Bortezomib [c]	Velcade	Anticancer
Bosutinib [c]	Bosulif	Anticancer
Capecitabine [c]	Xeloda	Anticancer
Ceritinib [c]	Zykadia	Anticancer
Chlorpromazine [a]	**Thorazine, Ormazine, Largactil, Megaphen**	**Antipsychotic/ Antiemetic**
Citalopram [a]	**Celexa**	**Antidepressant**
Clomipramine [c]	Anafranil	Antidepressant
Cocaine [a]	**Cocaine**	**Local anesthetic**
Crizotinib [c]	Xalkori	Anticancer
Dabrafenib [c]	Tafinlar	Anticancer
Dasatinib [c]	Sprycel	Anticancer
Degarelix [c]	Firmagon	Anticancer
Desipramine [c]	Norpramin	Antidepressant
Dolasetron [c]	Anzemet	Antinausea
Domperidone [a]	**See: *drugs.com/international/domperidone.html* for complete list**	**Antinausea**

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Generic Name	Brand Name	Class
Doxepin [b]	Silenor, Sinequa, Adapin	Antidepressant
Droperidol [a]	**Droleptan, Dridol, Inapsine, Innovar, Xomolix**	**Antinausea/ Anesthetic**
Epirubicin [c]	Ellence, Pharmorubicin PFS, Pharmorubicin RDF	Anticancer
Eribulin mesylate [c]	Halaven	Anticancer
Escitalopram [a]	**Animaxen, Anxiset-E, Cipralex, Elicea, Entact, Esitalo, Esto, Exodus, Lexam, Lexamil, Lexapro, Losita, Nexito, Reposil, Seroplex**	**Antidepressant**
Fluorouracil (5-FU) [c]	Adrucil	Anticancer
Fluoxetine [b]	Prozac, Prozac Weekly, Rapiflux, Sarafem	Antidepressant
Fluvoxamine [b]	Luvox, Luvox CR	Antidepressant
Granisetron [b]	Granisol, Kytril, Sancuso, Sustol	Antinausea
Imipramine (melipramine) [c]	Tofranil, Tofranil-PM	Antidepressant
Lapatinib [c]	Tykerb	Anticancer
Lenvatinib [c]	Lenvima	Anticancer
Leuprolide [c]	Eligard, Lupron, Lupron Depot, Viadur	Anticancer
Metoclopramide [b]	Maxolon, Metozolv ODT, Reglan	Antinausea
Mirtazapine [c]	Remeron, Remeron SolTab	Antidepressant
Necitumumab [c]	Portrazza	Anticancer
Nilotinib [c]	Tasigna	Anticancer
Nortriptyline [c]	Aventyl Hydrochloride, Pamelor	Antidepressant
Ondansetron [a]	**Anset, Emeset, Emetron, Ondavell, Ondemet, Ondisolv, Setronax, Zofran, Zuplenz**	**Antinausea**
Osimertinib [c]	Tagrisso	Anticancer
Oxaliplatin [a]	**Eloxatin**	**Anticancer**
Palonosetron [c]	Aloxi	Antinausea
Paroxetine [b]	Brisdelle, Paxil, Paxil CR, Pexeva	Antidepressant
Pazopanib [c]	Votrient	Anticancer
Promethazine [c]	Anergan 50, Phenadoz, Phenergan, Promethegan	Antinausea
Propofol [a]	**Diprivan, Propoven**	**Anesthetic**
Ribociclib [b]	Kisqali	Anticancer
Sertraline [b]	Zoloft	Antidepressant
Sevoflurane [a]	**Ulane, Sojourn**	**Anesthetic**
Sorafenib [c]	Nexavar	Anticancer
Sunitinib [c]	Sutent	Anticancer

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Generic Name	Brand Name	Class
Tamoxifen [c]	Nolvadex, Tamofen, Tamoxen, Tamoxifen Hexal	Anticancer
Tipiracil and Trifluridine [c]	Lonsurf	Anticancer
Toremifene [c]	Fareston	Anticancer
Trazodone [b]	Desyrel, Desyrel Dividose, Oleptro	Antidepressant
Trimipramine [c]	Surmontil	Antidepressant
Tropisetron [c]	Di Ou Ping, Gai Ge En, Guang Di, He Tai, Hensetron, Luo Ting, Navoban, NiTaiMei, Pu Luo Lin, Qi Qiong, Que Zhi Du, Rui Qi Tai, Sai Ge En, Setrovel, Shu Ji, Shu Ou Ting, Tropisetron-AFT, Tuo Li Shi Ning, Wei Rui Te, Xin Bei, Sin Shun Er, Yandi	Antinausea
Vandetanib [a]	**Caprelsa**	**Anticancer**
Vemurafenib [c]	Zelboraf	Anticancer
Venlafaxine [c]	Effexor, Effexor XR	Antidepressant
Vorinostat [c]	Zolinza	Anticancer

Source: crediblemeds.org/oncosupport/; drugs.com. Accessed 18 December 2017.
Abbreviation: TdP, torsades de pointes.
[a] Known risk of TdP: Substantial evidence supports the conclusion that these drugs prolong the QT interval *and* are clearly associated with a risk of TdP, even when taken as directed in official labeling.
[b] Conditional risk of TdP: Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP *but* only under certain conditions (eg, excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation).
[c] Possible risk of TdP: Substantial evidence supports the conclusion that these drugs can cause QT prolongation *but* there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

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Appendix F Drugs That Inhibit or Induce CYP3A

The list of drugs that inhibit or induce CYP3A can be found online at fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-2 [Accessed 07 February 2018]. Drugs listed as strong inhibitors and inducers of CYP3A should be avoided, if possible. See Section 8.5, for dose reduction recommendations in the event that medications that are strong CYP3A inhibitors are required and a suitable alternative cannot be identified.

Note: The website should be used as a guideline and is not necessarily comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as strong CYP3A4/5 inhibitors or inducers.

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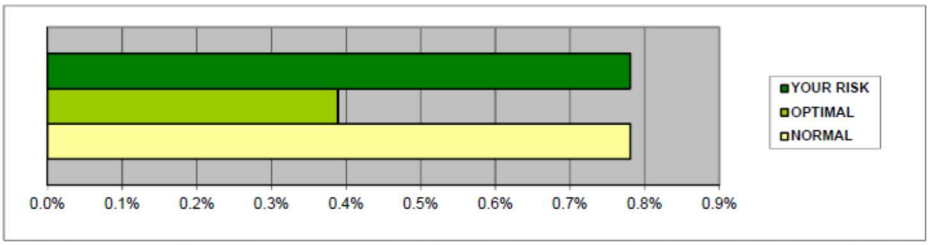
Appendix G Copy of Framingham Score

The following is a sample screenshot of the Framingham score; the Framingham score tool will be supplied in the study manual.

From The Framingham Heart Study		Enter Values Here	
General CVD Risk Prediction			
Risk Factor	**Units**	**(Type Over Placeholder Values in Each Cell)**	**Notes**
Sex	male (m) or female (f)	f	
Age	years	24	Enter a Value Between 30-74
Systolic Blood Pressure	mmHg	125.0	
Treatment for Hypertension	yes (y) or no (n)	n	
Smoking	yes (y) or no (n)	n	
Diabetes	yes (y) or no (n)	n	
HDL	mg/dL	45	
Total Cholesterol	mg/dL	180	
Your 10-Year Risk (The risk score shown is derived on the basis of an equation. Other print products, use a point-based system to calculate a risk score that approximates the equation-based one.)		0.8%	*If value is < the minimum for the field, enter the minimum value. If value is > the maximum for the field, enter the maximum value.*
Your Heart/Vascular Age		24	



Calculator prepared by R.B. D'Agostino and M.J. Pencina based on a publication by D'Agostino et al. in Circulation

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Appendix H EQ-5D-5L

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

SAMPLE

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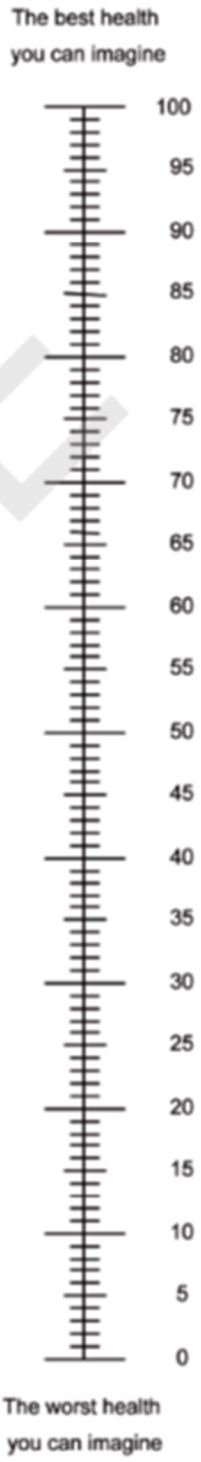
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SAMPLE

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Appendix I FACT-Leu

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

English (Universal)
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Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate

Loading dose:	
Leucovorin 50 mg IV or PO (× 1 dose)	Starting 12 (±2) h after completion of methotrexate infusion
Additional:	
Leucovorin 15 mg IV or PO q6 h (× 8 doses) until serum methotrexate level is <0.1 μM/L	Starting 6 h after completion of loading dose
Note:	
Increase leucovorin rescue to 50 mg IV or PO q6 h until serum methotrexate level is <0.1 μM/L	If methotrexate level is >20 μM/L at time "0" (first assessment) OR If methotrexate is >1 μM/L at 24 h OR If methotrexate is >0.1 μM/L at 48 h

Abbreviations: IV, intravenous; PO, by mouth; q, every.
Alterations per local guidelines are acceptable.

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Appendix K Cytarabine Dose Adjustments for Creatinine Clearance Levels

Serum Creatinine Clearance (CrCl) Level	Cytarabine Dose Adjustment
90-60 mL/min	1000 mg/m^2 q12 h on Days 1, 3, and 5
60-30 mL/min	500 mg/m^2 q12 h on Days 1, 3, and 5
30-15 mL/min	500 mg/m^2 q24 h on Days 1, 3, and 5 OR Option to stop
<15 mL/min or hemodialysis	Stop cytarabine.

Abbreviations: CrCl, creatinine clearance; q, every.

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A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib versus Imatinib, Administered in Combination with Reduced-intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia (Ph+ ALL)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	12-Mar-2018 23:57 UTC
	Biostatistics Approval	13-Mar-2018 00:47 UTC
	Clinical Approval	13-Mar-2018 15:20 UTC

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PROTOCOL

A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced-Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Sponsor: Takeda Development Center Americas, Inc.
95 Hayden Avenue
Lexington, MA 02421
USA

617-349-0200

Study Number: Ponatinib-3001

EudraCT Number: 2018-000397-30

Compound: Ponatinib

Date: 20 October 2021 **Amendment Number:** 10

Amendment History:

Date	Amendment Number	Amendment Type	Region
20 October 2021	10	Substantial	Global
07 May 2021	9	Substantial	Global
10 February 2021	8	Substantial	Global
13 August 2019	7	Substantial	Japan
29 July 2019	6	Substantial	Argentina
23 July 2019	5	Substantial	South Korea
09 May 2019	4	Substantial	Global
06 December 2018	3	Substantial	South Korea
08 November 2018	2	Substantial	Global
22 May 2018	1	Nonsubstantial	Global
12 March 2018	Initial Protocol	Not applicable	Global

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site. See the site operations manual for more information.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints. The names and contact information for the sponsor's medical monitor/designee and responsible medical officer are in the site operations manual.

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1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer and other signatures can be found on the signature page.

PPD

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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator's brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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1.3 Protocol Amendment 10 Summary of Changes and Rationale

This section describes the changes to the protocol incorporating Amendment 10. The primary reason for this amendment is to:

- Update the efficacy analysis to reflect a change in the sample size for the final analysis from 150 patients to 230 patients.

In addition, the protocol was updated to:

- Clarify that patients who achieve minimal residual disease (MRD)-negative status with incomplete complete remission (CRi) at the end of induction may remain on study drug treatment, at the investigator's discretion.
- Clarify that for MRD-negative complete remission (CR), the analysis will be based on the intent-to-treat (ITT) population who have been identified with BCR-ABL1 dominant variants of p190 or p210.
- Provide additional guidance to sites regarding survival follow up assessments, timing for end of treatment (EOT), reporting of mutation status if available at time of relapse, and the time period for requiring bone marrow (BM) at EOT.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included in this amendment for clarification and administrative purposes only and are not listed in the summary of changes below.

Protocol Amendment 10			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 2.0 Study Summary Section 6.1 Overview of Study Design Section 6.3.1 Duration of an Individual Patient's Study Participation Section 9.4.15.1 BM Aspirate Section 9.5 Completion of Study Treatment (for Individual Patients) Section 9.10 Post-treatment Follow-Up Assessments	Clarified that patients who achieve minimal residual disease (MRD)-negative status with incomplete complete remission (CRi) at end of induction may remain on study drug treatment, at the investigator's discretion.	Provide an option for patients who may be benefiting from therapy as evidenced by the MRD-negative status to continue study treatment.

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Protocol Amendment 10			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2.	Section 2.0 Study Summary Section 6.3.1 Duration of an Individual Patient's Study Participation Section 9.10 Post-treatment Follow-Up Assessments Appendix A Schedule of Events Table 2	Clarification that alternative therapies are to be collected.	Alternative therapies to be collected if available and to report possible confounding factors of event-free survival (EFS) endpoint
3.	Section 6.3.1 Duration of an Individual Patient's Study Participation	Clarified that all patients who discontinue study treatment will be followed for survival. Patients who discontinued without relapse from CR will have investigator-reported assessment of relapse, wherever available.	Requirement for analysis of key secondary endpoint of EFS to follow time to relapse from CR and/or death.
4.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Updated exclusion criterion 16 k to state that patients with superficial vein thrombosis (SVT) may be included after discussion with the sponsor's medical monitor/designee.	SVT has a low association rate with deep venous thrombosis (DVT). Patients with a SVT reported at screening, which may or may not be catheter-related, that has resolved or is manageable may be considered after discussion and review of potential risk factors for DVT with the medical monitor.
5.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Language edited and added for exclusion criterion 22 with clarification of minimum expectation for repeat testing to specify that patients with positive serum pregnancy test who have undergone a complete abortion in the last 60 days may be included after discussion with the sponsor's medical monitor/designee and that if positive, a repeat test is to be performed 7 to 14 days later and must be significantly lower to insure there is no active pregnancy for study eligibility.	Clarify that pregnancy test requirements for patients who may have undergone a complete abortion recently but presented with a positive pregnancy test must have repeat testing and review by the medical monitor to ensure there is no active pregnancy before study entry.

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Protocol Amendment 10			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
6.	Section 8.4 Dose Modification Guidelines for Safety	Language edited to read "Variation from these guidelines should be communicated with the medical monitor/designee, ideally before implementation, and resulting agreements/investigator decisions should be recorded in source documents."	Investigators are responsible for decisions related to discontinuation or variation in treatments as determined to be in the best interest of the patient. These decisions should be reported to the medical monitoring team in a timely manner but will not be a protocol deviation based on a reporting time period.
7.	Section 8.5 Excluded Concomitant Medications and Procedures	Added an exception to permit use of ondansetron if an alternative to the antiemetic agent is not feasible and the investigator considers this the only suitable medication to manage symptoms.	Provide additional guidance to sites.
8.	Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Added the following reasons for study drug discontinuation: Failure to achieve CR, Failure to achieve MRD-negative, Progressive disease, Relapse from CR, Hematopoietic stem cell transplantation.	Align with reasons for study drug discontinuation cited in other sections of the protocol.
9.	Section 9.10 Post-treatment Follow-Up Assessments	Added clarification for sentence "Patients who discontinue study treatment without relapse from CR, will be followed for investigator-reported disease status (eg, relapse from CR) and survival, and reporting of alternative therapies, wherever available"	Alternative therapies are to be collected if available to report possible confounding factors of EFS endpoint. SOE footnote ‘q’ already states this is collected.
10.	Section 9.10 Post-treatment Follow-Up Assessments	Added sentence "Date of relapse to be reported and noted in source documentation."	The date of relapse is required for EFS endpoint assessment, and for patients who discontinued study treatment reporting of later relapse should be documented in sourced notes to verify date and method of reporting relapse (i.e. bone marrow report).
11.	Section 9.10 Post-treatment Follow-Up Assessments	Provided clarification to the sentence: "Patients who proceed to alternative therapy will also be discontinued from study treatment and will be followed for investigator-reported disease status (eg, relapse from CR) and survival."	Clarified that date of relapse from CR is to be reported for EFS endpoint analysis and source documentation should be noted (i.e. bone marrow report)

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Protocol Amendment 10			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
12.	Section 13.1.3 Efficacy Analysis Section 13.2 IA and Criteria for Early Termination	Updated the efficacy analysis to reflect a change in the sample size for the final analysis from 150 patients to 230 patients and to add statistical testing for the endpoints of duration of CR, duration of MRD-negative CR, overall response rate and overall survival.	Change sample size to increase the accuracy, stability, and power of the primary endpoint analysis and specify statistical testing for other secondary endpoints that may be used to make labeling claims.
13.	13.1.3 Efficacy Analysis	Added that "for MRD-negative CR, the analysis will be based on the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210."	Clarify study population to be used for the analysis of MRD-negative CR.
14.	Section 13.3 Determination of Sample Size Figure 13.a Statistical Analysis Schema	Updated Figure 13.a to reflect the change in the sample size for the final analysis from 150 to 230 patients and added footnotes describing the analyses that are to be conducted if the efficacy boundary is crossed.	Change sample size to increase the accuracy, stability, and power of the primary endpoint analysis and specify statistical testing for other secondary endpoints that may be used to make labeling claims.
15.	Section 13.3 Determination of Sample Size	Updated the determination of sample size to reflect the change in sample size for the final analysis from 150 to 230 patients.	Change sample size to increase the accuracy, stability, and of the primary endpoint analysis.
16.	Appendix A Schedule of Events Table 2	Updated Footnote b to specify "end-of-treatment (EOT) is within 30 days after a patient has discontinued the study drug (last dose)."	Provide additional guidance to sites.
17.	Appendix A Schedule of Events Table 2	Updated Footnote c to specify that survival follow-up assessments will include patients who have been discontinued from study drug for any reason.	Provide additional guidance to sites.
18.	Appendix A Schedule of Events Table 2	Added Footnote z to specify time period for requiring bone marrow at EOT.	Provide additional guidance to sites.
19.	Appendix E Drugs With a Risk of TdP	Updated to align with the July 2021 list of drugs with a risk of torsades de pointes.	Provide sites with a current list of drugs with a risk of torsades de pointes.
20.	Appendix M Enrollment Projections at Primary Endpoint Analyses	Updated enrollment projections at primary endpoint analyses to reflect the change in sample size for the final analysis.	Change sample size to increase the accuracy, stability, and power of the primary endpoint analysis.

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Ponatinib
Title of Protocol: A Phase 3, Randomized, Open-Label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination With Reduced-Intensity Chemotherapy, in Patients With Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)	**EudraCT No.:** 2018-000397-30
Study Number: Ponatinib-3001	**Phase:** 3

Study Design: This phase 3 study is designed as an open-label, multicenter, randomized comparison of the tyrosine kinase inhibitors (TKIs) ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced-intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously until patients have completed the study, experienced relapse from complete remission (CR) or progressive disease (PD), have an unacceptable toxicity, withdraw consent, proceed to hematopoietic stem cell transplant (HSCT) or alternative therapy, or the sponsor terminates the study.

The primary endpoint of this study is minimal residual disease (MRD)-negative CR at the end of induction (defined in Table 13.a). Patients who achieve the primary endpoint will continue in the study in the consolidation and maintenance phases followed by a single-agent therapy phase. As CR must have been maintained for at least 4 weeks, patients who do not achieve CR by the end of Cycle 2 will be considered as having failed to achieve the primary endpoint (see Table 13.a for definitions). Patients who achieve CR or who achieve MRD-negative status with incomplete complete remission (CRi) but do not achieve the primary endpoint at the end of induction may, at the investigator's discretion, continue on study treatment. All patients who do not achieve CR at the end of induction will be discontinued from study treatment, with the exception of patients who are MRD-negative and CRi at end of induction; these patients may remain on study drug treatment at the investigator's discretion. For all discontinued patients, the patient's treating physician should consider alternative therapy options.

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib once daily (QD), which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Section 8.4.1). For patients in the ponatinib cohort who achieve CR but do not achieve the primary endpoint at the end of induction and who continue in the study at the investigator's discretion, the dose of ponatinib will be reduced, as described above, at any later time point when the patient achieves MRD-negative CR and re-escalated, as described above, upon loss of response. Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for central nervous system (CNS) disease prophylaxis. At the end of the 20 cycles, all patients remaining on study will continue on ponatinib or imatinib (administered as a single agent).

MRD status will be measured using quantitative polymerase chain reaction–based tests validated for the ability to detect breakpoint cluster region-Abelson (BCR-ABL1)/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as ≤0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale with traceability to the World Health Organization (WHO) first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported. To ensure uniformity of analysis, all samples will be tested using the same methodology in central laboratories. Assessment of the primary endpoint at the end of induction will be based on analysis of bone marrow (BM) samples. To minimize

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the number and volume of BM aspirates required, and in keeping with available recommendations [1] and evidence of general concordance between results [2], assessment of BCR-ABL1/ABL1 levels at other time points may use peripheral blood samples. Both sample types will be collected at a subset of time points to allow the levels of concordance between sample types to be broadly assessed.

The key secondary endpoint for this study is event-free survival (EFS). Other secondary endpoints will include rates of CR and incomplete CR (CRi) at the end of Cycle 1, end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of molecular response 3-log reduction (MR3, BCR-ABL1/ABL1 ≤0.1%), molecular response 4-log reduction (MR4, ≤0.01% BCR-ABL1/ABL1), and molecular response 4.5-log reduction (MR4.5, BCR-ABL1/ABL1 ≤0.0032%) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of primary induction failure (PIF) and overall response rate (ORR) at the end of induction; rates of MRD-negative CR at multiple intervals after the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; duration of MR4.5 in patients who achieved MR4.5; overall survival (OS) and relapse from CR for on-study patients with and without HSCT, and OS. (See Table 13.a for endpoint definitions.)

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all adverse events (AEs), serious adverse events (SAEs), arterial occlusive events (AOEs), and venous thrombotic/embolic events (VTEs); rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

Exploratory endpoints will include change from baseline in patient-reported quality-of-life and medical resource utilization (MRU) assessments; time to start of alternative therapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

Primary Objective:

To compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction.

Key Secondary Objectives:

- To compare EFS between the 2 cohorts.

Other Secondary Objectives:

- To compare the rates of CR and CRi between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of MR3, MR4, and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of PIF and ORR between the 2 cohorts, at the end of induction.
- To compare rates of MRD-negative CR at multiple intervals after the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare OS between the 2 cohorts.
- To characterize the incidence of AEs, SAEs, AOEs, VTEs, and other safety outcomes of interest in each of the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

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- To collect plasma concentration-time data to contribute to population pharmacokinetic (PK) and exposure-response analyses of ponatinib.

Subject Population: Male and female patients with newly diagnosed Ph+ ALL, aged 18 years and older

Number of Patients:	**Number of Sites:**
Ponatinib treatment group: Approximately 153-156 Imatinib treatment group (active comparator): Approximately 74-77 Estimated total randomized: Approximately 230	Estimated total: Approximately 120 sites in up to 35 countries globally
Dose Levels: Ponatinib: 30 mg QD Imatinib: 600 mg QD	**Route of Administration:** Both ponatinib and imatinib are administered by mouth.
Duration of Treatment: All patients will remain on study drug until they are deceased, have failed to achieve the primary endpoint of MRD-negative CR at the end of induction (patients who do not achieve the primary endpoint may remain on study treatment, at the investigator's discretion, if they have achieved CR or MRD-negative status with CRi at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.	**Period of Evaluation:** Study data will be evaluated for approximately 3-6 years after enrollment of the last patient.

Main Criteria for Inclusion:

1. Male or female patients aged 18 years or older.
2. Newly diagnosed Ph+ or BCR-ABL1 positive ALL, as defined by the 2017 National Comprehensive Cancer Network guidelines.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
4. Clinical laboratory values as follows, within 30 days before randomization:
   a) Total serum bilirubin ≤1.5× the upper limit of normal (ULN), unless due to Gilbert's syndrome.
   b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5× the ULN.
   c) Serum creatinine ≤1.5× the ULN and estimated creatinine clearance ≥30 mL/minute (Cockcroft-Gault formula).
   d) Serum lipase <1.5× the ULN.
5. Normal QT interval corrected per Fredericia method (QTcF) on screening electrocardiogram, defined as QTcF of ≤450 ms in males or ≤470 ms in females.
6. Female patients who:
   a) Are postmenopausal for at least 1 year before the screening visit, *or*
   b) Are surgically sterile, *or*
   c) If they are of childbearing potential, agree to practice 1 highly effective method of contraception (such as any form of hormonal contraception, eg, birth control pills or hormonal intra-uterine device [IUD]) and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 1 month after the last dose of study drug or a longer period per any local regulation, eg, 35 days for patients in France), *or*
   d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   a) Agree to practice effective barrier contraception during the entire study treatment period and through

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120 days after the last dose of study drug, or

b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
9. Willingness and ability to comply with scheduled visits and study procedures.

Main Criteria for Exclusion:

1. Patients with a history or current diagnosis of chronic phase, accelerated phase, or blast phase chronic myeloid leukemia.
2. Prior/current treatment with any systemic anticancer therapy (including but not limited to any TKI) and/or radiotherapy for ALL, with the exception of an optional prephase therapy or chemotherapy induction (no more than one cycle), which should be discussed with the sponsor's medical monitor/designee.
3. Treatment with any investigational products within 30 days before randomization or 6 half-lives of the agent, whichever is longer.
4. Currently taking drugs that are known to have a risk of causing prolonged QTc or torsades de pointes (unless these can be changed to acceptable alternatives or discontinued) (Appendix E).
5. Taking any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 3A4 within at least 14 days before the first dose of study drug (Appendix F).
6. Uncontrolled active serious infections that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
7. Major surgery within 28 days before randomization (minor surgical procedures such as catheter placement or BM biopsy are not exclusionary criteria).
8. Known seropositive HIV, known active hepatitis B or C infection.
9. History of acute pancreatitis within 1 year of study screening or history of chronic pancreatitis.
10. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
11. Diagnosed and treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
12. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
13. Clinical manifestations of CNS or extramedullary involvement with ALL other than lymphadenopathy or hepatosplenomegaly.
14. Autoimmune disease with potential CNS involvement.
15. Known significant neuropathy of Grade ≥2 severity.
16. Clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease, including, but not restricted to:

    a) Complete left bundle branch block.
    b) Right bundle branch block plus left anterior hemiblock, or bifascicular block.
    c) History of or presence of clinically significant ventricular or atrial tachyarrhythmias.
    d) Clinically significant resting bradycardia (<50 beats per minute).
    e) Uncontrolled hypertension (HTN; systolic blood pressure [BP] ≥150 mmHg and/or diastolic BP ≥90 mmHg). Patients with Stage 2 HTN (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) should be under treatment at study entry per the current American Heart Association guidelines to ensure BP control. Patients requiring 3 or more antihypertensive medications should have controlled HTN for the past 6 months. Isolated elevation(s) of systolic and/or diastolic BP during screening are not exclusionary.
    f) Any history of myocardial infarction, unstable angina, coronary artery disease, cerebrovascular accident,

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ischemic stroke, or transient ischemic attack. Note: Patients with *any* history of these events, whether considered clinically significant or not, are excluded.

g) History of congestive heart failure (New York Heart Association class III or IV) or left ventricular ejection fraction <40%, within 6 months before randomization.
h) Symptomatic peripheral vascular disease or history of infarction, including visceral infarction.
i) History of any revascularization procedure, including the placement of a stent.
j) Patients with documented significant pleural or pericardial effusions unless they are thought to be secondary to leukemia.
k) Any history of venous thromboembolism, including, but not limited to, deep venous thrombosis (DVT) or pulmonary embolism within 6 months before randomization; patients with catheter-associated DVTs or superficial vein thrombosis, which are considered to be resolved/controlled, may be included after discussion with the sponsor's medical monitor/designee.

17. Poorly controlled diabetes. Patients with preexisting, well-controlled diabetes are not excluded.
18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.
19. Ongoing uncontrolled nausea or vomiting of any severity.
20. Have a significant bleeding disorder unrelated to ALL.
21. Life-threatening illness unrelated to cancer, such as severe CNS, pulmonary, renal, or hepatic disease unrelated to cancer.
22. Female patients who are lactating or breastfeeding or have a positive serum pregnancy test during the screening period or have a positive urine pregnancy test on Day 1 before the first dose of study drug is administered
    - Patients with a positive serum pregnancy test who have undergone a complete abortion in the last 60 days may be included after discussion with the sponsor's medical monitor/designee. If the serum test is positive, a repeat test is to be performed 7 to 14 days later and must be significantly lower to insure there is no active pregnancy for study eligibility.
23. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
24. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

Main Criteria for Evaluation and Analyses:

Primary efficacy endpoint: MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 13.a).

Key secondary efficacy endpoint:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve CR by the end of induction.
  - Relapse from CR.

Other secondary endpoints (defined in Table 13.a):

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- MR3, MR4, and MR4.5 at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.
- Rates of MRD-negative CR at multiple intervals after the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.
- OS and rate of relapse from CR for on-study patients with and without HSCT.

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- OS.

Safety and tolerability endpoints:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

PK endpoint:

- Plasma concentration-time data to contribute to population PK and exposure-response analyses of ponatinib.

Exploratory endpoints:

- Change from baseline in patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]).
- Change from baseline in MRU assessments.
- Time to start of alternative therapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

Statistical Considerations:

Stratification and Test for MRD-negative CR Primary Endpoint

To adjust for the known confounding factors in the study, patients' randomization assignments will be stratified dependent on the following factor:

Ages: 18 through <45 years; ≥45 through <60 years; and ≥60 years.

Statistical Design Considerations

The standard *closed* sequential testing procedure will be used for testing the primary endpoint of MRD-negative CR, the key secondary endpoint of EFS, and other secondary endpoints (duration of CR, duration of MRD-negative CR, ORR, and OS) with one planned interim analysis (IA) and one final analysis (FA) for each. If the hypothesis test on the primary endpoint of MRD negative CR is statistically significant at either the IA or FA for MRD-negative CR, then the test for EFS and other secondary endpoints will be conducted. Each of these endpoints (MRD-negative CR, EFS, and other secondary endpoints) will be tested at a 2-sided alpha level of 0.05. To maintain the type I error family wise at 2-sided 0.05 level, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) will be used to determine the significance level at the IA or FA for MRD-negative CR; the Gamma Family (-1) alpha spending function will be used to determine the significance level at IA and FA for EFS; the other secondary endpoints will use the same efficacy boundaries determined by EFS at IA and FA. By employing such closed sequential testing procedure, the type I error for the primary endpoint, the key secondary endpoint, and other secondary endpoints are strongly controlled.

If the analysis of MRD-negative CR achieves statistical significance at the IA or FA for MRD-negative CR, then EFS, duration of CR, duration of MRD-negative CR, ORR, and OS will be tested at the IA or FA for EFS. The study will continue to enroll patients to achieve the accrual target of 230 patients for the final analysis for MRD-negative CR and EFS.

Sample Size Justification:

Assuming an effect size ranging from 20% to 28% (40% to 48% and 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of approximately 230 patients (approximately 153 versus 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 84% to 98% power for MRD-negative CR at the final analysis using the efficacy boundary of 0.036 according to the group sequential testing procedure with the IA performed using data from 116 patients. The O'Brien-Fleming alpha spending function (the Lan-DeMets method), will be implemented to determine the significance level at IA and FA

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for the primary endpoint, with an overall type I error rate at a 2-sided 0.05 level.

Inference for the key secondary endpoint of EFS will be conducted at $\alpha = 5\%$ level only if the primary endpoint is met either at IA or FA for the MRD-negative CR. Based on 3-year EFS data observed from various phase 2 studies, effect size is assumed as 67% versus 46% for EFS at year 3 for the active and control arms, respectively, or HR = 0.516 for non-HSCT patients. The effect size is assumed as 53% and 40% for EFS at year 3 for active and control arms, respectively or HR = 0.693 for patients who are undertaking HSCT. Also, it is assumed that 50% and 45% of patients from active and control arms will undertake HSCT, respectively. Based on simulation studies, approximately 230 patients will be enrolled to collect long-term EFS data. Among these 230 patients, approximately 173 events need to be accumulated at FA so that the power will be approximately 80% for the EFS endpoint. It is expected that the time of FA for EFS will be approximately 8.5 years after the first patient has been enrolled.

Interim Analyses:

There will be one IA and possibly an FA in the study for the MRD-negative CR primary endpoint using a group sequential testing approach. The IA was performed after the end of induction phase data were collected for 116 patients. The primary endpoint of MRD-negative CR was first tested at the IA with a 2-sided efficacy boundary of 0.022 and will be tested again at the FA with a 2-sided efficacy boundary of 0.036 after the end of induction phase data have been collected for 230 patients. If the significance boundary is crossed at the FA for MRD-negative CR, there will be testing for EFS and other secondary endpoints at a 2-sided alpha level of 0.05 using a group sequential testing approach.

The analyses for the IA and FA for MRD-negative CR, and the IA for EFS will be carried out by an independent statistical team in a manner that maintains the blinding of the study results to the team. The independent data monitoring committee (IDMC) will review both efficacy and safety data at the time of the IA, and will inform the sponsor's executive committee of its recommendation.

Dosing Regimen:

Upon enrollment, patients will be randomized in a 2:1 ratio (ponatinib:imatinib) to receive either 30 mg of oral ponatinib (QD) or 600 mg of oral imatinib (QD), to be taken throughout the study, beginning on Cycle 1 Day 1. All patients will receive reduced-intensity chemotherapy, with an initial induction phase (3 cycles). Patients who achieve the primary endpoint at the end of induction will continue in a consolidation phase (6 cycles) and a maintenance phase (11 cycles), for a possible total of 20 cycles of reduced-intensity chemotherapy. Patients who do not achieve the primary endpoint but have achieved CR at the end of induction may also continue on study treatment at the discretion of the investigator. At the end of the 20 cycles, patients will remain on ponatinib or imatinib (administered as a single agent).

Dose modifications for ponatinib and imatinib will be performed as per dose modification guidelines (defined in detail in the protocol Section 8.3 and Section 8.4). After completing the maintenance phase, patients will continue to receive only ponatinib or imatinib as long-term therapy. Patients in each cohort will remain on study treatment until they are deceased, have failed to achieve the primary endpoint (patients who do not achieve the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

Note: Dose modification guidelines for efficacy are detailed in the protocol Section 8.3 for ponatinib only. Dose modification guidelines for adverse drug reactions are detailed in Section 8.4 for both ponatinib and imatinib; investigators should refer to current local prescribing information for all other therapies included in the study.

Patients who discontinued study treatment without relapse from CR, will be followed for investigator-reported disease status (eg, relapse from CR) and survival, and collect alternative therapies, wherever available (see also footnote q in the Schedule of Events [SOE]).

Patients who proceed to HSCT will be discontinued from study treatment but will be followed per the on-study data collection schedule as specified in the SOE (Table 2) for post-transplantation data collection, including transplant-related procedures, investigator-reported disease status (eg, relapse from CR), survival, and the use of post-transplant treatment (chemotherapy, TKI). Patients who proceed to alternative therapy will also be discontinued from study treatment but will be followed for investigator-reported disease status (eg, relapse from CR) and

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<table>
<tr><td colspan="2">survival. All other patients who discontinue study treatment will be followed for survival as specified in the SOE (Table 2).</td></tr>
<tr><td colspan="2">The following table outlines the study dosing regimens.</td></tr>
<tr><td colspan="2">Induction Phase Treatment (Three 28-Day Cycles; Study Cycles 1, 2 and 3) [a,b]</td></tr>
<tr><td>Cohort A</td><td>Cohort B</td></tr>
<tr><td>Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)</td><td>Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)</td></tr>
<tr><td>Dexamethasone:
• Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14.
• Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14.</td><td>Dexamethasone:
• Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14.
• Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14.</td></tr>
<tr><td>Ponatinib [c]:
Starting dose: 30 mg QD, starting on Cycle 1 Day 1.</td><td>Imatinib [c]:
Starting dose: 600 mg QD, starting on Cycle 1 Day 1.</td></tr>
<tr><td colspan="2">Consolidation Phase Treatment (Six 28-Day Cycles; Study Cycles 4 - 9) [a,b]</td></tr>
<tr><td>Cohort A</td><td>Cohort B</td></tr>
<tr><td><u>Alternating methotrexate and cytarabine:</u>
• Methotrexate (odd consolidation cycles 1st, 3rd, and 5th) Study Cycles 4, 6 and 8:
– Patients aged <60 years: 1000 mg/m^2 IV Day 1, 24-h infusion.
– Patients aged ≥60 years: 250 mg/m^2 IV Day 1, 24-h infusion.
– Rescue: folinic acid (see Appendix J).
• Cytarabine (even consolidation cycles 2nd, 4th, and 6th) Study Cycles 5, 7 and 9:
– Patients aged <60 years: 1000 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).
– Patients aged ≥60 years: 250 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (if the patient has impaired renal function, reduce the dose or consider discontinuing cytarabine).</td><td><u>Alternating methotrexate and cytarabine:</u>
• Methotrexate (odd consolidation cycles 1st, 3rd, and 5th) Study Cycles 4, 6 and 8:
– Patients aged <60 years: 1000 mg/m^2 IV Day 1, 24-h infusion.
– Patients aged ≥60 years: 250 mg/m^2 IV Day 1, 24-h infusion.
– Rescue: folinic acid (see Appendix J).
• Cytarabine (even consolidation cycles 2nd, 4th, and 6th) Study Cycles 5, 7 and 9:
– Patients aged <60 years: 1000 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K).
– Patients aged ≥60 years: 250 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (if the patient has impaired renal function, reduce the dose or consider discontinuing cytarabine).</td></tr>
<tr><td>Ponatinib [c]: Start with the last induction phase dose; modify dose based on MRD-negative CR results (see Section 8.3).</td><td>Imatinib [c]: Start with the last induction phase dose.</td></tr>
<tr><td colspan="2">Maintenance Phase Treatment (Eleven 28-Day Cycles; Study Cycles 10 - 20)</td></tr>
<tr><td>Cohort A</td><td>Cohort B</td></tr>
<tr><td>Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)</td><td>Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)</td></tr>
<tr><td>Prednisone [d]:
Patients aged <60 years: 200 mg/d PO on Days 1-5</td><td>Prednisone [d]:
Patients aged <60 years: 200 mg/d PO on Days 1-5</td></tr>
</table>

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Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5	Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5
Ponatinib [c]: Start with the last consolidation phase dose; modify dose based on MRD-negative CR results (see Section 8.3).	Imatinib [c]: Start with the last consolidation phase dose.
Post–Cycle 20 Therapy	
Ponatinib monotherapy: Patients will continue on the last maintenance phase dose (or dose modified based on MRD-negative CR results) until they are deceased, have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.	**Imatinib monotherapy:** Patients will continue on the last maintenance phase dose until they are deceased, have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

Abbreviations: CNS, central nervous system; CR, complete remission; CrCl, creatinine clearance; HSCT, hematopoietic stem cell transplant; IV, intravenously; MRD, minimal residual disease; PO, by mouth; q, every; QD, once daily.

Note: Alternative dose modifications/schedules may be recommended after discussion with the investigator and sponsor's medical monitor/designee to maximize exposure of study treatment while protecting patient safety.

[a] Lumbar punctures will be performed to test cerebrospinal fluid for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples), and additionally as clinically indicated.

[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.

[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

[d] Prednisolone can be used instead of prednisone if prednisone is not available.

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3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical study supplier list in the site operations manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

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3.3 List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
ALL	chromosome-positive acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AP	accelerated phase
AOE	arterial occlusive event
AST	aspartate aminotransferase
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BM	bone marrow
BNP	B-type natriuretic peptide
BP	blood pressure
BSA	body surface area
CAD	coronary artery disease
CHF	congestive heart failure
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
CNS	central nervous system
COVID-19	coronavirus disease 2019
CP	chronic phase
CP-CML	chronic phase chronic myeloid leukemia
CR	complete remission (complete response)
CRi	incomplete complete remission
CrCl	creatinine clearance
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
cTnI	cardiac troponin-I
CV	cardiovascular
CVA	cerebrovascular accident
CVEAC	cardiovascular endpoint adjudication committee
DTP	direct-to-patient
CYP	cytochrome P450
DVT	deep venous thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

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EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	EuroQOL-5 Dimension-5 Level
ESMO	European Society for Medical Oncology
FA	final analysis
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HLT	High Level Term
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
HTN	hypertension
hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
IA	interim analysis
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IS	International Scale
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
K-M	Kaplan-Meier
LBBB	left bundle branch block
LVEF	left ventricular ejection fraction
MaHR	major hematologic response
MCyR	major cytogenetic response
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MI	myocardial infarction
MR3	molecular response 3-log reduction (BCR-ABL1/ABL1 $\leq$0.1%)
MR4	molecular response 4-log reduction (BCR-ABL1/ABL1 $\leq$0.01%)
MR4.5	molecular response 4.5-log reduction (BCR-ABL1/ABL1 $\leq$0.0032%)
MRD	minimal residual disease

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MRU	medical resource utilization
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NT-proBNP	N-terminal pro-brain natriuretic peptide
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
Ph+ ALL	Philadelphia chromosome–positive acute lymphoblastic leukemia
PIF	primary induction failure
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PP	per-protocol
PO	by mouth (orally)
PT	Preferred Term
PTE	pretreatment event
QD	once daily
qPCR	quantitative polymerase chain reaction
QTcF	QT interval corrected per Fredericia method
rSDR	remote source data review
rSDV	remote source data verification
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOE	Schedule of Events
SUSARs	suspected unexpected serious adverse reactions
TdP	torsades de pointes
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
UK	United Kingdom
ULN	upper limit of normal
URL	upper reference limit
US	United States
VTE	venous thrombotic/embolic event
WBC	white blood cell
WHO	World Health Organization

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3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan; TDC Asia; TDC Europe and/or TDC Americas; as applicable

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4.0 INTRODUCTION

4.1 Background

4.1.1 Disease State Background

4.1.1.1 Ph+ ALL

Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL) is a rare malignancy of the blood and bone marrow (BM), constituting approximately 20% to 30% of adult ALL [3,4]. ALL occurs at an age-adjusted incidence in the United States (US) of 1.58 per 100,000 individuals per year. In 2014, the estimated prevalence of Ph+ ALL was approximately 16,367 to 24,551 (20% to 30% of total ALL prevalence in 2014). Ph+ ALL is mainly a disease of adults, accounting for only approximately 3% of pediatric cases of ALL [3,4].

Ph+ ALL results from a translocation of chromosomes 9 and 22, referred to as the Philadelphia chromosome, which leads to the fusion of the breakpoint cluster region (BCR) coding sequence with the tyrosine kinase coding region of Abelson1 (ABL1). The consequence is expression of a BCR-ABL1 fusion oncoprotein with constitutive activation of ABL1 tyrosine kinase activity, which in turn activates cell signaling pathways promoting cell proliferation and survival. The constitutive ABL1 kinase activity is both necessary and sufficient for induction of both Ph+ ALL and chronic myeloid leukemia (CML) [5].

4.1.1.2 Treatment for Ph+ ALL

Ph+ ALL has been historically associated with very poor prognosis [6]. Before the introduction of tyrosine kinase inhibitors (TKIs), the outcome of treatment for patients with Ph+ ALL was poor. While treatment with chemotherapy alone (in the absence of a TKI) resulted in complete remission (CR) in many patients initially (45% to 90%), the median duration of CR was short (approximately 10 months), and most patients later relapsed, leading to few long-term survivors [7-9].

The National Comprehensive Cancer Network (NCCN) guidelines [4] contain widely accepted recommendations for the treatment of Ph+ ALL in the US. NCCN guidelines first recommend treatment of Ph+ ALL patients in a clinical study. If that is not possible, the guidelines then generally recommend first-line treatment of Ph+ ALL with a TKI, along with chemotherapy (which usually includes vincristine, and may also include doxorubicin or daunorubicin and/or cyclophosphamide) and/or a steroid (generally dexamethasone or prednisone). Similarly, the European Society for Medical Oncology (ESMO) has published clinical practice guidelines for treating Ph+ ALL in adults with TKIs; ESMO recommends that a TKI should be administered continuously and should be combined with chemotherapy in front-line therapy [10]. Central nervous system (CNS) prophylaxis is also recommended to be administered throughout treatment. HSCT is performed in some patients, depending on factors such as availability of a suitable donor and the suitability of the patient to withstand the procedure. HSCT, however, may

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have some limitations, as it is an option for only a limited number of patients (particularly younger patients) and is associated with significant rates of both mortality and relapse [9].

4.1.1.3 Use of TKIs and Unmet Medical Need

All regimens recommended by NCCN guidelines [4] include a TKI; however, in the US, no TKI has yet received regulatory approval for newly diagnosed Ph+ ALL in adult patients. In the US, imatinib (a first-generation BCR-ABL1 TKI) is approved for pediatric patients with newly diagnosed Ph+ ALL in combination with chemotherapy and for relapsed or refractory Ph+ ALL in adult patients; dasatinib (a second-generation BCR-ABL1 TKI) is approved for adults with Ph+ ALL with resistance or intolerance to prior therapy; and ponatinib (a third-generation BCR-ABL1 TKI) is approved for adult patients with Ph+ ALL for whom no other TKI therapy is indicated or who are T315I–mutation-positive.

First-line use of first- or second-generation TKIs in combination with chemotherapy results in 3- and 5-year overall survival (OS) rates of approximately 46% to 56% and 43%, respectively [11-13]. These relatively modest OS rates are generally due to relapse after achievement of an initial CR by hematologic criteria and create opportunity for considerable improvement in the treatment of Ph+ ALL. Relapse in Ph+ ALL is generally associated with TKI resistance, which can occur by multiple mechanisms. The most common mechanism of resistance to the first- and second-generation TKIs is single mutations in the ABL1 kinase domain [3,14,15]. While the second-generation TKIs are more potent inhibitors of BCR-ABL1 compared with imatinib and have inhibitory activity against most imatinib-resistant mutations, several mutations such as T315I, V299L, and F317L are also resistant to dasatinib [4]. Of these, the T315I mutation is the most common mutation associated with resistance to both imatinib and dasatinib [14,15]. In one study with dasatinib, the T315I mutation was observed in 75% of relapsed patients on whom mutation analysis by Sanger sequencing was performed [15].

Rationale therefore exists that there is an unmet medical need for a more potent TKI that can suppress the development of mutations and is also active against the single mutations associated with resistance to the early generation TKIs. This more potent TKI could result in deeper and more durable responses in the first-line treatment of Ph+ ALL compared with the earlier generation TKIs.

There also remains an unmet medical need for effective treatment regimens in older patients with Ph+ ALL and in patients who are unable to tolerate intensive chemotherapy regimens. Increasing age is a risk factor for the development of Ph+ ALL, and generally the older the patient, the worse the prognosis [4,14,16]. In older patients (aged ≥65 years), NCCN guidelines recommend either reduced-intensity chemotherapy or no chemotherapy (steroid only) in combination with a TKI. Even among younger adults, the use of a TKI along with reduced-intensity chemotherapy may have a more favorable benefit-risk profile compared with more intensive regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD). The combination of a more potent TKI (ponatinib) with a chemotherapy regimen that is more intensive than steroids but less intensive than chemotherapy such as

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hyper-CVAD, may be a good option for the first-line treatment of Ph+ ALL and warrants further investigation in a broad Ph+ ALL patient population.

In summary, the increased potency of ponatinib compared with the early generation TKIs, along with ponatinib's activity toward the single mutations associated with resistance to the early generation TKIs and its ability to suppress the development of resistance mutations, forms the rationale for the use of ponatinib in combination with less intensive chemotherapy in the treatment of first-line Ph+ ALL in this phase 3 study.

4.1.2 Ponatinib Design and Mechanism of Action

Ponatinib is the product of a computational and structure-based approach to the design of a small-molecule TKI [17]. Ponatinib was designed to optimally inhibit native BCR-ABL1 and mutant forms of the protein that cause resistance to other TKIs, including the T315I gatekeeper mutation that confers resistance to all approved BCR-ABL1 inhibitors other than ponatinib (ie, imatinib, nilotinib, dasatinib, and bosutinib).

A critical feature of ponatinib's design is the incorporation of multiple contact points with the ABL1 kinase domain, which balances and distributes overall binding affinity [18]. This leads not only to high-affinity binding to ABL1, but also renders binding less susceptible to disruption by any single amino acid mutation. A second critical structural feature is a carbon-carbon triple bond linkage that allows ponatinib to make a productive hydrophobic contact with the bulky isoleucine residue present in the T315I mutation rather than being sterically hindered by it.

Through direct inhibition of native BCR-ABL1 and its variants, ponatinib inhibits aberrant downstream signaling by reducing phosphorylated CRKL (pCRKL), thereby promoting apoptosis and cell death in BCR-ABL1–positive cells [17].

4.1.3 Ponatinib: Nonclinical to Clinical

Nonclinical studies have demonstrated that ponatinib potently inhibits native BCR-ABL1, and all single-mutation variants, at clinically relevant concentrations [17,19]. In a cell line expressing native BCR-ABL1, ponatinib inhibited viability with a half-maximal inhibitory concentration (IC_{50}) <1 nM, which is more than 200-fold lower than that of imatinib. Ponatinib also potently inhibited viability (with IC_{50}s <40 nM) of cell lines expressing 14 major clinically observed imatinib-resistant BCR-ABL1 mutations, including T315I. Ponatinib exhibited potent in vivo activity in 2 mouse tumor models expressing the T315I mutation of BCR-ABL1. Using an in vitro mutagenesis screen approach that has successfully predicted mutations that confer clinical resistance to imatinib and nilotinib and dasatinib [20], a concentration between 20 nM and 40 nM of ponatinib was found to suppress the emergence of any resistant BCR-ABL1 mutation [17].

While nonclinical studies have shown that no single BCR-ABL1 mutation can cause resistance to ponatinib, it has been shown that certain compound mutations (2 mutations in the same BCR-ABL1 protein) can confer resistance [17,21]. For example, the presence of a T315I mutation on the same allele with Y253H or E255K can confer nonclinical resistance to ponatinib, though ponatinib is able to inhibit each of those mutants individually. Development of

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compound mutations is a risk associated with sequential use of BCR-ABL1 TKIs [22], whereby expansion of a leukemic progenitor cell that has a single resistance mutation provides a template on which a second mutation can develop.

The association between ponatinib efficacy and BCR-ABL1 mutation status in patients has been studied most extensively in the phase 2 PACE study (Study AP24534-10-201), the pivotal study upon which full marketing approval was granted by the US Food and Drug Administration (FDA) for the indications described in the current Iclusig label. The PACE study enrolled 449 heavily pretreated patients, including 267 patients with chronic phase CML (CP-CML) and 32 patients with Ph+ ALL [23]. All patients previously had been treated with at least 1 approved BCR-ABL1 inhibitor, with the majority having been treated with 3 or more. A starting dose of 45 mg was used, which was the recommended dose established in the phase 1 study (Study AP24534-07-101) [24].

Though response rates were high in heavily pretreated patients with CP-CML or Ph+ ALL, long-term outcomes differed substantially [23]. Among patients with CP-CML, 56% of patients achieved the primary endpoint of a major cytogenetic response (MCyR), and these responses were durable: The estimated rate of a sustained MCyR for at least 12 months was 91%. Among patients with Ph+ ALL, 41% achieved the primary endpoint of a major hematologic response (MaHR); however, these responses were not durable: The estimated rate of a sustained MaHR of at least 12 months was 8%. It is important to note that short- and long-term outcomes in patients with CP-CML and Ph+ ALL could be rationalized based on the relationship between BCR-ABL1 mutation status and ponatinib efficacy, as assessed in these patients.

First, analysis of efficacy based on baseline mutation status demonstrated that high response rates were observed in patients regardless of BCR-ABL1 mutation status (ie, in patients with or without BCR-ABL1 mutations), and responses were observed for each of the 15 mutations present in more than 1 patient with CP-CML at baseline. Thus, high initial response rates observed in patients with CP-CML and Ph+ ALL are likely explained by the ability of ponatinib to potently inhibit native and single-mutation variants of BCR-ABL1 that exist before ponatinib therapy and which constitute most of the leukemic cell population.

Second, analysis of BCR-ABL1 mutation status at the end of ponatinib treatment revealed that the acquisition of compound mutations was rare in patients with CP-CML but common in patients with Ph+ ALL treated with ponatinib [23,25]. Among 130 patients with CP-CML, 19 patients (15%) were found to have acquired any mutation at the end of treatment (EOT) that was not detected at baseline, and 4 patients (3%) were found to have acquired a compound mutation. In contrast, among 20 patients with Ph+ ALL, 13 patients (65%) were found to have acquired any mutation, and 12 patients (60%) were found to have acquired a compound mutation. In all the patients who acquired a compound mutation, 1 of the mutations was detected at baseline.

In summary, nonclinical and clinical data consistently indicate that ponatinib is a highly potent and a “pan” BCR-ABL1 inhibitor, defined as having the ability to inhibit all single BCR-ABL1 mutations. This likely explains the high degree of efficacy initially observed in patients with CP-CML and Ph+ ALL, even if they had been heavily pretreated. However, certain compound

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mutations, which emerge during prior treatment with a non–pan-BCR-ABL1 inhibitor, can confer resistance to ponatinib. Development of compound mutations is common in Ph+ ALL but not in CP-CML, likely explaining the durable response induced by ponatinib in heavily pretreated patients with CP-CML but not in patients with Ph+ ALL.

4.2 Rationale for the Proposed Study

4.2.1 Rationale for Ponatinib in Newly Diagnosed Ph+ ALL

As described previously (Section 4.1.1.3), in newly diagnosed patients with Ph+ ALL treated with first- or second-generation TKIs, the development of secondary resistance mutations in BCR-ABL1 is strongly associated with disease progression. When these patients with relapsed or refractory Ph+ ALL are then treated with ponatinib, many have developed a second (compound) mutation in BCR-ABL1. Some of these compound mutations may be resistant to ponatinib and to the first- and second-generation TKIs. Options for further treatment with TKIs are then exhausted.

The rationale for use of ponatinib in the first-line treatment of Ph+ ALL is that, by suppressing all single BCR-ABL1 resistance mutations, the predominant mechanism by which a leukemic cell is expected to develop a BCR-ABL1-mediated mechanism of resistance to ponatinib would be to develop 2 independent mutations simultaneously. The decreased likelihood of this occurring in patients only treated with ponatinib, compared with patients treated with a first- or second-generation TKI and then ponatinib, leads to the hypothesis of more durable responses in patients with newly diagnosed Ph+ ALL treated with ponatinib compared with sequential treatment with first- or second-generation TKIs followed by ponatinib.

On the basis of this rationale, the data summarized in Section 4.1.3, and the greater potency of ponatinib compared with the earlier generation TKIs, the sponsor hypothesizes that ponatinib treatment in patients with newly diagnosed Ph+ ALL will lead to superior outcomes compared with those treated with first- or second-generation TKIs. In contrast to heavily pretreated patients with Ph+ ALL, where long-term outcomes were limited by development of compound resistance mutations, this is not expected to be the case in newly diagnosed patients. Preliminary clinical data are consistent with this hypothesis.

Ph+ ALL is a fast and aggressive disease for which the long-term prognosis remains poor, even when treated with the first- and second-generation TKIs. An improvement in long-term outcome may justify the risk of using a more potent TKI (ponatinib) in patients with newly diagnosed Ph+ ALL. Furthermore, if clinical data suggest that a more potent TKI could allow for the use of less intensive chemotherapy, the first-line use of ponatinib in adult patients with newly diagnosed Ph+ ALL may be additionally justified.

4.2.2 Ponatinib Dose Rationale

Clinical information on the safety and efficacy of different doses of ponatinib comes from multiple sources which, taken together, led to the selection of 30 mg as the starting dose for this protocol, with a dose reduction to 15 mg upon achievement of minimal residual disease

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(MRD)-negative CR and re-escalation to 30 mg if response is lost, as permitted by safety and tolerability in individual patients. Although a starting dose of 45 mg is recommended in the current prescribing information for ponatinib, it is acknowledged that the optimal dose of ponatinib remains to be defined; this is the objective of an ongoing, phase 2, dose-ranging study (Study AP24534-14-203) evaluating the efficacy and safety of starting doses of 15 mg, 30 mg, or 45 mg once daily (QD) in patients with resistant CP-CML. The proposed starting dose of 30 mg QD for the current protocol is based upon consideration of the expected superior benefit-risk balance at 30 mg versus 45 mg, informed by previously conducted dose intensity-response analyses of data from the completed Studies AP24534-07-101 and AP24534-10-201.

Logistic regression analyses of dose intensity-AE relationships in patients with CP-CML in the phase 2 Study AP24534-10-201 indicated a dose-dependent increase in AEs, and notably in arterial occlusive event (AOE) rates, which are of specific importance for ponatinib. Dose intensity was a statistically significant predictor of AOE rates in that multivariate analysis after adjustment for known cardiovascular (CV) risk factors, leading to the expectation that the 30 mg QD dose will have a superior safety profile compared with 45 mg QD, thus supporting 30 mg QD selection as the starting dose.

In addition, a dose intensity-efficacy logistic regression analyses in Study AP24534-10-201 demonstrated a statistically significant relationship between dose intensity and the probability of achieving MCyR at 12 months. These analyses clearly indicated that 30 mg (versus 15 mg) is within the dynamic range of the inferred dose-response relationship, with the estimated probability of MCyR by 12 months at 30 mg (~60%) being meaningfully greater than at 15 mg (~25%), and both the 30 mg and 15 mg doses are likely to be biologically active on the basis of data that demonstrated average plasma concentrations exceeding the IC_{50} for all BCR-ABL1 mutations at the 30 mg dose, and for most BCR-ABL1 mutations at the 15 mg dose. Although a direct translation of exposure-efficacy relationships in a resistant CP-CML population to a previously untreated Ph+ ALL population is not possible, the estimated dose intensity-efficacy relationship in Study AP24534-10-201 nevertheless provides valuable prior information regarding expectations of dose-response relationships for efficacy of ponatinib in BCR-ABL1–driven hematologic malignancies. Accordingly, the results of these analyses provide the supporting rationale for selecting the 30 mg QD starting dose for this phase 3 protocol.

4.2.3 Rationale for Selection of MRD-Negative CR as Primary Endpoint

Treatment guidelines for patients with ALL [4] recommend an initial minimal threshold for response to be the achievement of a CR (also referred to as *complete response*), with no recurrence for 4 weeks, by the end of the induction phase.

More important, the absence of MRD has been found to have strong long-term prognostic power in patients with ALL, with a large body of evidence demonstrating a strong correlation between MRD negativity and improved event-free survival (EFS) and OS [4,26]. Consistent with most studies, NCCN guidelines recommend that MRD be assessed upon completion of the initial induction [4]. MRD assessment relies on accurate and sensitive detection of the relative proportion of leukemic cells, with an assay sensitivity of at least 0.01% (ie, the ability to detect

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1 ALL cell among at least 10,000 normal cells) generally being required to consider a sample to be MRD-negative [4,27].

In Ph+ ALL, MRD status can be assessed by detecting the specific genetic abnormality that defines the leukemic cells (ie, the presence of the BCR-ABL1 fusion gene transcript). In this approach, quantitative polymerase chain reaction (qPCR) is used to measure BCR-ABL1 levels (present in leukemic cells) relative to ABL1 levels (present in normal cells and leukemic cells) to assess disease levels.

In a meta-analysis that included 5 studies conducted in adult Ph+ ALL patients, MRD negativity at the end of induction was associated with significantly improved EFS and OS [26]. In the study most pertinent to the phase 3 study described here, Short performed a retrospective analysis to test the association between achievement of MRD negativity and long-term outcomes in 85 patients with newly diagnosed Ph+ ALL treated with 1 of 3 TKIs (imatinib [N = 23], dasatinib [N = 39], or ponatinib [N = 23]) and a hyper-CVAD chemotherapy backbone, who did not undergo allogeneic stem cell transplantation. In this study, achievement of MRD negativity at 3 months, which was defined as absence of detectable BCR-ABL1 transcripts with a sensitivity of 0.01%, was associated with significantly longer OS and relapse-free survival. Importantly, though rates of MRD negativity were different according to the TKI (eg, 39% and 87% for patients receiving imatinib and ponatinib, respectively), among patients who achieved MRD negativity at 3 months, there was no impact on either OS or relapse-free survival according to the TKI received [28].

Given the reliance of this test on assessment of the genetic abnormality underlying Ph+ ALL, the assay used to assess BCR-ABL1 levels must be able to quantify the variants present in most patients with Ph+ ALL. More specifically, differences in the location of the BCR breakpoint result in 2 major variants of the BCR-ABL1 fusion transcript [29], which require separate polymerase chain reaction (PCR) primers for detection. In the variant present in the majority (~75%) of adult patients with Ph+ ALL, the first exon of the BCR gene is fused to the second exon of the ABL1 gene, resulting in a fusion transcript that encodes a 190 kDa oncoprotein. These are referred to as the e1a2 or p190 variants. In the second most common variant (~25% of patients), exons 13 or 14 (also known as exons b2 or b3) of the BCR gene are fused to the second exon of the ABL1 gene, resulting in a fusion transcript that encodes a 210 kDa oncoprotein. These are referred to as the e13a2 (or b2a2), e14a2 (or b3a2), or p210 variants. Thus, assessment of BCR-ABL1 levels in patients with Ph+ ALL requires use of 2 separate assays able to quantitatively measure levels of p190 and p210 variants, with a minimal sensitivity of at least 0.01%.

In summary, current treatment guidelines and multiple retrospective analyses support assessment of MRD negativity at the end of the induction phase of treatment as a meaningful surrogate for long-term efficacy (coupled with achievement of CR for at least 4 weeks). These studies also support defining MRD negativity as BCR-ABL1/ABL1 levels ≤0.01% (also referred to as molecular response 4-log reduction [MR4]) and measuring MRD negativity with appropriately qualified assays. Assessment of alternate residual disease thresholds, including BCR-ABL1/ABL1 levels ≤0.1% (molecular response 3-log reduction [MR3]) and ≤0.0032%

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(molecular response 4.5-log reduction [MR4.5]), at multiple timepoints, may further inform response milestones that may help guide future optimization of treatment regimens.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

The primary objective of the study is to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction (see Table 13.a for the definitions of MRD negativity and CR).

5.1.2 Secondary Objectives

The key secondary objective is to compare EFS between the 2 cohorts.

Other secondary objectives are:

- To compare the rates of CR and incomplete CR (CRi) between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of MR3, MR4, and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of primary induction failure (PIF) and overall response rate (ORR) between the 2 cohorts, at the end of induction.
- To compare rates of MRD-negative CR at multiple intervals after the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare OS between the 2 cohorts.
- To collect plasma concentration-time data to contribute to population pharmacokinetic (PK) and exposure-response analyses of ponatinib.

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5.1.3 Safety Objectives

The safety objectives are:

- To characterize the rates of AEs/SAEs, AOEs, venous thrombotic/embolic events (VTEs), and other safety outcomes of interest in the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

5.1.4 Exploratory Objectives

The exploratory objectives are:

- To compare patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]) results between the 2 cohorts.
- To compare medical resource utilization (MRU) results between the 2 cohorts.
- To compare the time to start of alternative therapy between the 2 cohorts.
- To compare the time to HSCT between the 2 cohorts.
- To explore biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is MRD-negative CR at the end of induction (see Table 13.a for the definitions of MRD negativity and CR).

5.2.2 Secondary Endpoints

5.2.2.1 Key Secondary Endpoints

The key secondary endpoint is:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve CR by the end of induction.
  - Relapse from CR.

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5.2.2.2 Other Secondary Endpoints

Other secondary endpoints (defined in Table 13.a) are:

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.
- Rates of MRD-negative CR at multiple intervals after the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.
- OS and rate of relapse from CR for on-study patients with and without HSCT.
- OS.

5.2.3 Safety Endpoints

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic blood pressure [BP] and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

5.2.4 PK Endpoint

The PK endpoint is plasma concentration-time data to contribute to population PK and exposure-response analyses of ponatinib.

5.2.5 Exploratory Endpoints

The exploratory endpoints are (see Table 13.a for the definitions):

- Change from baseline in patient-reported quality of life (FACT-Leu and EQ-5D-5L).

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- Change from baseline in MRU assessments.
- Time to start of alternative therapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This phase 3 study is designed as an open-label, multicenter, randomized comparison of the TKIs ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced-intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously. Patients will remain on study treatment until they are deceased, have failed to achieve the primary endpoint at the end of induction (patients who do not achieve the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR or MRD-negative status with CRi at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

The primary endpoint of this study is MRD-negative CR at the end of induction (defined in Table 13.a). Patients who achieve the primary endpoint will continue in the study in the consolidation and maintenance phases followed by a single-agent therapy phase. As CR must have been maintained for at least 4 weeks, patients who do not achieve CR by the end of Cycle 2 (ie, C3D1) will be considered as having failed to achieve the primary endpoint (see Table 13.a for definitions). Patients who achieve CR but do not achieve MRD-negative status or who achieve MRD-negative status with CRi at the end of induction may continue on study treatment at the investigator's discretion. All other patients will be discontinued from study drug. For all discontinued patients, the patient's treating physician should consider alternative therapy options.

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib QD, which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Section 8.4.1). For patients in the ponatinib cohort who achieve CR or MRD-negative CRi but do not achieve the primary endpoint at the end of induction and who continue in the study at the investigator's discretion, the dose of ponatinib will be reduced, as described above, at any time when the

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patient achieves MRD-negative CR and re-escalated, as described above, upon loss of response. Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for CNS disease prophylaxis. At the end of the 20 cycles, all patients remaining on study will remain on ponatinib or imatinib (administered as a single agent).

MRD status will be measured using qPCR-based tests validated for the ability to detect BCR-ABL1/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as ≤0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale (IS) with traceability to the World Health Organization (WHO) first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported. To ensure uniformity of analysis, all samples will be tested using the same methodology in central laboratories. Assessment of the primary endpoint at the end of induction will be based on analysis of BM samples, but in rare cases where the BM samples are not evaluable or not available, blood samples could also be used. To minimize the number and volume of BM aspirates required, and in keeping with available recommendations [1] and evidence of general concordance between results [2], assessment of BCR-ABL1/ABL1 levels at other time points may use peripheral blood samples. Both sample types will be collected at a subset of time points to allow the levels of concordance between sample types to be broadly assessed.

The key secondary endpoint for this study is EFS. Other secondary endpoints will include rates of CR and CRi at the end of Cycle 1, Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MR3, MR4, and MR4.5 at the end of Cycle 1, the end of Cycle 2, the end of induction and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MRD-negative CR at multiple intervals after the end of induction; rates of PIF and ORR at the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; duration of MR4.5 in patients who achieved MR4.5; OS and rate of relapse from CR for on-study patients with and without HSCT, and OS. (See Table 13.a for endpoint definitions.)

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all AEs, SAEs, AOEs, and VTEs; rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

Exploratory endpoints will include change from baseline in patient-reported quality-of-life and MRU assessments; time to start of alternative therapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

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6.2 Number of Patients

Approximately 230 patients will be enrolled in this study from approximately 120 study sites globally. Enrollment is defined as randomized to study drug.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

All patients will remain on study treatment until they are deceased, have failed to achieve the primary endpoint of MRD-negative CR at the end of induction (patients who fail the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR or MRD-negative status with CRi at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

All patients who discontinue study treatment will be followed for survival as specified in the SOE. Patients who discontinued study treatment without relapse from CR, will be followed for investigator-reported disease status (eg, relapse from CR) and survival, and reporting of alternative therapies, wherever available. Patients who proceed to HSCT will be discontinued from study treatment but will be followed per the on-study data collection schedule as specified in the Schedule of Events (SOE) for post-transplantation data collection, including transplant-related procedures, investigator-reported disease status (eg, relapse from CR), survival, and the use of post-transplant treatment (chemotherapy, TKI). Patients who proceed to alternative therapy will also be discontinued from study treatment and will be followed for investigator-reported disease status (eg, relapse from CR) and survival.

After disease progression, all patients will be contacted every 3 months for survival follow-up. Patients will be followed until completion of the study or until the patient's death has been reported.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be considered completed when the death of all patients has been recorded or when the study has been terminated by the sponsor.

Study results will be reported in a CSR.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Table 6.a provides disclosures information for all primary and secondary endpoints.

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Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: MRD-negative CR	BCR-ABL1/ABL1 ratio ≤0.01% and meeting criteria for CR (see Table 13.a)	The end of induction, ie, approximately 3 months
Key Secondary: EFS	The dates of randomization until: • Death due to any cause. • Failure to achieve CR by the end of induction. • Relapse from CR.	Approximately 3-6 years; EFS is event-driven, exact time period to be specified in statistical analysis plan
Secondary: CR and CRi	See Table 13.a	At approximately 1 month, 2 months, 3 months, and up to 9 months
Secondary: Molecular response rates (MR3, MR4, and MR4.5)	MR3 is defined as molecular response 3-log reduction (≤0.1% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts; MR4 is defined as molecular response 4-log reduction (≤0.01% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts; MR4.5 is defined as molecular response 4.5-log reduction (≤0.0032% BCR-ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.	At approximately 1 month, 2 months, 3 months, and up to 9 months
Secondary: PIF and ORR	See Table 13.a for definition of PIF. ORR is defined as CR + CRi.	At approximately 3 months
Secondary: MRD-negative CR	BCR-ABL1/ABL1 ratio ≤0.01% and meeting criteria for CR (see Table 13.a).	Up to approximately 3-6 years
Secondary: Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.	Up to approximately 3-6 years
Secondary: Duration of CR	The interval between the first assessment at which the criteria for CR are met until the earliest date at which relapse from CR occurs.	Up to approximately 3-6 years
Secondary: Time to treatment failure	Time to end of study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or efficacy reasons.	Up to approximately 3-6 years
Secondary: MR4.5, including best response	MR4.5 is defined as ≤0.0032% BCR-ABL1.	Up to approximately 3-6 years
Secondary: Duration of MR4.5 in patients who achieved MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.	Up to approximately 3-6 years
Secondary: OS and relapse from CR for on-study patients with and without HSCT	See Table 13.a for a definition of relapse from CR. OS: The interval between randomization and death due to any cause, censored at the last contact date when the patient was alive.	Up to approximately 3-6 years

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Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Secondary: OS	The interval between randomization and death due to any cause.	Up to approximately 3-6 years

Abbreviations: AEs, adverse events; BCR-ABL, breakpoint cluster region-Abelson; cDNA, complementary DNA; CR, complete remission; CRi, incomplete CR; EFS, event-free survival; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction; MR4, molecular response 4-log reduction; MR4.5, molecular response 4.5-log reduction; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PIF, primary induction failure.

6.3.4 Total Study Duration

The duration of the study will be approximately 6 to 9 years, including approximately 36 months for enrollment and approximately 3-6 years of follow-up from the date that the last patient enrolled.

6.3.5 Posttrial Access

Participants who have met the primary (and/or secondary) endpoints of the study and, in the opinion of the investigator and confirmed by the sponsor, experienced a clinically important benefit from ponatinib may continue to receive ponatinib in an extension phase of this study or a separate open-label rollover study.

Continued access to ponatinib for participants will be terminated for those individuals who no longer benefit from ponatinib (eg, they have completed the recommended course of therapy or their disease has resolved), the benefit-risk no longer favors the individual, if ponatinib becomes available either commercially or via another access mechanism, or when an alternative appropriate therapy becomes available. Posttrial access may be terminated in a country or geographical region where marketing authorization has been rejected, the development of ponatinib has been suspended or stopped by the sponsor, or ponatinib can no longer be supplied.

7.0 STUDY POPULATION

The study population will include male and female adult patients aged 18 years and older who have newly diagnosed Ph+ ALL.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study and randomized to treatment:

1. Male or female patients aged 18 years or older.
2. Newly diagnosed Ph+ or BCR-ABL1-positive ALL, as defined by the 2017 NCCN guidelines.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

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4. Clinical laboratory values as follows, within 30 days before randomization:
   a) Total serum bilirubin ≤1.5× the upper limit of normal (ULN), unless due to Gilbert's syndrome.
   b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5× the ULN.
   c) Serum creatinine ≤1.5× the ULN and estimated creatinine clearance (CrCl) ≥30 mL/minute (Cockcroft-Gault formula).
   d) Serum lipase <1.5× the ULN.
5. Normal QT interval corrected per Fridericia method (QTcF) on screening electrocardiogram (ECG), defined as QTcF of ≤450 ms in males or ≤470 ms in females.
6. Female patients who:
   a) Are postmenopausal for at least 1 year before the screening visit, OR
   b) Are surgically sterile, OR
   c) If they are of childbearing potential, agree to practice 1 highly effective method of contraception (such as any form of hormonal contraception, eg, birth control pills or hormonal intra-uterine device [IUD]) and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 1 month after the last dose of study drug or a longer period per any local regulation, eg, 35 days for patients in France), OR
   d) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
7. Male patients, even if surgically sterilized (ie, status postvasectomy), who:
   a) Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
   b) Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
8. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
9. Willingness and ability to comply with scheduled visits and study procedures.

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7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study or randomized to treatment.

1. Patients with a history or current diagnosis of chronic phase, accelerated phase, or blast phase CML.
2. Prior/current treatment with any systemic anticancer therapy (including but not limited to any TKI) and/or radiotherapy for ALL, with the exception of an optional prephase therapy or chemotherapy induction (no more than 1 cycle), which should be discussed with the sponsor's medical monitor/designee.
3. Treatment with any investigational products within 30 days before randomization or 6 half-lives of the agent, whichever is longer.
4. Currently taking drugs that are known to have a risk of causing prolonged QTc or torsades de pointes (TdP) (unless these can be changed to acceptable alternatives or discontinued) (Appendix E).
5. Taking any medications or herbal supplements that are known to be strong inhibitors or strong inducers of cytochrome P450 (CYP)3A4 within at least 14 days before the first dose of study drug (Appendix F).
6. Uncontrolled active serious infections that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
7. Major surgery within 28 days before randomization (minor surgical procedures such as catheter placement or BM biopsy are not exclusionary criteria).
8. Known HIV seropositivity, known active hepatitis B or C infection.
9. History of acute pancreatitis within 1 year of study screening or history of chronic pancreatitis.
10. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
11. Diagnosed and treated for another malignancy within 5 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
12. History or presence of clinically relevant CNS pathology such as epilepsy, childhood or adult seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
13. Clinical manifestations of CNS or extramedullary involvement with ALL other than lymphadenopathy or hepatosplenomegaly.
14. Autoimmune disease with potential CNS involvement.
15. Known significant neuropathy of Grade ≥2 severity.

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16. Clinically significant, uncontrolled, or active cardiovascular, cerebrovascular, or peripheral vascular disease, or history of or active VTE disease, including, but not restricted to:
    a) Complete left bundle branch block.
    b) Right bundle branch block plus left anterior hemiblock, or bifascicular block.
    c) History of or presence of clinically significant ventricular or atrial tachyarrhythmias.
    d) Clinically significant resting bradycardia (<50 beats per minute).
    e) Uncontrolled hypertension (HTN); systolic BP ≥150 mmHg and/or diastolic BP ≥90 mmHg). Patients with Stage 2 HTN (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg should be under treatment at study entry per the current American Heart Association guidelines to ensure BP control. Patients requiring 3 or more antihypertensive medications should have controlled HTN for the past 6 months. Isolated elevation(s) of systolic and/or diastolic BP during screening are not exclusionary.
    f) Any history of myocardial infarction (MI), unstable angina, coronary artery disease (CAD), cerebrovascular accident (CVA), ischemic stroke, or transient ischemic attack (TIA). Note: Patients with *any* history of these events, whether considered clinically significant or not, are excluded.
    g) History of congestive heart failure (CHF) (New York Heart Association class III or IV) or left ventricular ejection fraction (LVEF) <40%, within 6 months before randomization.
    h) Symptomatic peripheral vascular disease or history of infarction, including visceral infarction.
    i) History of any revascularization procedure, including the placement of a stent.
    j) Patients with documented significant pleural or pericardial effusions unless thought to be secondary to leukemia.
    k) Any history of venous thromboembolism, including, but not limited to, deep venous thrombosis (DVT) or pulmonary embolism within 6 months before randomization; patients with catheter-associated DVTs or superficial vein thrombosis, which are considered to be resolved/controlled, may be included after discussion with the sponsor's medical monitor/designee.
17. Poorly controlled diabetes. Patients with preexisting, well-controlled diabetes are not excluded.
18. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of study drug, including difficulty swallowing.
19. Ongoing uncontrolled nausea or vomiting of any severity.
20. Have a significant bleeding disorder unrelated to ALL.
21. Life-threatening illness unrelated to cancer, such as severe CNS, pulmonary, renal, or hepatic disease unrelated to cancer.

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22. Female patients who are lactating or breastfeeding or have a positive serum pregnancy test during the screening period or have a positive urine pregnancy test on Day 1 before the first dose of study drug is administered
    - Patients with positive serum pregnancy test who have undergone a complete abortion in the last 60 days may be included after discussion with the sponsor's medical monitor/designee. If the serum test is positive, a repeat test is to be performed 7 to 14 days later and must be significantly lower to insure there is no active pregnancy for study eligibility.
23. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
24. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

8.0 STUDY DRUG

Investigational therapy: Ponatinib

Reference therapy: Imatinib

Backbone (reduced-intensity) chemotherapy:

- Induction phase: Three 28-day cycles of vincristine and dexamethasone.
- Consolidation phase: Six 28-day cycles of alternating cytarabine (even-numbered cycles) and methotrexate (odd-numbered cycles).
- Maintenance phase: Eleven 28-day cycles of vincristine and prednisone.

8.1 Study Drug Administration

8.1.1 Investigational Therapy: Ponatinib

Ponatinib will be supplied by the sponsor as 10 mg (oval-shaped), 15 mg, and 30 mg (round-shaped), white, film-coated tablets. All protocol-specific criteria for administration of ponatinib must be met and documented before ponatinib administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Ponatinib will be self-administered by the patient on a daily schedule at a starting dose of 30 mg by mouth (PO) QD. Each 28-day dosing period is referred to as 1 Cycle. Patients should be instructed to take the prescribed number of tablets with water, with or without food, at approximately the same time each day, continuously throughout the study, and not to take more than the prescribed dose at any time. Patients should swallow the study medication whole and not chew it or manipulate it in any way before swallowing.

Patients will be provided a diary or equivalent where the date and time of administration will be recorded; complete instructions will be provided with the site operations manual.

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Patients who forget to take their dose more than 6 hours after it is due should not make up the missed dose. Any missing doses should be recorded, and subsequent training of patients should be documented in the appropriate source record (eg, clinic chart) and in the electronic case report form (eCRF).

If severe emesis or mucositis prevents the patient from taking a ponatinib dose, that dose will be skipped. Under no circumstance should a patient repeat a dose or double-up doses.

8.1.2 Induction Phase (Cycles 1 Through 3)

The induction phase will begin on Day 1 of the study (Cycle 1 Day 1) and will comprise three 28-day cycles, including ponatinib (Cohort A; study drug; 30 mg QD), imatinib (Cohort B; active comparator; 600 mg QD), and reduced-intensity chemotherapy (Table 8.a).

Table 8.a Induction Phase Treatment (Cycles 1 Through 3)

Induction Phase Treatment (Three 28-Day Cycles) [a,b]	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV on Days 1 and 14 (capped at 2 mg)
Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14	Dexamethasone: Patients aged <60 years: 40 mg PO on Days 1-4 and Days 11-14 Patients aged ≥60 years: 20 mg PO on Days 1-4 and Days 11-14
Ponatinib [c] Starting dose: 30 mg QD, starting on Cycle 1 Day 1	Imatinib [c] Starting dose: 600 mg QD, starting on Cycle 1 Day 1

Abbreviations: IV, intravenous; PO, by mouth; QD, once daily.

Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to current local prescribing information for all other therapies included in this protocol. Alternative dose modifications/schedules may be recommended after discussion with the investigator and medical monitor/designee to maximize exposure of study treatment while protecting patient safety.

[a] Lumbar punctures will be performed to test CSF for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples), and additionally as clinically indicated.

[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.

[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

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8.1.3 Consolidation Phase (Cycles 4 Through 9)

The consolidation phase will begin after Cycle 3 of the induction phase is complete and will comprise six 28-day cycles, including ponatinib or imatinib and alternating cytarabine (even-numbered cycles) and methotrexate (odd-numbered cycles) (Table 8.b).

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Table 8.b Consolidation Phase Treatment

Consolidation Phase Treatment (Six 28-Day Cycles; Study Cycle 4-9) [a,b]	
Cohort A	**Cohort B**
Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation cycles 1st, 3rd, and 5th) Study Cycles 4, 6 and 8: – Patients aged <60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged ≥60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation cycles 2nd, 4th, and 6th) Study Cycles 5, 7 and 9: – Patients aged <60 years: 1000 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K). – Patients aged ≥60 years: 250 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (if the patient has impaired renal function, reduce the dose or consider discontinuing cytarabine).	Alternating methotrexate and cytarabine: • Methotrexate (odd consolidation cycles 1st, 3rd, and 5th) Study Cycles 4, 6 and 8: – Patients aged <60 years: 1000 mg/m^2 IV Day 1, 24-h infusion. – Patients aged ≥60 years: 250 mg/m^2 IV Day 1, 24-h infusion. – Rescue: folinic acid (see Appendix J). • Cytarabine (even consolidation cycles 2nd, 4th, and 6th) Study Cycles 5, 7 and 9: – Patients aged <60 years: 1000 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (dose adapted by CrCl; see Appendix K). – Patients aged ≥60 years: 250 mg/m^2 q12 h IV, Days 1, 3, and 5, 2-h infusion (if the patient has impaired renal function, reduce the dose or consider discontinuing cytarabine).
Ponatinib [c] Start with the last induction phase dose; modify dose based on MRD-negative CR results (see Section 8.3).	Imatinib [c] Start with the last induction phase dose.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; PO, by mouth; q, every; QD, once daily.

Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to current local prescribing information for all other therapies included in this protocol**.** Alternative dose modifications/schedules may be recommended after discussion with the investigator and medical monitor/designee to maximize exposure of study treatment while protecting patient safety.

[a] Lumbar punctures will be performed to test CSF for CNS disease on Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples), and additionally as clinically indicated.

[b] CNS prophylaxis will be administered on Day 1 and Day 14 of the first 3 consolidation phase cycles (total with the induction phase administration: 6 cycles, 12 intrathecal injections) and comprises a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center. If patients move to the maintenance phase directly from the induction phase or before completing the consolidation phase, they will still be required to receive the complete course of intrathecal CNS prophylaxis to complete the total of 12 intrathecal injections.

[c] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

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8.1.4 Maintenance Phase (Cycles 10 Through 20)

The maintenance phase will begin after Cycle 9 of the consolidation phase is complete and will comprise eleven 28-day cycles, including the following (Table 8.c):

Table 8.c Maintenance Phase Treatment

Maintenance Phase Treatment (Eleven 28-Day Cycles)	
Cohort A	**Cohort B**
Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)	Vincristine: 1.4 mg/m^2 IV injected over 1 minute on Day 1 of each maintenance phase cycle (1 injection/mo; capped at 2 mg)
Prednisone [a] Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5	Prednisone [a] Patients aged <60 years: 200 mg/d PO on Days 1-5 Patients aged ≥60-69 years: 100 mg/d PO on Days 1-5 Patients aged ≥70 years: 50 mg/d PO on Days 1-5
Ponatinib [b]: Start with the last consolidation phase dose; modify dose based on MRD-negative CR results (see Section 8.3).	Imatinib [b]: Start with the last consolidation phase dose.

Abbreviations: IV, intravenous; PO, by mouth; QD, once daily.

Administration guidelines are provided for ponatinib only in this protocol; investigators should refer to current local prescribing information for all other therapies included in this protocol. Alternative dose modifications/schedules may be recommended after discussion with the investigator and medical monitor/designee to maximize exposure of study treatment while protecting patient safety.

[a] Prednisolone can be used instead of prednisone if prednisone is not available.

[b] Ponatinib and imatinib will be dispensed to patients on Day 1 of each cycle.

8.1.5 Postcycle 20 Therapy

Patients will continue on the last maintenance phase dose (or dose modified based on MRD-negative CR results) of TKI alone until they are deceased, have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first. During this single-agent therapy phase, study drug will be dispensed at each visit (ie, every 3 months).

Patients who proceed to HSCT will be discontinued from study treatment but will be followed per the on-study data collection schedule as specified in the SOE for post-transplantation data collection, including transplant-related procedures, investigator-reported disease status (eg, relapse from CR), survival, and the use of post-transplant treatment (chemotherapy, TKI). Patients proceeding to alternative therapy will also be discontinued from study treatment but will be followed for investigator-reported disease status (eg, relapse from CR) and survival. All other patients who discontinue study treatment will be followed for survival as specified in the SOE (Table 2).

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8.2 Reference/Control Therapy: Imatinib

The active comparator in this study is imatinib, to be administered at 600 mg PO QD continuously during the study. Imatinib was chosen primarily because it is currently the most widely used standard of care throughout the world in the first-line treatment of adult patients with Ph+ ALL. The use of imatinib in combination with the reduced-intensity chemotherapy proposed in this phase 3 study is consistent with the recommended NCCN treatments for both adolescent and young adults and adult patients [4].

Patients will be provided a diary or equivalent where the date and time of administration will be recorded; complete instructions will be provided with the site operations manual.

Investigators should refer to the current local prescribing information for details on imatinib therapy.

8.3 Dose Modification Guidelines for Efficacy

8.3.1 Mandatory Dose Reduction for Response

The primary endpoint of this study will be achievement of MRD-negative CR at the end of induction (as defined in Section 13.1.3.4). Ponatinib dose reductions to 15 mg QD will be implemented in patients who achieve MRD-negative CR after completion of the induction phase. In patients who achieve CR or MRD-negative status with CRi but do not achieve the primary endpoint at the end of induction therapy and continue in the study at the investigator's discretion, ponatinib dose reductions to 15 mg QD will be implemented at any later time point when the patient achieves MRD-negative CR. No dose reductions for response will be implemented for patients in the imatinib cohort.

All patients who do not achieve CR at the end of induction will be discontinued from study treatment (both ponatinib and imatinib), after which the patient's treating physician should consider alternative therapy options.

Note: It is recommended that the mandatory dose reduction for response be implemented as soon as feasible (preferably within 2-3 weeks from the time the investigator is made aware of the response results). Unscheduled visits may be performed to implement the dose reduction.

8.3.2 Loss of Response After Dose Reduction for MRD-Negative CR

Patients in the ponatinib cohort who achieve MRD-negative status (defined in Table 13.a), undergo dose reduction, and subsequently lose MRD-negative status at a single time point, can have dose re-escalation to 30 mg upon review and agreement with the sponsor's medical monitor/designee and in the absence of AEs requiring dose modification.

8.4 Dose Modification Guidelines for Safety

Dose modification guidelines detailed in this section are for ponatinib and imatinib only. Investigators should refer to the current local prescribing information for all other therapies

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included in this study. In instances where local prescribing information is not available, the sponsor will provide dose modification guidelines to the sites.

These guidelines should be followed by clinical investigators; however, for an individual patient, dose interruptions, reductions, and treatment discontinuation and any variation from these guidelines can also be based on the clinical circumstance (eg, the investigator assesses that the potential benefit outweighs the risk of continued therapy). Variation from these guidelines should be communicated with the medical monitor/designee, ideally before implementation, and resulting agreements/investigator decisions should be recorded in source documents.

8.4.1 Ponatinib

8.4.1.1 Dose Reduction for Drug-Related Adverse Events

Dose reduction guidelines for ponatinib are summarized in Table 8.d and Table 8.e, and adverse events (AEs) should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0 [30].

Grade 4 nonhematologic toxicities (considered related to treatment) will, in general, require that treatment with study drug be permanently discontinued. If, in the opinion of the investigator and the sponsor's medical monitor or designee, it is in the patient's best interest to continue treatment with study drug, then the dose of study drug will be reduced by at least 1 dose level in subsequent cycles of treatment after recovery of the toxicity or toxicities in question to Grade 1 or to baseline values.

Dose reduction below 10 mg QD is not permitted (see Table 8.d, Table 8.e, Table 8.f, and Table 8.g). Doses may be interrupted for study drug-related toxicities for up to 28 days; longer interruptions need to be discussed with the sponsor's medical monitor/designee.

See Section 8.4.1.3 for dose re-escalation guidelines after the resolution of drug-related AEs.

Table 8.d Dose Modifications for Nonhematologic Drug-Related Adverse Events: Ponatinib

General Toxicities	Modification
Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days with optimal care	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg Discontinue ponatinib

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Table 8.d Dose Modifications for Nonhematologic Drug-Related Adverse Events: Ponatinib

Grade 3 or 4	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib
Pancreatitis and Elevation of Lipase	**Modification**
Asymptomatic Grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
Asymptomatic Grade 3 elevation of lipase (>5 × the ULN), or symptomatic Grade 3 (>2 × the ULN), or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib
Grade 4 elevation of lipase (>5 × the ULN and with signs or symptoms), or symptomatic Grade 3 pancreatitis (severe pain, vomiting, medical intervention indicated [eg, analgesia, nutritional support])	Occurrence [a] at 30 mg: Hold until complete resolution of symptoms and after recovery of lipase elevation to Grade ≤1 Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg Discontinue ponatinib
Grade 4 pancreatitis	Discontinue ponatinib
Hepatic Toxicity	**Modification**
Elevation of liver transaminase >3 × ULN (Grade 2 or higher)	Occurrence [a] at 30 mg: Hold ponatinib and monitor hepatic function until event is Grade ≤1 (≤3× the ULN) or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Elevation of AST or ALT >3× the ULN concurrent with an elevation of bilirubin >2× the ULN and ALP <2× the ULN	Discontinue ponatinib
LVEF/CHF [c]	**Modification**
Grade 1	No dose adjustment

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Table 8.d Dose Modifications for Nonhematologic Drug-Related Adverse Events: Ponatinib

Grade 2	Monitor by ECHO First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 3	Monitor by ECHO Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib
Skin Rash	**Modification**
Grade 1	No intervention
Grade 2 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib

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Table 8.d Dose Modifications for Nonhematologic Drug-Related Adverse Events: Ponatinib

Grade 3 persistent despite optimal symptomatic therapy	First occurrence at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; ECHO, echocardiogram; LVEF, left ventricular ejection fraction; ULN, upper limit of normal.

[a] "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

[b] "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

[c] For Grade 2: LVEF <50%-40%, Grade 3: LVEF <39-20%, Grade 4: refractory CHF or LVEF <20%.

Note: NCI CTCAE, version 5.0, 2018 criteria should be used to interrupt or discontinue study drug for Grades 2, 3, or 4 events considered to be study drug–related.

Table 8.e Dose Modifications for Hematologic Drug-Related Adverse Events: Ponatinib

Drug-Related ANC/Platelets	**Modification**
Grade 1 or 2	No dose adjustment
Grade 3 or 4	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib

Abbreviation: ANC, absolute neutrophil count.

NCI CTCAE, v5.0, 2018 criteria should be used to interrupt or discontinue study drug for Grades 2, 3, or 4 events considered to be study drug–related.

[a] "Occurrence" means the first time an AE is encountered by a patient at a given dose level.

[b] "Recurrence" means the second time an AE is encountered by a patient at a given dose level.

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8.4.1.2 Dose Modifications for AOEs and VTEs

AOEs and VTEs are broadly defined in Section 10.1.4. Additionally, the sponsor has a list of a broad range of nonspecific terms that could meet the criteria for AOEs and VTEs. The sponsor will periodically look at the safety data and inform the site if any AE qualifies for AOEs/VTEs as per that criteria. Dose modification guidelines presented here also apply to these sponsor-identified AOEs/VTEs.

Investigator discretion should be used to judge the event as a vascular pathology when applying these dose-modifying schemes.

8.4.1.2.1 AOEs

In patients suspected of developing any serious or clinically significant AOE requiring urgent intervention or hospitalization, ponatinib should be immediately interrupted. Ponatinib should not be re-administered to these patients with serious or clinically significant AOEs unless the investigator assesses that the potential benefit outweighs the risk of continued therapy.

Patients should be discontinued from ponatinib in the event of MI, unstable angina, CVA, TIA, or revascularization procedures. For all other AOEs, dose modification guidelines are outlined in Table 8.f.

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Table 8.f Dose Modifications for AOEs: Ponatinib

Arterial Occlusion: Cardiovascular and Cerebrovascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 3 and 4	Discontinue ponatinib.
Other Arterial Occlusions, including Peripheral Vascular Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves.
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [c] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib Any recurrence [b] at any dose level: discontinue ponatinib
Grade 4	Discontinue ponatinib

Abbreviations: AOE, arterial occlusive event; CVA, cerebrovascular accident; MI, myocardial infarction; TIA, transient ischemic attack.
Patients should be discontinued from ponatinib in the event of MI, unstable angina, CVA or TIA, or revascularization procedures.
[a] "Occurrence" means the first time an AOE is encountered by a patient at a given dose level.
[b] "Recurrence" means the second time any AOE is encountered by a patient at a given dose level, not necessarily recurrence of the same AOE.

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8.4.1.2.2 VTEs

In patients suspected of developing any serious or clinically significant VTE requiring urgent intervention or hospitalization, ponatinib should be immediately interrupted. Ponatinib should not be re-administered to these patients with serious or clinically significant VTEs unless the investigator assesses that the potential benefit outweighs the risk of continued therapy. Patients should be discontinued from study drug in the event of life-threatening pulmonary embolism or retinal vein thrombosis.

For all other VTEs, dose modification guidelines are outlined in Table 8.g.

Table 8.g Dose Modifications for Venous Thrombotic/Embolic Events: Ponatinib

Venous Thrombotic/Embolic Events	
Grade 1	Consider interruption or dose reduction of ponatinib until the event resolves
Grade 2	First occurrence [a] at any dose level: Hold until event is Grade ≤1, or has returned to baseline Resume at current dose level Recurrence [b] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Recurrence [b] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Recurrence [b] at 10 mg: Discontinue ponatinib
Grade 3	Occurrence [a] at 30 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 15 mg Occurrence [a] at 15 mg: Hold until event is Grade ≤1, or has returned to baseline Resume at 10 mg Occurrence [a] at 10 mg: Discontinue ponatinib
Grade 4	Discontinue ponatinib.

Abbreviation: VTE, venous thrombotic/embolic event.

[a] "Occurrence" means the first time a VTE is encountered by a patient at a given dose level.

[b] "Recurrence" means the second time any VTE is encountered by a patient at a given dose level, not necessarily recurrence of the same VTE.

8.4.1.3 Dose Re-Escalation after Drug-Related AEs

After dose reductions for toxicity, the dose of ponatinib can be re-escalated from the reduced dose level to the previously administered dose level if either of the following criteria is met:

- All Grade ≥2 nonhematologic toxicities have recovered to Grade ≤1 for at least 1 month, or

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- All Grade ≥3 hematologic and nonhematologic toxicities have recovered to Grade ≤2 and are manageable with supportive therapy.

Patients may receive stepwise dose escalations (eg, 10 mg QD to 15 mg QD to 30 mg QD) up to the starting dose if the above criteria continue to be met. In no circumstances should a patient receive a ponatinib dose higher than 30 mg QD.

Note: Patients with Grade ≥3 left ventricular dysfunction, CHF, or arterial occlusion are not eligible for dose re-escalation after resolution of their symptoms.

8.4.2 Imatinib

Doses of imatinib should be modified for toxicities according to standard practice and current local prescribing information. General guidelines are presented below.

8.4.2.1 Hepatotoxicity and Nonhematologic Drug-Related AEs

If patients experience bilirubin >3× the ULN or liver transaminases >5× the ULN, imatinib should be withheld until bilirubin levels have returned to <1.5× the ULN and transaminase levels to <2.5× the ULN. Treatment with imatinib may then continue at a reduced daily dose (ie, 600 to 400 mg or 400 to 300 mg if a patient experiences an adverse reaction at a daily dose of 400 mg).

If patients experience a severe nonhematologic adverse reaction (such as severe hepatotoxicity or severe fluid retention), imatinib should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event and local practice.

8.4.2.2 Hematologic Drug-Related AEs

If patients experience severe neutropenia or thrombocytopenia (ie, absolute neutrophil count [ANC] $<0.5 \times 10^9$/L and/or platelets $<10 \times 10^9$/L):

1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy)
2. If cytopenia is unrelated to leukemia, reduce imatinib dose to 400 mg
3. If cytopenia persists for 2 weeks, reduce further to 300 mg
4. If cytopenia persists for 4 weeks and is still unrelated to leukemia, stop imatinib until ANC $\geq 1\times 10^9$/L and platelets $\geq 20\times 10^9$/L, then resume treatment at 300 mg

8.4.2.3 Dose Re-Escalation after Resolution of Drug-Related AEs

The dose of imatinib can be re-escalated from the reduced dose level to the previously administrated dose level if the following criteria are met:

- All Grade ≥2 non-hematologic toxicities have recovered to Grade ≤1 for at least 1 month
- All Grade ≥3 hematologic and non-hematologic toxicities have recovered to Grade ≤2 and are manageable with supportive therapy

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Patients may receive stepwise dose escalations (eg, 300 mg QD to 400 mg QD to 600 mg QD) up to the starting dose if the above criteria continue to be met. In no circumstances should a patient receive an imatinib dose higher than 600 mg QD.

8.5 Excluded Concomitant Medications and Procedures

The following concurrent medications and treatments are prohibited:

- Other anticancer therapies (except for optional prephase treatment, protocol-defined combination treatment [Section 8.1])
- Other investigational drugs or devices
- Herbal preparations or related over-the-counter preparations containing herbal ingredients
- Elective surgery requiring inpatient care that can be postponed until study completion

The following concurrent medications should be avoided while taking ponatinib:

- Medications that are strong inhibitors or inducers of CYP3A4 should be avoided, but are not prohibited (Appendix F) in patients assigned to the ponatinib arm. Consider alternatives to strong CYP3A4 inhibitors or inducers. If coadministration of ponatinib with strong inhibitors of CYP3A4 is unavoidable, a dose reduction is recommended; the ponatinib dose is to be lowered by 1 dose level from the current dose (that is, 15 mg for a patient receiving 30 mg, or 10 mg for a patient receiving 15 mg).
- Medications with a known risk of TdP (see Appendix E):
  - Medications that are associated with the prolongation of the QT interval may interact with ponatinib and imatinib as well. Some medications associated with QT prolongation also interact with CYP3A4.
  - Medications that prolong the QT interval, but are not associated with a known risk of TdP, should be avoided, but are not prohibited. If such medications are necessary and used while a patient is on study, additional ECG monitoring should be performed as clinically indicated. Exception, if an alternative to the antiemetic agent ondansetron is not feasible and the investigator considers this the only suitable medication to manage symptoms then additional ECG monitoring should be performed and documented. Consult the medical monitor to discuss study drug discontinuation if any possible cardiac changes are noted.

Please refer to the current local prescribing information for information regarding drug interactions with imatinib and the other components of chemotherapy.

8.6 Permitted Concomitant Medications and Procedures

All treatments/therapy received within 30 days before the first dose of study drug will be recorded as prior treatments.

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All concomitant medications administered from the time of informed consent signature through the EOT visit (either the last dose of study drug or the investigator/patient decision to discontinue, whichever occurs later) are to be reported on the appropriate eCRF for each patient.

All routine and appropriate supportive care (including blood products, and hematopoietic growth factors) will be allowed during this study, as clinically indicated, and in accordance with standard-of-care practices. Clinical judgment should be exercised in the treatment of any AE experienced by an individual patient.

Information on all concomitant medications, administered blood products, and interventions occurring during the study must be recorded on each patient's eCRF. Among other treatments for concurrent illnesses, the following therapies are allowed:

- Medical or surgical treatment necessary for the patient's well-being
- Where appropriate, treatment with hematopoietic growth factors
- Antiplatelet agents and anticoagulants are permitted with caution in patients who may be at risk of bleeding events

8.7 Precautions and Restrictions

To participate in this study, female and male patients must qualify for the study per the inclusion and exclusion criteria (Section 7.1 and Section 7.2, respectively).

It is not known what effects the study therapies have on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Before starting treatment, male patients considering reproduction should be advised to seek counseling on sperm storage, and female patients considering pregnancy should be advised to seek counseling on egg storage. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment. Lactating females should be advised not to breast feed. All patients must meet the inclusion criteria for female and male patients as outlined in Section 7.1.

8.8 Management of Clinical Events

Although the study excludes patients with active hepatitis B at the time of screening, both imatinib and ponatinib have been associated with reactivation of hepatitis B. It is recommended to consult an expert in liver disease before initiating treatment of patients with evidence of prior hepatitis B infection, and monitor these patients for clinical and laboratory signs of hepatitis B virus reactivation or hepatitis during study drug treatment and for several months following treatment discontinuation.

Patients with ALL are at increased risk of tumor lysis syndrome (TLS) with cytotoxic/cytolytic therapy. In patients with ALL, those with white blood cell (WBC) count ≥100,000 are considered high risk, and those with WBC count 50,000 to 100,000 are considered intermediate risk. Pre-existing uremia or hyperuricemia, decreased urinary flow or acidic urine, dehydration,

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oliguria, anuria, and renal insufficiency or renal failure may increase the risk of TLS. Consequences of TLS include hyperphosphatemia, hyperkalemia, hypocalcemia, and uremia. Clinical manifestations of TLS may include nausea, vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death. If clinically presented, TLS should be managed according to local practice and guidelines, including prophylaxis where indicated. Guidelines on prophylaxis and management are included in Appendix L.

Refer to the current local ponatinib prescribing information for details on management of patients who have or who develop the following conditions: AOEs; VTEs; HTN; neuropathy; hepatotoxicity; CHF or left ventricular dysfunction; serious ocular toxicities; pancreatitis or lipase/amylase elevations; ocular toxicity, bleeding events; fluid retention/edema; cardiac arrhythmias; myelosuppression; tumor lysis syndrome; posterior reversible encephalopathy syndrome; compromised wound healing; or GI perforation.

Note: Monitor and manage BP elevations during the study and treat hypertension to normalize BP.

In patients with persistent elevation of cardiac troponin-I (cTnI) or N-terminal pro-brain natriuretic peptide (NT-proBNP)/B-type natriuretic peptide (BNP), performing an echocardiogram and/or consulting a cardiologist should be considered.

For all other therapies to be administered per this protocol, investigators should refer to the current local prescribing information for specific drugs for management of clinical events.

8.9 Blinding and Unblinding

This is an open-label study; patients and investigators will know the identity of each patient's study drug. However, to protect study integrity, the study team (except a few members who are included in the patient management) will be blinded to the treatment assignment for data review.

8.10 Description of Investigational Agent

8.10.1 Ponatinib

Ponatinib investigational drug product is supplied as white, oval or round, film-coated tablets for oral administration. Each tablet contains 10 mg, 15 mg, or 30 mg of active ingredient. Other ingredients are typical pharmaceutical excipients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and a tablet coating comprised of polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

8.10.2 Imatinib

Imatinib 100 mg is supplied as the following 2 formulations:

- A round, biconvex with beveled edges, film-coated tablet, scored on one side with letters S and A on each side of the score and "NVR" on the other side. The color is very dark yellow to brownish orange. Each tablet contains 100 mg of active ingredient.

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- Dark yellow to brownish-orange round film-coated tablets, embossed with "I" and "1" on both sides of the notch on one side and smooth on the other side of the tablet. The round tablets have a diameter of 7.65 mm x 0.20 mm. Each tablet contains 100 mg of active ingredient.

Imatinib 400 mg is supplied as the following 2 formulations:

- A biconvex, ovaloid film-coated tablet with beveled edges and is unscored. The color is very dark yellow to brownish orange with "glivec" on one side. Each tablet contains 400 mg of active ingredient.
- Dark yellow to brownish-orange oval film-coated tablets, embossed with "I" and "2" on both sides of the notch on one side and smooth on the other side of the tablet. The oval tablets are 15.15 mm x 0.20 mm long and 8.15 mm x 0.20 mm wide. The tablet can be divided into 2 equal doses. Each tablet contains 400 mg of active ingredient.

8.11 Preparation, Reconstitution, and Dispensation

8.11.1 Ponatinib

Ponatinib tablets should be swallowed whole with water and should not be crushed or dissolved in liquid [31].

8.11.2 Imatinib

Imatinib is dispensed as film-coated tablets, as described in the local prescribing information.

8.12 Packaging and Labeling

8.12.1 Ponatinib

Ponatinib tablets will be supplied as follows:

- 10 mg tablets: 30 count in white high-density polyethylene (HDPE) bottles with foil induction seal and cap
- 15 mg tablets: 30 count in white HDPE bottles with foil induction seal and cap
- 30 mg tablets: 30 count in white HDPE bottles with foil induction seal and cap

Bottle labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

8.12.2 Imatinib

Imatinib will either be dispensed from local supplies or provided by Takeda according to country regulatory requirements. If provided by Takeda, imatinib will be supplied as 100 mg and 400 mg film-coated tablets in appropriate packaging.

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8.13 Storage, Handling, and Accountability

8.13.1 Storage

Ponatinib and imatinib should be stored as described on the study drug labels.

8.13.2 Handling and Accountability

8.13.2.1 Ponatinib

The study pharmacist or designee at the investigative site will be responsible for handling and dispensing study drug and completing associated documentary paperwork.

Ponatinib supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. Supply shipping will be managed by interactive response technology (IRT). The site must use either an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute. Each time study medication is dispensed for a patient, the following information is recommended to be recorded: the patient's study number, tablet strength, the number of tablets dispensed (with the corresponding lot number), and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study (or as per local legal requirements), and will be periodically verified by a representative of the sponsor. The investigator is responsible for ensuring that the patient diary and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

In the event that a patient cannot visit the site to obtain the study drug due to unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic, sites should contact the sponsor's medical monitor/designee to arrange for an alternate mechanism (eg, direct-to-patient [DTP] shipping).

8.13.2.2 Imatinib

The study pharmacist or designee at the investigative site will be responsible for handling and dispensing study drug and completing associated documentary paperwork.

The site must use either an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute. Each time study medication is dispensed for a patient, the following information is recommended to be recorded: the patient's study number, tablet strength, the number of tablets dispensed (with the corresponding lot number), and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study (or as per local legal requirements), and will be periodically verified by a representative of the sponsor. The investigator is responsible for ensuring that the patient diary and study drug provided to the patient and returned from the patient are accounted for and noted in source documentation.

In the event that a patient cannot visit the site to obtain the study drug due to unavoidable circumstances such as the COVID-19 pandemic, sites should contact the sponsor's medical monitor/designee to arrange for an alternate mechanism (eg, DTP shipping).

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8.13.3 Disposition of Used and Unused Study Drug

No other use of ponatinib in this study is authorized by the sponsor. The principal investigator or designee will be responsible for the appropriate handling and disposition of residual study drug.

During the study and at termination, patients must return all unused study drug supplies and the return of these unused study drug supplies must be recorded. Returned supplies must not be redispensed.

Periodically throughout and at the conclusion of the study, a representative of the sponsor will conduct an inventory of unused study drug. At the completion of the study, a final study drug accountability review will be conducted, and any discrepancies must be investigated. All used and unused bottles or packs of study drug must be destroyed in an appropriate manner according to the standard practice at each study center (ie, destroyed at the site or returned to the local distribution center). Destruction of such supplies will be documented, and a representative of the sponsor will verify disposition records.

8.14 Other Protocol-Specified Materials

No other drugs or ancillary material are supplied for use in this study, unless otherwise required by national local law or regulations.

9.0 STUDY CONDUCT

This study will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the sponsor's medical monitor/designee for this study, the central laboratories, the coordinating investigator, and any other vendors may be found in the site operations manual. For 24-hour contact information, please refer to the site operations manual or equivalent.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC) and Takeda (or designee).

It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

9.3 Treatment Group Assignments

The randomization scheme will be generated by an independent statistician at Takeda. Prior to dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by IRT.

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9.4 Study Procedures

Refer to the SOE (Appendix A, Table 1 and Table 2) for timing of assessments. Additional details are provided as necessary in the sections that follow and in the SOE footnotes.

Tests and procedures should be performed on schedule, but occasional changes may be allowed for holidays, vacation, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure collection of assessment is completed before dosing.

9.4.1 Screening Period Procedures

Screening tests and procedures are used to establish eligibility of the patient for the study. If any given procedure or laboratory test is repeated before randomization, patients must continue to maintain laboratory values within eligibility parameters. Any patient who is re-screened after screen failure must, in addition to the failed test, repeat only those screening tests that have fallen outside the specified screening period, as outlined in the SOE (Appendix A, Table 1). See Appendix A, Table 1 for all screening procedures.

9.4.2 Informed Consent

Each patient must provide written informed consent by signing and dating an IRB/IEC-approved informed consent form (ICF) before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Adequate time must be allowed for questions and for the patient to make a voluntary decision.

9.4.3 Enrollment and Randomization

Enrollment is defined as randomization to a treatment cohort. See Appendix A, Table 1 for enrollment procedures. Specific instructions for randomization will be supplied in the site operations manual. Randomization procedures should be performed following complete eligibility assessments and just before the initiation of the assigned dose cohort.

Patients will be randomized in a 2:1 ratio to receive oral ponatinib or imatinib (Cohort A and Cohort B, respectively) QD throughout the study. Study drug administration is detailed in Section 8.1. Each cycle of therapy will comprise 28 days of treatment, regardless of dose.

This study is open-label; patients and investigators will know the identity of each patient's study drug. However, to protect study integrity, the study team (except a few members who are included in the patient management) will be blinded to the treatment assignment for data review.

9.4.4 Medical/Surgical History and Demographics

During the screening period, demographic data and a complete medical and surgical history will be compiled for each patient. Details of the data to be collected are specified in the SOE footnotes (Appendix A, Table 1).

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9.4.5 Initial Leukemia Diagnosis

The initial leukemia diagnosis must be recorded during the screening period. Only patients who are newly diagnosed with Ph+ ALL or BCR-ABL1-positive ALL are eligible for this study.

9.4.6 Pregnancy Test

The screening pregnancy test must be a serum beta-human chorionic gonadotropin test and must be performed as specified in the SOE (Appendix A, Table 1). Monthly urine pregnancy testing will be performed during the study (through the first 20 cycles); from that point forward, urine pregnancy tests will be performed at quarterly patient visits (serum pregnancy test may be instead performed at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations) (Appendix A, Table 1 and Table 2). Additional pregnancy testing may be performed at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

9.4.7 Physical Examination and ECOG Performance Status

Complete physical examinations (including weight) will be completed as specified in the SOE (Appendix A, Table 1 and Table 2). Sites should calculate body surface area (BSA) from the weight and height measured at baseline as specified in the SOE (Appendix A, Table 1) and the additional weight assessments will be documented in the eCRF without the need to calculate the BSA. Height will be measured at screening only.

The ECOG performance status should be evaluated during each complete physical examination, as specified in the SOE (Appendix A, Table 1 and Table 2). Patients must have an ECOG performance status ≤2 to be eligible for this study. Additional details on assessing ECOG status are provided in the site operations manual.

9.4.8 Eye Examinations

A detailed eye history and eye examinations must be performed as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.9 Vital Signs

Vital sign measurements will include systolic and diastolic BP, heart rate, respiratory rate, and body temperature. Vital sign measurements will be assessed as specified in the SOE (Appendix A, Table 1 and Table 2) and the SOE footnotes.

9.4.10 CV Risk Assessments

9.4.10.1 Framingham Score

The Framingham risk score (Appendix G) estimates the risk of various CV disease outcomes, and will be performed as specified in the SOE (Appendix A, Table 1 and Table 2). Details of assessing the Framingham risk scores are provided in the site operations manual.

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9.4.10.2 Ankle-Brachial Index

An assessment of the ankle-brachial index (ABI) will be performed to assess patients for the risk of peripheral arterial disease, as specified in the SOE (Appendix A, Table 1 and Table 2). Additional details on assessing the ABI are provided in the site operations manual.

9.4.10.3 12-Lead ECG

All ECGs must be 12-lead ECGs, performed as specified in the SOE (Appendix A, Table 1 and Table 2). If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

If the timing of a PK blood sample or other blood draw coincides with the timing of an ECG, the ECG should be performed first, followed by the blood draw.

9.4.11 Echocardiogram

An echocardiogram for assessment of LVEF must be performed as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.12 Prior and Concomitant Medications and Procedures

All medications/therapies and therapeutic procedures used/completed by the patient within 30 days before the first dose of study drug will be recorded as prior medication in the eCRF. All medications/therapies and therapeutic procedures used/completed by the patients from the signing of the ICF until the EOT visit (30 days after the last dose) will be recorded in the eCRF as concomitant medications, as specified in the SOE (Appendix A, Table 1 and Table 2). See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited and/or allowed during the study.

9.4.13 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study, starting on the date of signed ICF, and continuing until the 30-day EOT visit, as specified in the SOE (Appendix A, Table 1 and Table 2). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

It is expected that new and updated AEs and concomitant medications will be reported within the treatment period; ongoing AEs thought to be at least possibly study drug–related; and all ongoing SAEs should be followed at least every 4 weeks until they resolve to baseline (or to NCI CTCAE, version 5.0, Grade ≤1), stabilize, or are considered to be chronic/irreversible.

9.4.14 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed as specified in the SOE (Appendix A, Table 1 and Table 2). Laboratory test results should be assessed before dosing. Handling and shipment of clinical laboratory samples will be outlined in the laboratory manual.

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9.4.14.1 Hematology

Blood samples for complete blood count with differential will be obtained as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

9.4.14.2 Serum Analysis

a) **Chemistry**
The full chemistry panel must be obtained as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

If CrCl is to be estimated, the Cockcroft-Gault formula will be employed as follows:

Estimated CrCl = [(140 - Age) * weight (kg)] / [72 * serum creatinine (mg/dL)]
For female patients, the result of the formula above should be multiplied by 0.85.

b) **Fasting Glucose, Cholesterol, Lipids, and Glycosylated Hemoglobin (HbA1c)**
Fasting glucose, glycosylated hemoglobin (HbA1c), and serum lipid panel (total, high-density lipoprotein, and low-density lipoprotein), including triglycerides, must be collected during screening and at subsequent time as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

c) **C-Reactive Protein, cTnI, and NT-proBNP or BNP**
C-reactive protein, cTnI, and NT-proBNP or BNP assessments must be performed as specified in the SOE (Appendix A, Table 1 and Table 2), or more frequently as clinically indicated.

d) **Hepatitis B Serology**
At the time of screening and during the study if clinically indicated, blood serum must be tested for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum, as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.15 Disease Assessment

9.4.15.1 BM Aspirate

BM samples needed to assess the MRD-negative CR rate at the end of induction and other efficacy endpoints will be collected as specified in the SOE (Appendix A, Table 1 and Table 2). The optimal sample for MRD assessment is the first pull or early pull of the BM aspirate. Additional details regarding handling, shipping, and analysis of BM aspirates are provided in the laboratory manual.

Note: The BM aspirate on Cycle 3 Day 1 is only required in patients who have not achieved CR at Cycle 2 Day 1 (see Table 13.a for the definition of CR). Patients who achieve CR but do not achieve MRD-negative status or who achieve MRD-negative status with CRi at the end of induction (ie, end of Cycle 3) may continue on study treatment at the investigator's discretion.

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All other patients will be discontinued from the study drug. For all discontinued patients, the patient's treating physician should consider alternative therapy options.

Quantitative assessment of BCR-ABL1/ABL1 levels will be performed by a central molecular diagnostics laboratory, and the results will be reported to the participating investigator. For patients with the p190 BCR-ABL1 variant, the absolute ratio of BCR-ABL1 to ABL1 transcripts will be reported. For patients with the p210 BCR-ABL1 variant, the ratio of BCR-ABL1 to ABL1 transcripts will be reported on the IS (see Table 13.a for the definition of MRD negativity).

While BM samples will be sent to a central laboratory for molecular assessment, a portion of the BM aspirate sample will also be sent to a local laboratory for CR and relapse from CR assessments. A portion of the BM aspirate sample may also be used for exploratory biomarker assessments as described in Section 9.4.15.2.

BM aspirates may be performed at other times when clinically indicated. Results from the local laboratory testing of any BM aspirate, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

9.4.15.2 Peripheral Blood Samples for Molecular Response, CR and Exploratory Biomarker Assessments

Peripheral blood samples needed to assess molecular response and exploratory biomarkers will be collected as specified in the SOE (Appendix A, Table 1 and Table 2). Details of handling, shipping, and analysis of peripheral blood samples are provided in the laboratory manual.

Quantitative assessment of BCR-ABL1 levels (ie, molecular response assessments) will be performed by a central molecular diagnostics laboratory, and the results will be reported to the participating investigator. For patients with the p190 BCR-ABL1 variant, the absolute ratio of BCR-ABL1 to ABL1 transcripts will be reported. For patients with the p210 BCR-ABL1 variant, the ratio of BCR-ABL1 to ABL1 transcripts will be reported on the IS.

Peripheral blood samples will also be collected for local laboratory CR and relapse from CR assessments, and results from the local laboratory testing, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

Exploratory biomarker assessments will include analysis of molecular determinants of response or resistance to ponatinib and imatinib, including those present at the initiation of study drug or those that develop during study treatment. Exploratory biomarker assessments could also include analysis of biomarkers affecting ponatinib efficacy or safety. This testing will include, but may not be limited to, analysis of BCR-ABL1 mutation status.

9.4.15.3 Extramedullary Disease

Extramedullary disease assessments will be performed locally as clinically indicated and will include lumbar punctures to test cerebrospinal fluid (CSF) for CNS disease as specified in the SOEs (Appendix A, Table 1 and Table 2). Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should

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be performed as clinically indicated throughout the study. Results from local laboratory testing, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

9.4.16 Quality of Life and Health Outcomes Measures

Both the EQ-5D-5L and the FACT-Leu forms are validated and self-administered forms. The EQ-5D-5L is a general questionnaire of health-related quality of life (HRQOL) issues, developed by the EuroQOL Group. The FACT-Leu questionnaire was developed specifically for patients with leukemia by the Functional Assessment of Chronic Illness Therapy Measurement System (www.facit.org) which manages administration, scoring, and interpretation of questionnaires that measure HRQOL for people with chronic illnesses. Patients for whom a validated translation exists in a language in which they are fluent will complete the EQ-5D-5L and the FACT-Leu during study visits, as specified in the SOE (Appendix A, Table 1 and Table 2) [32-35]. Details on administration of the EQ-5D-5L are provided in the site operations manual.

9.4.17 Medical Resource Utilization Data Collection

All medical care encounters will be collected for all patients until study closure, as specified in the SOE (Appendix A, Table 1 and Table 2).

9.4.18 PK Measurements: Ponatinib

Blood samples for plasma PK assessments will be collected as specified in the SOE (Appendix A, Table 1 and Table 2) in patients assigned to the ponatinib cohort. Details on sample collection times are provided in the SOE footnotes. Details of collection and handling of plasma PK samples are provided in the laboratory manual. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples should be recorded in the eCRF.

9.4.19 Changes to Study Procedures Due to COVID-19 Pandemic

The following information provides guidance regarding changes to the study procedures that could be implemented for study participants or study sites which are affected by the COVID-19 pandemic. This guidance takes references from the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency - Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, updated 02 July 2020, and the EMA Guidance on the Management of Clinical Trials During the COVID 19 (Coronavirus) Pandemic, Version 3 (28 April 2020).

As the COVID-19 pandemic may peak in different regions at different times and restrictions implemented by local laws and recommendations may vary, any decision on procedural changes should be made on a case-by-case basis by the investigator in consultation with the study team and the medical team sponsor's medical monitor/designee as needed, while maintaining patient safety and confidentiality as the priority.

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Procedural changes due to COVID-19 may include the following:

- Informed Consent Procedure: If necessary, informed consent from a potential or current study participant may be obtained via alternate methods, including but not limited to, electronic informed consent (eIC), remote consenting process, or an electronic face-to-face consent interview (if approved by IRB/IEC) when these individuals are unable to travel to the site.
- During the first 20 cycles of treatment (induction, consolidation, and maintenance phases), it is expected that the patient will visit the site at least once per cycle for chemotherapy drug administration (as they are administered intravenously) and/or bone marrow aspiration or any other procedures critical for patient management. Other visits may be conducted at the clinic or by home health care visits to extend flexibility to patients during the COVID-19 pandemic. The data collected from home health care visits may be handled differently in the final data analysis, with this documented in the statistical analysis plan (SAP).
- All attempts should be made to perform the assessments with the patient present at the site. However, in cases where patient's visit to the site is not feasible (patient cannot travel to the site or in cases where the investigator believes that is best for patient's and site staff's safety not to visit to the site), alternative evaluation such as local laboratories and/or telehealth (the ability to connect a physician to a patient)/telemedicine (remote clinical assessments) or home health care (performing some assessments in a patient's home by a qualified health care professional) will be allowed if permitted by local laws and regulations.
  - For home health care visits, collection of clinical laboratory samples (blood specimen collection or other diagnostic tests) may be performed by the investigator or qualified health care professional who can visit the study participant's residence.
  - ECG procedures: For home health care visits, ECGs may be performed by a qualified health care professional who is authorized/certified to perform such tests routinely.
  - Remote visits via virtual communications (eg, telehealth application) may be performed as a safety check on patient well-being.
- Deviations from the protocol-specified procedures (eg, not collecting a protocol-specified specimen, such as postdose bloodwork) will be recorded as related to COVID-19.
- Allow the use of alternate means to capture patient-reported outcomes/quality-of-life data (eg, a paper-based or web-based questionnaire) as a back-up only if these data cannot be captured on tablet devices at site.
- Allow transfer of study participants to investigational sites away from risk zones or closer to their home to sites already participating in the study or new ones.
- Alternate study drug delivery mechanisms, eg, dispensing additional study drug at clinic visits or DTP delivery of the study drug from the investigational site to patients in compliance with national laws or temporary national emergency measures and Takeda processes (Section 8.13.2 Handling and Accountability).

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9.5 Completion of Study Treatment (for Individual Patients)

All patients will be considered to have completed study treatment when they are deceased, have failed to achieve the primary endpoint at the end of induction (patients who do not achieve the primary endpoint may remain on study treatment, at the investigator's discretion, if they have achieved CR or MRD-negative status with CRi at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

9.6 Completion of Study (for Individual Patients)

The study will be completed for individual patients when death occurs, or the study has been terminated by the sponsor.

9.7 Discontinuation of Treatment With Study Drug and Patient Replacement

Discontinuation of treatment with study drug is to be reviewed and confirmed by the sponsor's medical monitor or designee.

Study drug must be discontinued immediately for patients who become pregnant.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- Failure to achieve CR
- Failure to achieve MRD-negative
- Progressive disease
- Relapse from CR
- HSCT
- Other

Patients who discontinue study drug will not be replaced.

Once study drug has been permanently discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Table 2). The primary reason for study drug discontinuation will be recorded on the eCRF. Investigators should refer to the current local prescribing information for details on criteria for discontinuing imatinib therapy. Regardless of

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the duration of treatment, all patients will remain on study for follow-up as described in Section 9.10.

9.8 Withdrawal of Patients From Study

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or sponsor by the terminating party.

A patient may be withdrawn from the study for any of the following reasons; the reason for withdrawal from the study must be documented in the eCRF:

- Death
- Study terminated by sponsor
- Withdrawal by patient
- Lost to follow-up
- Other

9.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing. (See also Section 8.13.2 and Section 8.13.3.) Patients will be provided a diary or equivalent where the date and time of ponatinib and imatinib administration will be recorded; complete instructions will be provided with the site operations manual.

9.10 Post-treatment Follow-Up Assessments

Patients who stop study treatment due to failure to achieve the primary endpoint (patients who do not achieve the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR or MRD-negative status with CRi at the end of induction), withdrawal of informed consent, having relapse from CR or having progressive disease, proceeding to HSCT or alternative therapy, or until the patient's death will be followed for OS. Survival data will be collected every 3 months ±14 days, starting after the last dose of study drug or the investigator/patient decision to discontinue treatment (whichever occurs later).

All patients who discontinue study treatment will be followed for survival as specified in the SOE (Table 2). Patients who discontinue study treatment without relapse from CR, will be followed for investigator-reported disease status (eg, relapse from CR) and survival, and reporting of alternative therapies, wherever available. Date of relapse to be reported and noted in source documentation. Patients who discontinue study treatment due to HSCT will be followed per the on-study data collection schedule as specified in the SOE for posttransplantation data collection, including transplant-related procedures, investigator-reported disease status (eg,

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relapse from CR), survival, and the use of post-transplant treatment (chemotherapy, TKI). Patients who proceed to alternative therapy will also be discontinued from study treatment and will be followed for investigator-reported disease status (eg, relapse from CR) and survival.

Survival, HSCT, and the start of alternative therapy data may be collected by methods that include, but are not limited to, telephone, email, mail, and retrieval from online social security indexes and other public records as permitted by local regulations. The EOS eCRF page is to be completed at the time the patient discontinues from the survival follow-up period. See the SOE for appropriate assessments during follow-up.

Note: Related SAEs occurring during the posttreatment period must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to study drug that occur during the post-treatment follow-up period. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

Pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

Adverse event means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

Serious adverse event means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).

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- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, 2018 [30]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grades 3 or 4), because the terms *serious* and *severe* are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grades 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.1.4 AEs of Special Interest Definitions

AOEs and VTEs have been identified as AEs of special interest (AESIs) for ponatinib. These include serious or nonserious arterial and venous thrombotic and occlusive AEs.

The sponsor has determined that the events in the following list should be considered AESIs:

- MI: The Third Universal Definition of Myocardial Infarction [36] is to define MI. Acute MI is used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Any one of the following:
  - A rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following:
    - Symptoms of ischemia.

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- New or presumed new significant ST-segment T-wave changes or new left bundle branch block (LBBB).
- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

– Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained or would be increased.

– Percutaneous coronary intervention-related MI was arbitrarily defined by elevation of cTn values (>5 × 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values were elevated and were stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic ECG changes, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality were required.

– Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the 99th percentile URL.

– Coronary artery bypass grafting-related MI was arbitrarily defined by elevation of cardiac biomarker values (>10 × 99th percentile URL) in patients with normal baseline cTn values (<99th percentile URL). In addition, either (1) new pathological Q waves or new LBBB, (2) angiographic documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- Angina (newly diagnosed or worsening of existing or unstable angina).
- CAD (newly diagnosed or worsening of existing CAD) or symptoms that may reflect CV disease [36].
- Cerebrovascular ischemic disease, including ischemic or hemorrhagic stroke, vascular stenosis, TIA, cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease [37].
- New onset or worsening of peripheral artery occlusive disease (eg, of the renal artery, mesenteric artery, or femoral artery) or symptoms that may reflect peripheral vascular disease.
- Retinal vascular thrombosis, both venous and arterial.

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- Venous thromboembolism that could result in significant compromise of organ function or other significant consequences (eg, pulmonary embolism, portal vein thrombosis, or renal vein thrombosis), or symptoms that may reflect venous thrombosis.
- Additionally, the sponsor has a list of a broad range of nonspecific terms that could meet the criteria for AOEs and VTEs. The sponsor will periodically look at the safety data and inform the site if any AE qualifies for AOEs/VTEs as per that criteria. Dose modification guidelines for AOEs/VTEs are presented in Section 8.4.1.2.
  - AOEs and VTEs will be documented in both cohorts for comparison.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, SAEs must be reported by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event. Reporting details and contact information are provided in the site operations manual.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up electronic data capture (EDC) SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any laboratory abnormality, will be determined using the NCI CTCAE, version 5.0, 2018 [30]. The criteria are provided in the site operations manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: Is there a reasonable possibility that the AE is associated with the study drug?

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10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the signing of the ICF through 30 days after administration of the last dose of study drug and recorded in the eCRFs. AEs should be monitored until they are resolved or return to baseline or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es); the exception is peripheral neuropathy, which will be followed monthly until (1) resolution of peripheral neuropathy, (2) the start of a second-line alternative antineoplastic treatment, or (3) 6 months after PD has occurred, whichever occurs first.
- SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of informed consent through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved, return to baseline, or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female study participant or a female partner of a male study participant becomes pregnant or suspects that she is pregnant during this study, the sponsor must be contacted immediately. Reporting details and contact information are provided in the site operations manual.

Study drug must be discontinued immediately for patients who become pregnant (see Section 9.7).

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided in the pharmacy manual for ponatinib and imatinib (refer to local guidelines or labeling instructions for backbone chemotherapy agents).

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided in the pharmacy manual for ponatinib and imatinib (refer to local guidelines or labeling instructions for backbone chemotherapy agents).

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, the SAE should be reported. Medication errors should also be documented accurately in the patient diary.

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10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the study. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Steering Committee

The steering committee will comprise medical experts involved in the study, the sponsor, and an independent statistician. The steering committee will remain blinded to treatment assignments throughout the conduct of the study. The steering committee will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality, and making any necessary modifications to the protocol. The Steering Committee Charter will define the responsibilities of the committee.

11.2 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) supported by an independent statistician will review safety and efficacy data at the planned primary analysis and at regular intervals outlined in the charter and make recommendations on study conduct if needed. The IDMC will review the outcomes at the interim and final analyses for MRD-negative CR, EFS, and the futility analysis for OS.

The IDMC will provide a recommendation regarding study continuation based on the safety and efficacy parameters. If the study is terminated early based on the IDMC recommendation, Takeda will notify the appropriate regulatory authorities. In addition, the IDMC will periodically review safety data at regularly scheduled meetings prespecified in the IDMC charter.

Study accrual will not be interrupted because of the scheduled safety reviews. The IDMC or study team may request an ad hoc meeting for any reason, including a significant unexpected safety event, follow-up of an observation during a planned IDMC meeting, or a report external to the study, such as publication of study results from a competing product. At each review, patient incidence rates of AEs (including all SAEs, treatment-related AEs, serious treatment-related events, and events requiring the discontinuation of study drug) will be tabulated by System

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Organ Class (SOC), Preferred Term, and severity grade. Listings and/or narratives of on-study deaths and other serious and significant AEs, including any early withdrawals because of AEs, will be provided. Records of all meetings will be archived. The IDMC will communicate major safety concerns and recommendations regarding study modification or termination to Takeda.

Details of the IDMC will be captured in a charter before the start of the study. Further details will be provided in the IDMC charter.

11.3 Cardiovascular Endpoint Adjudication Committee

The cardiovascular endpoint adjudication committee (CVEAC) will comprise independent experts with experience and training appropriate for reviews of the CV AOE and VTE endpoints. They will review all CV events defined as AOEs and VTEs reported by the sites (ie, initial diagnoses, laboratory values, results of procedures, hospital discharge summaries) to determine the occurrence of CV endpoints. The adjudication of these events will be performed based on the CVEAC adjudication charter, which will document details for performing adjudication, to be written before the start of the study. The CVEAC's assessment of each potential CV endpoint will be documented and will be used in the endpoint analysis. The process will be coordinated by the contract research organization (CRO), and the CVEAC charter will define the endpoints and the responsibilities of the committee.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the patient's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The following procedure applies to all countries except for Japan (Section 12.2.1). The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated ICFs, patient authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, ICH E6 Guideline, Section 4.9.5, requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

12.2.1 Japan Record Retention

The following procedure applies to Japanese sites only.

The investigator and the head of the institution agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating patients, medical records, temporary media such as thermal-sensitive paper, source worksheets, all original signed and dated informed consent forms, patient authorization forms regarding the use of personal health information (if separate from the informed consent forms), copies of all paper CRFs and query responses/electronic copy of eCRFs, including the audit trail, and detailed records of drug

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disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal-sensitive paper should be photocopied by the site and filed with the original in the patient's chart to ensure long-term legibility. Furthermore, International Council for Harmonisation (ICH) E6 Section 4.9.5 requires the investigator and the head of the institution to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and/or the head of the institution and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

Further details regarding the definition of analysis variables and analysis methodology to address all study objectives will be provided in the SAP.

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided CIs for time-to-event data. In case survival distributions cannot be summarized appropriately, alternative approaches will be defined in the SAP.

The SAP will be written by Takeda and will be finalized before the planned interim analysis (IA). Deviations from the statistical analyses outlined in this protocol will be indicated in the SAP; the sensitivity analyses and the imputation rules of missing data due to COVID-19 pandemic will also be specified in the SAP; any further modifications will be noted in the final CSR.

13.1.1 Analysis Sets

13.1.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

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13.1.1.2 Per-Protocol Population

The per-protocol (PP) population is a subset of the ITT population. The PP population consists of all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the sponsor's medical monitor/designee. All decisions to exclude patients from the PP population will be made before the database lock for the analyses.

The PP population will be used as a sensitivity analysis of the ITT population for the efficacy endpoints as needed if more than 5% of patients are excluded from this analysis.

13.1.1.3 Safety Population

The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, those patients who are randomized to the active arm but received the regimen in the control arm will be included in the control arm; those patients who are randomized to the control arm but received the regimen in the active arm will be included in the active arm for safety analyses.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions and summary statistics based on the ITT population for each treatment cohort and for all patients combined.

13.1.3 Efficacy Analysis

The standard *closed* sequential testing procedure will be used for testing the selected efficacy endpoints with the following testing order:

1. MRD-negative CR rate will be tested at the IA or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method [38]) using the group sequential testing approach. At the IA, alpha = 0.022 with an efficacy boundary of 0.022 given that 116 patients have been observed, and at the FA, alpha = 0.028 with an efficacy boundary of 0.036 if the number of patients is 230 [39].
2. EFS will be tested at the IA or FA at the significance level determined by the Gamma Family (-1) alpha spending function using group sequential testing approach [40]. At the IA, alpha = 0.033 with an efficacy boundary of 0.033, and the FA, alpha = 0.017 with an efficacy boundary of 0.034 for EFS if the observed number of events at the IA and FA are 130 and 173, respectively. If the efficacy boundary is crossed at either the IA or FA for EFS, the following endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA) [41]:
   a) Duration of CR
   b) Duration of MRD-negative CR
   c) ORR
   d) OS

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Therefore, the overall type I error rate for these 2 endpoints is strongly controlled at a 2-sided 0.05 alpha level.

The boundaries for hypothesis testing for MRD-negative CR and EFS will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

All other efficacy endpoints, if tested, will be at a 2-sided alpha level of 0.05.

For MRD-negative CR, the analysis will be based on the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210. Other efficacy analyses will be conducted in the ITT population, unless otherwise specified.

MRD negativity will be based on the central laboratory results, and CR status will be based on the investigator's assessment Table 13.a. See the SOE (Appendix A, Table 1 and Table 2) for details.

13.1.3.1 Primary Efficacy Endpoint Assessment

The primary endpoint is defined as achievement of MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 13.a for endpoint definitions). The analysis of the primary efficacy endpoint will test for differences comparing the proportion of patients who achieve the primary endpoint at the end of induction in the ponatinib arm versus the imatinib arm.

There will be one IA and possibly an FA in the study for the primary endpoint of MRD-negative CR in the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210.

The IA is planned to be performed after the end of induction phase data have been collected for 115 patients. The power is approximately 82% at the IA with 115 patients enrolled (2-sided alpha=0.021) corresponding to a minimal detectable effect size of 22% (48% and 26% MRD-negative CR rates for the active and control arms, respectively).

If the MRD-negative CR does not achieve the significance boundary at the IA, the study will continue and the FA will be triggered after the end of induction phase data have been collected for approximately 230 patients. The significance boundary at the FA with 230 patients enrolled would be 0.036 (2-sided) using a group sequential testing approach, which corresponds to a minimal detectable effect size of 14% (48% and 34% MRD-negative CR rates for the active and control arms, respectively).

The primary analysis for MRD-negative CR will be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square p-value and the relative risk along with its 95% 2-sided CI will be provided.

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Sensitivity analyses for the primary endpoint may be performed, including:

1. MRD-negative CR will be analyzed in the PP population if more than 5% of patients are excluded from this analysis
2. MRD-negative CR will be analyzed with nonmissing observed cases

Subgroup analyses will be performed for the primary endpoint relative to the baseline randomization stratification factor (age); demographic data, such as sex and race; and disease characteristics, as appropriate.

Further details on the analyses of primary endpoint will be discussed in the SAP.

13.1.3.2 Key Secondary Efficacy Endpoint Assessment

The key secondary endpoint is EFS, defined as the date of randomization until:

- Death due to any cause
- Failure to achieve CR by the end of induction
- Relapse from CR

EFS will be tested only if the primary endpoint comparison achieves statistical significance at the IA or FA for MRD-negative CR. EFS endpoint will be tested at the 5% level at IA or FA for EFS, per the closed sequential testing procedure, to maintain the family-wise type I error rate at 5% level.

One IA and one FA will be planned for EFS. When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The FA will be performed when approximately 173 EFS events have been observed. The test significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary of 0.033 at IA. The final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

The power for the EFS analysis is estimated based on 3-year EFS data observed from various phase 2 studies [12,28]. The primary analysis for EFS will be based on time-to-event analysis. Since it is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT, the number of events needed for EFS analysis may change depending on how HSCT cases are handled in the EFS. The primary analysis of EFS will not consider censoring at the time of HSCT or initiation of alternative therapy. Other analysis methods will also be considered and specified in the SAP.

Sensitivity analyses for EFS may be considered, including:

1. EFS will be analyzed in the PP population if more than 5% of patients are excluded from this analysis

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2. A different approach will be used in dealing with HSCT cases from the one used in the primary analysis for the EFS endpoint
3. Inverse Probability of Censoring Weighted analysis of EFS will be used, adjusting for possible confounding caused by informative censoring from imbalance in the proportion of HSCT between the 2 cohorts

Subgroup analyses will be performed for EFS relative to the baseline randomization stratification factor age; demographic data, such as sex and race; and disease characteristics, as appropriate.

Further details on the key secondary endpoint analyses will be discussed in the SAP.

13.1.3.3 Other Secondary Efficacy Endpoint Assessments

The following other secondary endpoints will be analyzed (see Table 13.a for endpoint definitions):

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier)
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5), at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier)
- Rates of PIF and ORR at the end of induction
- Rates of MRD-negative CR at multiple intervals after the end of induction
- Duration of MRD-negative CR
- Duration of CR
- Time to treatment failure
- Duration of MR4.5 in patients who achieved MR4.5
- OS and rate of relapse from CR for on-study patients with and without HSCT
- OS

If the efficacy boundary is crossed at either IA or FA for EFS, the following secondary endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA):

a) Duration of CR

b) Duration of MRD-negative CR

c) ORR

d) OS

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The remaining secondary efficacy endpoints may be tested at $\alpha = 0.05$ level in a nonhierarchical fashion without adjustments for multiplicity, as appropriate.

For analysis of time-to-event endpoints (eg, time to treatment failure, OS), 2-sided, stratified log-rank tests will be used to compare the treatment groups with respect to the endpoints. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio (HR) and its 95% CIs for the treatment effect using the stratification factor. K-M survival curves and K-M medians (if appropriate and estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

For the secondary endpoint of OS, a futility analysis with be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

OS results are expected to be confounded by alternative therapies after patients discontinue from the study assigned drug. Thus, sensitivity analyses will be outlined in the SAP for OS analysis adjusting for time depending on confounding factors occurring due to taking alternative therapies. In addition, a post-transplantation competing risk analysis for disease-related and non-relapse mortality will be conducted and details of this analysis will be outlined in the SAP.

The primary analysis for duration of MRD-negative CR will be based on time-to-event analysis. The primary analysis for duration MRD-negative CR will not consider censoring at the time of HSCT or alternative therapies. Sensitivity analyses handling censoring for HSCT or alternative therapies may be considered and will be specified in the SAP.

The proportion-based other secondary endpoints (eg, CR, and CRi rates) will be analyzed in the same fashion as the primary endpoint. The CMH chi-square p-value and the relative risk, along with its 95% 2-sided CI, will be provided.

Further details on the analyses of other secondary endpoints will be discussed in the SAP.

13.1.3.4 Definitions of Response Criteria

Definitions of response criteria for the purpose of efficacy analyses are provided in Table 13.a.

Table 13.a Definitions of Efficacy Response Criteria

Term	Definition
CNS-1	CNS-1: No lymphoblasts in the CSF regardless of WBC count.
CNS-2	WBC count <5 leukocytes/µl in the CSF with the presence of blasts.
CNS-3 a	WBC count of ≥5 leukocytes/µl with the presence of blasts.
CNS disease remission	No lymphoblasts in CSF regardless of WBC count in a patient with CNS-2 or CNS-3 at diagnosis.
CNS relapse	Development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).

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Table 13.a Definitions of Efficacy Response Criteria

Term	Definition
CR	Complete remission; meeting all the following for at least 4 weeks (ie, no recurrence): • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass). • ANC >1000/µl (or >1.0 × 10^9/L). • Platelets >100,000/µl (or >100 × 10^9/L).
CRi	Hematologic complete remission with incomplete hematologic recovery. Meets all criteria for CR except platelet count and/or ANC.
Duration of CR	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.
Duration of MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.
Duration of MRD negativity	The interval between the first assessment at which the criteria for MRD negativity are met until the earliest date at which loss of MRD negativity occurs or relapse from CR occurs.
Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.
EFS	Event-free survival (EFS), defined as the dates of randomization until: • Death due to any cause. • Failure to achieve CR by the end of induction. • Relapse from CR.
Loss of MR3	An increase to >0.1% BCR-ABL1/ABL1.
Loss of MR4.5	An increase to >0.0032% BCR-ABL1/ABL1. This result must be confirmed at the subsequent visit, unless it is associated with loss of MR3 or relapse from CR.
Loss of MRD negativity	An increase to ≥0.01% BCR-ABL1/ABL1. This result must be confirmed within 4 weeks with either a BM aspirate (optional) or peripheral blood, unless it is associated with loss of MR3 or relapse from CR.
MR3	Molecular response 3-log reduction (≤0.1% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts.
MR4.5	Molecular response 4.5-log reduction (≤0.0032% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.
MRD-negative CR	Meeting the criteria for both MRD negativity and CR.
MRD negativity (MR4)	≤0.01% BCR-ABL1/ABL1, or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. Also referred to as MR4.
ORR	Overall response rate: CR + CRi.

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Table 13.a Definitions of Efficacy Response Criteria

Term	Definition
OS	Overall survival. The interval between randomization and death due to any cause.
PD	Progressive disease. Increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease.
PIF	Primary induction failure: Patients who received treatment for ALL but never achieved CR or CRi by the end of induction. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi.
Relapse from CR	Reappearance of blasts in the blood or BM (≥5%) or in any extramedullary site after a CR.
Time to treatment failure	Time to end of study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or efficacy reasons.

Abbreviations: ANC, absolute neutrophil count; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; CR, complete remission; CRi, incomplete blood count recovery; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MR4, molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%); MR4.5, molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%); MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; RBC, red blood cell; WBC, white blood cell.

[a] If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥5/μL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

13.1.4 Safety Endpoints

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP, and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

13.1.5 Exploratory Endpoints

The exploratory endpoints are:

- Change from baseline in patient-reported HRQOL (FACT-Leu and EQ-5D-5L).
- Change from baseline in MRU assessments.
- Time to start of alternative therapy.

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- Time to HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

Further details on the exploratory endpoint analyses will be discussed in the SAP.

13.1.5.1 Time-to-Next-Treatment and Time-to-HSCT Analyses

Time to subsequent antineoplastic therapy will be defined as the time from randomization to the date of first documentation of subsequent antineoplastic therapy or the last contact date for patients who never received subsequent antineoplastic therapy.

Likewise, time to HSCT will be defined as the time from randomization to the date of first documentation of HSCT or the last contact date for patients who did not receive an HSCT.

A Cox regression model with treatment as explanatory variable will be used for the time-to-event analyses. Median follow-up will be calculated by K-M method.

13.1.5.2 Patient-Reported Outcomes Analysis

Quality of life and health outcomes measures are being collected using the EQ-5D-5L and FACT-Leu instruments. Means and medians of scores of these questionnaires will be summarized for each cohort by time point, overall, and for each domain. Assessments based on the FACT-Leu will be analyzed to determine if treatments affect all domains.

Analyses of HRQOL scores, including global health status, will be performed using longitudinal models for scores and change from baseline scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point.

Initially, the manuals published for FACT-Leu will be used for scoring and handling missing data. Further investigation of missing patterns and details of imputation will be discussed in the SAP.

EQ-5D-5L scores will be summarized in descriptive statistics for treatment groups. Both utility scores and change from baseline scores will be assessed across time using longitudinal models.

13.1.5.3 Health Economics Analysis Using Medical Resource Utilization

Medical resource utilization data will be summarized in descriptive statistics for hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities, by patient and caregiver, and by treatment group.

13.1.5.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib

The mutation status of BCR-ABL1 and other genes implicated in tumor biology and/or drug metabolism will be determined, as clinically needed, through analyses of tumor cells collected at study entry, on study, and/or at EOT. Analysis methodologies include, but are not limited to, DNA sequencing, digital PCR, and mass spectrometry.

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13.1.6 PK Analysis (Ponatinib)

The PK data collected in this study are intended to contribute to future population PK analyses of ponatinib. These population PK analyses may additionally include data collected in other ponatinib clinical studies. The analysis plan for the population PK analysis will be defined separately and the results of these analyses will be reported separately.

13.1.7 Safety Analysis

The safety analysis will be carried out at interim and final analyses. In addition, an extended safety analysis for the study will be carried out at study completion.

Safety evaluations will be based on incidence, severity, and type of AEs; clinically significant changes or abnormalities in the patient's physical or neurological examinations; vital signs; and clinical laboratory test results.

Descriptive statistics will be calculated. Treatment-emergent adverse events (TEAEs) will be tabulated by primary SOC, High Level Term (HLT), and preferred term (PT). MedDRA will be used for coding AEs. A TEAE is defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

To summarize the number of patients with AEs, patients reporting the same event more than once will have that event counted only once within each SOC, HLT, and PT. Events that are considered related to treatment will also be tabulated. AEs will also be summarized by intensity. Deaths, AEs, SAEs, AOEs, VTEs, and events resulting in study discontinuation, if present, will be presented in separate data listings.

Additionally, a descriptive safety analyses of OS will be conducted at the IA (or FA, as applicable) for MRD-negative CR if there are a sufficient number of deaths to perform such an analysis. The details of this analysis will be provided in the SAP.

13.2 IA and Criteria for Early Termination

MRD-negative CR

There will be one IA and possibly an FA in the study for the MRD-negative CR primary endpoint using a group sequential testing approach.

The IA was performed after the end of induction phase data were collected for 116 patients. The primary endpoint of MRD-negative CR was first tested at the IA with a 2-sided efficacy boundary of 0.022 and will be tested again at the FA with a 2-sided efficacy boundary of 0.036 after the end of induction phase data have been collected for 230 patients. If the significance boundary is crossed at the FA for MRD-negative CR, there will be testing for EFS and other secondary endpoints at a 2-sided alpha level of 0.05 using a group sequential testing approach.

The boundaries for hypothesis testing for MRD-negative CR will be updated according to the observed data in the IA and FA using the prespecified alpha spending function.

Enrollment projections for patients anticipated to be enrolled at the time of the planned analyses are provided in Appendix M.

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EFS

There will be one IA and possibly an FA in the study for the key secondary endpoint EFS using a group sequential testing approach.

When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The IA is expected to occur approximately 5.5 years after the first patient is enrolled. The FA is expected to be performed approximately 8.5 years after the first patient enrolled, when all approximately 173 EFS events have been observed.

The test of significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary ($p = 0.033$) at IA and this will be the FA for EFS for statistical testing purposes. If EFS does not achieve statistical significance at the IA, the final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

If the efficacy boundary is crossed at either IA or FA for EFS, the following secondary endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA):

a) Duration of CR.

b) Duration of MRD-negative CR.

c) ORR.

d) OS.

The boundaries for hypothesis testing for EFS will be updated according to the observed data in the IA and FA using the prespecified alpha spending function.

Overall Survival

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

The IA and FA for MRD-negative CR and the IA for EFS will be carried out by an independent statistical center in a manner that maintains the blinding of the study results to the team (see Section 13.4). The IDMC will review both efficacy and safety data at the time of the IA, and will inform the sponsor's executive committee of their recommendation.

13.3 Determination of Sample Size

Assuming an effect size ranging from 20% to 28% (40% to 48% and 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of approximately 230 patients (approximately 153 versus 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 84% to 98% power for MRD-negative CR at the final analysis using the efficacy boundary of 0.036 according to the group sequential

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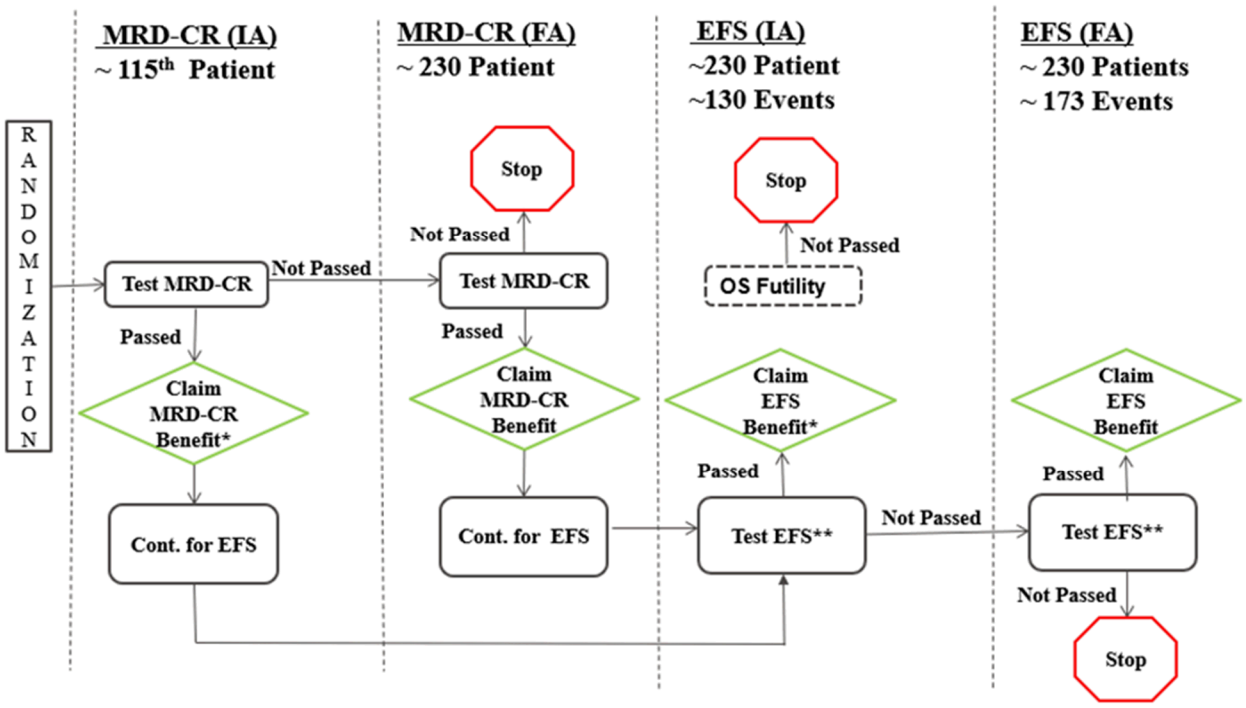
testing procedure with the IA performed using data from 116 patients [39]. The O'Brien-Fleming alpha spending function (the Lan-DeMets method [38]) will be implemented to determine the significance level at IA and FA for the primary endpoint, with an overall type I error rate at a 2-sided 0.05 level.

Inference for the key secondary endpoint of EFS will be conducted at $\alpha = 5\%$ level only if the primary endpoint is met either at IA or FA for the MRD-negative CR (Figure 13.a). Based on 3-year EFS data observed from various phase 2 studies [12,28], effect size is assumed as 67% versus 46% for EFS at year 3 for the active and control arms, respectively, or HR = 0.516 for non-HSCT patients. The effect size is assumed as 53% and 40% for EFS at year 3 for active and control arms, respectively, or HR = 0.693 for patients who are undertaking HSCT. Also, it is assumed that 50% and 45% of patients from active and control arms will undertake HSCT, respectively. Based on simulation studies, approximately 230 patients will be enrolled to collect long-term EFS data. Among these 230 patients, approximately 173 events need to be accumulated at FA so that the power will be approximately 80% for the EFS endpoint. It is expected that the time of EFS will be approximately 8.5 years after first patient has been enrolled.

Figure 13.a Statistical Analysis Schema



Abbreviations: Cont.: continue; CP: conditional probability; CR: complete response; EFS: event-free survival; FA: final analysis; IA: interim analysis; LPI: last patient in; MRD: minimal residual disease; ORR: overall response rate; OS: overall survival.

*If the efficacy boundary is crossed at the IA, it is the final analysis, and no formal hypothesis testing will be performed.

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**If the efficacy boundary is crossed at either the IA or FA for EFS, the following endpoints will be tested in the following order using the same boundaries: a) Duration of CR; b) Duration of MRD-negative CR; c) ORR; and d) OS.

13.4 Blinding of Trial Management Team for Data Review

This is an open-label study. To protect study integrity, the study team will be blinded to treatment assignment for aggregate efficacy-related data, unless publicly released, as well as individual patient-level data (except a few members who are included in patient management and monitoring of the study; however, generation of any aggregate summary of efficacy data by treatment arm is not allowed). Details will be specified in a separate data and blinding plan, which will be finalized prior to the IA.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC. In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic or other limited circumstances defined in the monitoring plan, alternative monitoring approaches such as remote source data verification (rSDV), remote source data review (rSDR), or telephone contact may be used to ensure data quality and integrity and maintain patient safety. Local regulations and guidances are to be followed regarding rSDV and rSDR.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. In unavoidable circumstances such as the COVID-19 pandemic, deviations from the protocol specified procedures will be recorded as related to COVID-19. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

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The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment.

The investigator should document all protocol deviations.

14.2.1 Japan Protocol Deviations

The procedure below applies to patients enrolled at Japanese sites only.

The investigator can deviate and change from the protocol for any medically unavoidable reason (eg, to eliminate an immediate hazard to study patients) without a prior written agreement with the sponsor or a prior approval from the IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from the IRB should be obtained.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom [UK] Medicines and Healthcare products Regulatory Agency [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors and regulatory agency inspectors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, patients) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH E6 Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of

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Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal-wide Assurance number or comparable number assigned by the US Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the investigator's brochure, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug and notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from a competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH E6 Guideline for GCP and will be in accordance with all applicable laws and regulations. The ICF describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and

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benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF. The ICF must be approved by both the IRB or IEC and the sponsor before use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. A copy of the signed and dated ICF shall be given to the subject.

All revised ICFs must be reviewed, signed, and dated by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, UK MHRA, EMA, Japan PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical

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records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed (eg, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via e-mail/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their

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established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws and/or regulations.

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases

Study Procedures	**Screening / Baseline**	**Induction Phase**						**Consolidation Phase**											
28-Day Cycles		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7**		**Cycle 8**		**Cycle 9**	
Cycle Days	**-28 to -1**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**
Window (days) [a]	**N/A**		±3	±3	±3	±3	±3	**±4**	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed consent [b]	X																		
Enrollment [b]	X																		
Med/Surg history and demographics [c]	X																		
Pregnancy test [d]	X	X		X		X		X		X		X		X		X		X	
Leukemia diagnosis	X																		
Prior medications [e]	X																		
Vital signs [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exams [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG [g]	X	X						X						X					
ABI [h]	X	Additional Assessments as Clinically Indicated																	
Framingham score [i]	X																		
12-Lead ECG [j]	X							X						X					
ECHO [k]	X	Additional Assessments as Clinically Indicated																	
Eye exams l	X	Additional Assessments as Clinically Indicated																	
PROs [m]	X	X						X						X					
MRU [n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CNS prophylaxis [o]		X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]	X	X [o]						
AE monitoring	Recorded at every visit from the signing of ICF through 30 days after last dose of study drug (See Section 10.0)																		

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Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases

Study Procedures	**Screening / Baseline**	**Induction Phase**						**Consolidation Phase**											
28-Day Cycles		**Cycle 1**		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**		**Cycle 7**		**Cycle 8**		**Cycle 9**	
Cycle Days	**-28 to -1**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**	**1**	**7, 14, 21**
Window (days) [a]	**N/A**		±3	±3	±3	±3	±3	**±4**	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Concomitant medications [p]		Recorded at every visit from Cycle 1 Day 1 through 30 days after last dose of study drug.																	
Alternative therapy and/or HSCT [q]		Documented Per Occurrence																	
Clinical Laboratory Sampling																			
Hep B serology [r]	X	Additional Assessments as Clinically Indicated																	
Plasma samples for PK (Cohort A)		X [s]	X [t]	X [s]	X [t]	X [s]		X [s]				X [s]						X [s]	
CBC with diff [u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry [v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting glucose, cholesterol, lipids, and HbA1c [w]	X	X						X						X					
CRP, cTnI, and NT-proBNP or BNP [x]	X	X	X [x]	X	X [x]	X	X [x]	X		X		X		X		X		X	
Bone marrow aspirate [y,z,aa,]	X [y]	X [y]		X [y]		X [aa y]		X [y]				X [y]				X [y]			
Peripheral blood sample [bb]	X [bb]	X [bb]		X		X		X				X				X			
Extramedullary assessments [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	Additional Assessments as Clinically Indicated					

Abbreviations: β-HCG, beta-human chorionic gonadotropin; ABI, ankle-brachial index; AE, adverse event; ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCR-ABL, breakpoint cluster region-Abelson; BP, blood pressure; BM, bone marrow; BNP, B-type natriuretic peptide; BSA, body surface area; BUN, blood urea nitrogen; CAD, coronary artery disease; CBC with Diff, complete blood count with differential; CNS, central nervous system; CR, complete remission; CRP, C-reactive protein; cTnI, cardiac troponin-I; CSF, cerebrospinal fluid; CV, cardiovascular; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case

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report form; ECG, electrocardiogram; ECHO, echocardiogram; EOT, end of treatment; EQ-5D-5L, EuroQOL-5 dimension-5 level (patient-reported outcome tool); FACT-Leu, Functional Assessment of Cancer Therapy – Leukemia; F/U, follow-up; HbA1c, glycosylated hemoglobin; Hep, hepatitis; HSCT, hematopoietic stem cell transplant; ICF, informed consent form; IEC, independent ethics committee; IRB, institutional review board; IRT, interactive response technology; IV, intravenous; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; Med/Surg, medical and surgical; MI, myocardial infarction; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MRD, minimum residual disease; MRU, medical resource utilization; MUGA, multigated acquisition; N/A, not applicable; NT-proBNP, N-terminal pro-brain natriuretic peptide; PK, pharmacokinetic; PROs, patient-reported outcomes; QTcF, QT interval corrected per Fridericia method; SOC; standard of care; TIA, transient ischemic attack; TKI, tyrosine kinase inhibitor; Tx, therapy; WBC, white blood cell.

COVID-related safety and/or logistical issues: All attempts should be made to perform the assessments with the patient present at the site. However, in cases where patient's visit to the site is not feasible (patient cannot travel to the site or in cases where the investigator believes that is best for patient's and site staff's safety not to visit to the site), alternative evaluation such as local laboratories and/or telehealth (the ability to connect a physician to a patient)/telemedicine (remote clinical assessments) or home healthcare (performing some assessments in a patient's home by a qualified health care professional) will be allowed if permitted by local regulations. Sites will contact the sponsor's medical monitor/designee to discuss individual cases. The data collected from home healthcare visits may be handled differently in the final data analysis, with this documentation included in the statistical analysis plan. Separate consent may be required. In the event that a patient cannot visit the site to obtain the study drug, sites should contact the sponsor's medical monitor/designee to arrange for an alternate mechanism of drug dispensation (eg, dispensing additional study drug at clinic visits or direct-to-patient shipment). Additionally, it is expected that during the first 20 cycles of treatment (induction, consolidation, and maintenance phases), patient will visit the site at least once per cycle for chemotherapy administration (as they are administered intravenously) and/or bone marrow aspiration or any other procedures critical for patient management.

Subject safety will be monitored during the time between on-site visits. At minimum, there will be a phone call with a study site physician within specified-visit window time frame which will include AE assessments, documentation of concomitant medication, and an assessment of clinical symptoms. There will be no interval longer than 8 weeks without a clinical safety lab and vital signs collection.

[a] Visit windows: Tests and procedures should be performed on schedule, but occasional changes are allowable within a window (±3 days; a window of ±4 days is allowed only for Cycle 4/Day 1 visit or Cycle 10/Day 1 visit) for holidays, vacations, and other administrative reasons. See Table 2 for acceptable visit window at the 30-day follow-up visit and for survival follow-up. See footnote y and bb for additional guidance on the permitted windows for the bone marrow aspirate and peripheral blood sample, respectively.

[b] Enrollment: Screening and randomization procedures should be performed within the 28-day screening period. Central laboratory results will be used for determination of eligibility criteria, but local laboratory results may also be used. The ICF may be signed more than 28 days before Cycle 1 Day 1. An Eligibility Verification Form and required supporting documentation, as allowed by local regulations, should be sent to the sponsor's medical monitor or designee as soon as the screening procedures are completed for confirmation of patient eligibility (specific instructions for randomization will be supplied in the site operations manual).Confirmation of patient eligibility by the sponsor's medical monitor or designee is required before randomization and first dose administration. Cycle 1 Day 1 should be no later than 7 days after the date of enrollment call in IRT. Specific instructions for randomization will be supplied in the site operations manual.

[c] Medical and surgical history and demographic information will include all diagnoses, therapies, and medical and surgical treatments.

Special attention should be paid to documenting risk factors for cardiovascular, cerebrovascular, peripheral vascular, and venous thromboembolic disease, including but not limited to any history of ischemic heart disease (eg, angina, MI, acute coronary syndrome); valvular heart disease; congestive heart failure; arrhythmias; myocarditis; peripheral arterial occlusive disease (eg, claudication, distal extremity amputation, angioplasty); or stroke (eg, TIAs, cerebral atherosclerosis). Any type of revascularization procedures (eg, stent, arterial bypass grafts) must also be recorded.

In addition, diabetes mellitus; hypertension; hypercholesterolemia; hyperlipidemia; DVT; pulmonary embolism; any other coagulopathy (for example, protein S or protein C deficiency or anticardiolipin antibody); physical activity status; obesity; and history of and current smoking status.

Family medical history will be collected, and should include any history of CAD, early death from MI or CVA, sudden death, or bleeding or clotting diatheses in first-degree relatives.

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Demographic information will include the patient's date of birth (outside European Economic Area) or age (European Economic Area), sex, race, and ethnicity (optional depending on country), to be recorded during screening (as allowed by local law and regulations).

[d] Pregnancy test must be performed for patients of childbearing potential during screening and again at Cycle 1 Day 1 before the first dose of study drug, if the screening test was performed >4 days before the visit. For screening, a serum β-HCG test must be performed. The results must be negative within 4 days before the first dose of study drug is administered (ie, within the 4 days before Cycle 1 Day 1), or as otherwise required by local regulations (patients with positive serum pregnancy test who have undergone a complete abortion in the last 60 days may be included in the study [See Section 7.2]). Monthly urine pregnancy testing will be performed during the study (through Cycle 20). Women who are not of childbearing potential (status posthysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. Serum pregnancy testing (instead of urine) or additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

[e] Prior medication data collection should include those listed in the exclusion criteria to determine the patient's eligibility for the study, as well as all other medications/therapies received within 30 days before the first dose of study drug. Prior medications that are ongoing as of the first dose of study drug will then be recorded as concomitant medications.

[f] Vital signs will be performed at every visit before IV chemotherapy dosing and will include systolic and diastolic BP, heart rate, respiratory rate, and body temperature. On Cycle 1 Day 1 only, vital signs should be performed before IV chemotherapy dosing, as well as at 1, 3, and 8 hours (±15 minutes) postdose. All BP measurements should be assessed in a seated position after the patient has been sitting quietly for 5 minutes, performed 3 times with 2-minute intervals between BP assessments. BP can be measured manually or with an automated device, but must be done using a consistent method for all patients at a given site. Monitor and manage BP elevations during the study and treat hypertension to normalize BP.

[g] Physical examinations will include a complete physical (including weight) performed at screening and at every visit before IV chemotherapy dosing during the induction and consolidation phases. The examination at Cycle 1 Day 1 should be performed before the first administration of study drug, but is not required if the screening physical examination was conducted and medical history obtained within 2 days before administration of the first dose of study drug. Sites should calculate BSA from the weight and height measured at baseline, and the additional weight assessments will be documented in the eCRF without the need to calculate the BSA. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. All physical examinations should address the presence or absence of hepatomegaly and splenomegaly, and all findings should be recorded in the eCRF. ECOG performance status should be evaluated during physical examination at screening, Day 1 of Cycle 1, end of Cycle 3 (Day 1 of Cycle 4) and end of Cycle 6 (Day 1 of Cycle 7). Height measurement is required at screening only.

[h] ABI will be performed at screening and as clinically indicated to assess patients for the risk of peripheral arterial disease (see also Table 2). In a supine position, the patient's BP will be assessed in both arms and again in both ankles with BP measured three times at each side. A hand-held Doppler ultrasound may be used to confirm the diastolic pressure in the arms and ankles. Instructions for scoring the ABI will be provided in the site operations manual, however, local standard of care process may be used.

[i] Framingham Score will be done at screening to assess patients who may be at risk for cardiovascular events (see also Table 2).

[j] ECGs must all be 12-lead ECGs, performed at screening and before IV chemotherapy dosing on Day 1 after every 3 cycles (ie, Cycles 4 and 7) (see also Table 2 for assessments continuing with the maintenance phase). ECGs may be performed at other times as clinically indicated. Ventricular rate (or heart rate in case ventricular rate is not available), PR interval, RR interval, QRS duration, QT interval, and QTcF interval must be documented in the eCRF. ECGs are to be interpreted by a local cardiologist in cases where there are significant findings or when the investigator cannot interpret the findings. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated. If the timing of a PK blood sample or other blood draw coincides with the timing of an ECG measurement, the ECG measurement should be taken first, followed by the blood draw.

[k] ECHO for assessment of LVEF must be performed at screening; additional ECHOs need only be performed if clinically indicated. As deemed appropriate by the investigator, ECHO could be substituted with multigated acquisition (MUGA) scan.

[l] Eye examinations must be performed at screening (including a detailed history) and as clinically indicated. If performing the screening eye examination is not feasible during the screening period (eg, in-patient, no ophthalmologist available, etc), the screening eye examination should be performed by the end of Cycle 1. It is recommended to use

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Ophthalmoscopy to perform the eye examination (additional tests may be used as clinically indicated or as per physician discretion). The eye examinations should test the retinal vasculature and any clinically significant abnormalities should be noted in the CRF.

[m] PROs include both the EQ-5D-5L instrument from the EuroQOL group and the FACT-Leu instrument, used to collect patient-assessed quality-of-life and health outcomes measures, respectively. The instruments will be implemented at screening; at Cycle 1 Day 1, and at Day 1 of Cycles 4 and 7 (see Table 2 for assessments continuing with the maintenance phase). All instruments will be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures. Patients are required to complete the instruments if there is a validated translation available in a language in which they are fluent.

[n] MRU: All medical care encounters will be collected each time an AE or unscheduled physician visit occurs. Examples of data to be collected are the number of medical care encounters, such as hospital admissions or major diagnostic procedures.

[o] CNS prophylaxis will be administered on Day 1 and Day 14 of the 3 induction phase Cycles 1, 2, and 3 and the first 3 consolidation phase Cycles 4, 5, and 6 (total: 6 cycles, 12 intrathecal injections). CNS prophylaxis will comprise a triple intrathecal injection of methotrexate, cytarabine, and corticosteroids (recommended: dexamethasone) as per current practice in each center.

[p] Concomitant medications include all medications/therapies that are ongoing as of or started on Cycle 1 Day 1.

[q] Alternative therapy and/or proceeding to HSCT will be documented if applicable. Patients who proceed to alternative therapy and/or HSCT will be discontinued from study treatment and the date that the patient starts an alternative therapy and/or HSCT should be noted. These patients will, however, continue in the study to be followed additionally every 3 months until they withdraw from the study (Section 9.8). Every effort should be made to capture transplant-related procedures, investigator-reported disease status (eg, relapse from CR), survival, and the use of alternative therapy and/or post-transplant treatment (chemotherapy, TKI).

[r] Hepatitis B serology will be performed during screening and as clinically indicated for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum. Note: Patients who are chronic carriers of hepatitis B virus and receive a BCR-ABL1 TKI therapy may have a reactivation of hepatitis B. For patients with evidence of prior or current hepatitis B infection, please refer to Section 8.8 and the investigator's brochure. If the patient was found to be HBsAg negative but HBcAb positive, a PCR HBV DNA needs to be conducted. The patient may be accepted if the PCR HBV DNA is not detectable.

[s] Pre- and postdose ponatinib plasma sample for PK: Patients should be instructed to not take their dose of ponatinib on the days of predose PK sampling, ie, at Day 1 of Cycles 1, 2, 3, 4, 6, 9, and 12 (see also Table 2). Patients will be administered ponatinib at the site on those days no later than 1 hour after the predose sample is obtained. Additional plasma samples for PK will be obtained postdose during Cycle 2 Day 1 only, at 1 hour (±15 minutes), and at 4 and 6 hours (±30 minutes) postdose. Note: An unscheduled trough (predose) sample will be collected at the first scheduled visit following a dose reduction of at least 7 days duration before the visit. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples, should be recorded in the eCRF.

[t] Postdose ponatinib plasma sample for PK: Ponatinib should be taken early in the morning at home on the days of postdose PK sampling, ie, on Day 14 of Cycle 1 and Cycle 2, and sites should obtain the first postdose PK sample before initiating the vincristine infusion. An additional PK sample will be obtained on these days (Day 14 of Cycles 1 and 2) after the vincristine infusion is completed and immediately before leaving the clinic. Note: A distribution of visit times during the day is recommended for these visits to provide a range of PK blood sampling times relative to the timing of early morning at-home dosing of ponatinib. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples, should be recorded in the eCRF.

[u] CBC with differential testing will be performed centrally at screening and at every visit throughout the induction and consolidation phase, and additionally as clinically indicated. Testing should be completed within 24 hours before IV chemotherapy dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Eligibility verification during screening and dose modifications for hematologic adverse drug reactions (see Table 8.e for ponatinib and Section 8.4.2.2 for imatinib) and could be based on local laboratory results. CBC with differential is defined as peripheral blood total WBC count, hemoglobin, hematocrit, platelet count, ANC, and WBC differential, reported individually for each cell type. Cell types required for diagnosis and response assessment (including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present) must be quantified. Additionally, tests related to CR or relapse from CR assessments should be performed locally at these visits, and at other times when clinically indicated. Results from local laboratory hematology testing (including CR or relapse from CR assessments), whether scheduled or unscheduled, must be entered in the patient's eCRF.

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[v] Serum chemistry testing will be performed centrally at screening and at every visit throughout the induction and consolidation phase, and additionally as clinically indicated. Testing should be completed within 24 hours before IV chemotherapy dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Eligibility verification during screening and dose modifications for nonhematologic adverse drug reactions related to serum chemistry (see Table 8.d for ponatinib and Section 8.4.2.1 for imatinib) could be based on local laboratory results. Serum chemistry testing consists of a peripheral blood draw with the following assessments: sodium; potassium; chloride; bicarbonate (or CO_2); BUN (urea); uric acid; albumin; creatinine; total, direct, and indirect bilirubin; AST; ALT; ALP; LDH; magnesium; phosphorous; calcium; amylase; and lipase. In case of a suspicion for disseminated intravascular coagulation (DIC), sites should perform tests at the local laboratory according to the applicable local guidelines. Results from any local laboratory chemistry testing, whether scheduled or unscheduled, must be entered in the patient's eCRF (local laboratory results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions).

[w] Fasting glucose, cholesterol, lipids, and HbA1c must be performed at screening, at Cycle 1 Day 1, and on Day 1 of every third cycle thereafter (ie, Cycle 4, Cycle 7, Cycle 10, etc), or more frequently as clinically indicated. Tests performed within 3 days before Cycle 1 Day 1 need not be repeated at that visit.

[x] CRP, cTnI assessments, and NT-proBNP or BNP assessments will be performed at Days 1 and 14 of Cycles 1-3 (induction phase) and at Day 1 of Cycles 4-9 (consolidation phase), or more frequently as clinically indicated. For maintenance phase, CRP, cTnI assessments and NT-proBNP or BNP testing must be included with every blood draw (except Cycle 10, Day 7). In patients with persistent elevation of cTnI or NT-proBNP/BNP, performing an ECHO and/or consulting a cardiologist should be considered.

[y] BM aspirates will be obtained at screening and within ±7 days before Day 1 of Cycles 1, 2, 3, and 4, and also before Day 1 of Cycles 6 and 8 (if MRD- negativity has not been achieved by this time) (see Table 2 for assessment schedule during the remainder of the study). Cycle 1 Day 1 assessments need not be repeated if the screening assessment was within 14 days before Cycle 1 Day 1. BM aspirates may be performed at other times as per SOC or when clinically indicated. Tests related to CR and relapse from CR assessments should be performed locally. A portion of BM aspirate sample will be sent to a local laboratory for CR and relapse from CR assessments. At any point that a BM aspirate is collected for tests related to CR and relapse from CR assessments, a portion of BM aspirate sample should also be sent to central laboratory for molecular assessment. In instances where a BM aspirate is a dry tap, BM biopsy could be used (any BM biopsy sample, if collected, will be evaluated locally). Results from local laboratory testing of any BM aspirate (or biopsy, if performed), whether scheduled or unscheduled, must be recorded in the patient's eCRF (local BCR-ABL1 results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions). Note: A screening/diagnostic dry tap will not make the patient ineligible for the study as peripheral blood specimen is also collected at the same time and will be used for transcript determination.

[z] Confirmation of loss of MRD negativity: For assessments beyond Cycle 4, if a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks at the central laboratory, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[aa] BM aspirate on Cycle 3 Day 1: This sample is only required in patients who have not achieved CR at Cycle 2 Day 1.

[bb] Peripheral blood sample collection for assessment of molecular response and exploratory biomarkers must occur at screening and within ±7 days before Day 1 of Cycles 1, 2, 3, 4, 6, and 8 (see Table 2 for assessment schedule during the remainder of the study). Cycle 1 Day 1 molecular response assessments need not be repeated if the screening assessment was within 7 days before Cycle 1 Day 1. A portion of the sample collected for molecular response assessment may also be used for exploratory biomarker assessment; which will include analysis of molecular determinants of response or resistance to ponatinib or imatinib, including BCR-ABL1 mutation analysis and/or biomarkers affecting ponatinib efficacy or safety. Specific instructions for collection of peripheral blood for molecular response and exploratory assessments will be provided in the laboratory manual. For assessments beyond Cycle 4, in the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[cc] Extramedullary assessments will be performed locally and will include lumbar punctures to test CSF for CNS disease at screening (if clinically indicated), on Day 1 and Day 14 of Cycles 1, 2, 3, 4, 5, and 6 and as clinically indicated thereafter. Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should be performed as clinically indicated throughout the study. When imaging studies have been used to assess extramedullary involvement, the same imaging methods should be used consistently throughout the study for individual patients. Results from local laboratory testing, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

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Table 2 Schedule of Events: Maintenance Phase, Single-Agent Therapy, End-of-Treatment, and Follow-up

Study Procedures	**Maintenance Phase**												**Single Agent Tx [a]**	**EOT 30 Days After Last Dose or D/C [b]**	**Survival Follow-up Q3 mo after D/C [c,d,e]**
28-Day Cycles	**Cycle 10**		**Cycle 11**	**Cycle 12**	**Cycle 13**	**Cycle 14**	**Cycle 15**	**Cycle 16**	**Cycle 17**	**Cycle 18**	**Cycle 19**	**Cycle 20**			
Cycle Days	**1**	**7**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1, Q3 mo**		
Window (days) [f]	**±4**	±3	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**+7**	**±14**
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X	X	X [g]	X	
Physical exams [h]	X	X	X	X	X	X	X	X	X	X	X	X	X [h]	X	
ECOG [h]	X				X			X			X		X [h]	X	
12-lead ECGs [i]	X				X			X			X		X [i]	X	
PROs [j]	X				X			X			X		X [j]	X	X [j]
MRU [k]	X		X	X	X	X	X	X	X	X	X	X	X [k]	X	
Diary review [l]	X		X	X	X	X	X	X	X	X	X	X	X [l]	X	
AEs	Recorded at every visit through the 30-day EOT visit or longer														
Concomitant medications [m]	Recorded at every visit through the 30-day EOT visit or longer														
Pregnancy test [n]	Performed monthly through Cycle 20; subsequently, pregnancy test to be performed quarterly (at every scheduled patient visit which occurs every 3 months).													X	
ABI [o]	Additional Assessments as Clinically Indicated													X	
Framingham score [p]														X	
ECHOs [q]	Additional Assessments as Clinically Indicated													X	
Eye exams [r]	Additional Assessments as Clinically Indicated													X	
Clinical Laboratory Sampling															
Plasma samples for PK [s]				X											
CBC with diff [t]	X	X	X	X	X	X	X	X	X	X	X	X	X [t]	X	
Chemistry [u]	X	X	X	X	X	X	X	X	X	X	X	X	X [u]	X	
Fasting glucose, cholesterol, lipids, and HbA1c [v]	X				X			X			X		X [v]	X	

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Study Procedures	**Maintenance Phase**												**Single Agent Tx** [a]	**EOT 30 Days After Last Dose or D/C** [b]	**Survival Follow-up Q3 mo after D/C** [c,d,e]
28-Day Cycles	**Cycle 10**		**Cycle 11**	**Cycle 12**	**Cycle 13**	**Cycle 14**	**Cycle 15**	**Cycle 16**	**Cycle 17**	**Cycle 18**	**Cycle 19**	**Cycle 20**			
Cycle Days	**1**	**7**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1, Q3 mo**		
Window (days) [f]	**±4**	±3	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**+7**	**±14**
CRP, cTnI, and NT-proBNP or BNP [w]	X		X	X	X	X	X	X	X	X	X	X	X [w]	X	
BM aspirate [x,y,z]	X							X					X [x,y]	X[z]	
Peripheral blood sample [aa]	X				X			X			X		X [aa]	X	
Hep B serology [bb]	Additional assessments as Clinically Indicated														
Extramedullary assessments [cc]	Additional Assessments as Clinically Indicated													X [cc]	

Abbreviations: β-HCG, beta-human chorionic gonadotropin; ABI, ankle-brachial index; AE, adverse event; ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AOE, arterial occlusive event; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; BNP, B-type natriuretic peptide; BP, blood pressure; BSA, body surface area; BUN, blood urea nitrogen; CBC with Diff, complete blood count with differential; chemo, chemotherapy; CNS, central nervous system; CR, complete remission; CRP, C-reactive protein; CSF, cerebrospinal fluid; cTnI, cardiac troponin-I; CV, cardiovascular; D/C, discontinuation; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOS, end of study; eCRF, electronic case report form; EOT, end of treatment; EQ-5D-5L, EuroQOL-5 dimension-5 level (patient-reported outcome tool); FACT-Leu, Functional Assessment of Cancer Therapy – Leukemia; F/U, follow-up; HbA1c, glycosylated hemoglobin; Hep, hepatitis; HSCT, hematopoietic stem cell transplant; IEC, independent ethics committee; IRB, institutional review board; LDH, lactic dehydrogenase; LVEF, left ventricular ejection fraction; Med/Surg, medical and surgical; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MRD, minimum residual disease; MRU, medical resource utilization; MUGA, multigated acquisition; NT-proBNP, N-terminal pro-brain natriuretic peptide; PD, progressive disease; PROs, patient-reported outcomes (EQ-5D-5L and FACT-Leu); Q3 mo, every 3 months; QTcF, QT interval corrected per Fridericia method; SAE, serious adverse event; SOC, standard of care; TKI, tyrosine kinase inhibitor; Tx, therapy; VTE, venous thrombotic/embolic event;; WBC, white blood cell.

COVID-related safety and/or logistical issues: All attempts should be made to perform the assessments with the patient present at the site. However, in cases where patient's visit to the site is not feasible (patient cannot travel to the site or in cases where the investigator believes that is best for patient's and site staff's safety not to visit to the site), alternative evaluation such as local laboratories and/or telehealth (the ability to connect a physician to a patient)/telemedicine (remote clinical assessments) or home healthcare (performing some assessments in a patient's home by a qualified health care professional) will be allowed if permitted by local regulations. Sites will contact the sponsor's medical monitor/designee to discuss individual cases. The data collected from home healthcare visits may be handled differently in the final data analysis, with this documentation included in the statistical analysis plan. Separate consent may be required. In the event that a patient cannot visit the site to obtain the study drug, sites should contact the sponsor's medical monitor/designee to arrange for an alternate mechanism of drug dispensation (eg, dispensing additional study drug at clinic visits or direct-to-patient shipment). Additionally, it is expected that during the first 20 cycles of treatment (induction, consolidation, and maintenance phases), patient will visit the site at least once per cycle for chemotherapy administration (as they are administered intravenously) and/or bone marrow aspiration or any other procedures critical for patient management.

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Subject safety will be monitored during the time between on-site visits. At minimum, there will be a phone call with a study site physician within specified-visit window time frame which will include AE assessments, documentation of concomitant medication, and an assessment of clinical symptoms. There will be no interval longer than 8 weeks without a clinical safety lab and vital signs collection.

[a] Single-Agent Therapy: After the end of Cycle 20, patients will receive single-agent TKIs (ponatinib or imatinib) continuously until they have experienced relapse from CR or PD, have an unacceptable toxicity, withdraw consent, proceed to HSCT or alternative therapy, have completed the study, or until the sponsor terminates the study, whichever occurs first. **Note: Efficacy and safety data (as indicated on the table) will be collected Q3 months after the end of Cycle 20 (ie, Day 1 of Cycles 21, 24, 27, etc).**

[b] EOT visit should occur 30 days after a patient has discontinued the study drug (last dose) (a window of + 7 days is acceptable), with the exception of less than 30 days because that the EOT visit must occur before HSCT or before initiation of any alternative treatment (if applicable).

[c] Survival follow-up: Patients who have been discontinued from study drug for any reason will be contacted every 3 months (±14 days) and followed for investigator-reported disease status (eg, relapse from CR) with date of relapse reported and source documentation should be noted, and survival until they withdraw from the study or until the patient's death has been reported. Delayed treatment-related SAEs, AOEs, and VTEs will be followed until resolution or the start of subsequent alternative anticancer therapy. The EOS eCRF page is to be completed at the time the patient discontinues from the survival follow-up period.

[d] Alternative therapy: The start date of alternative therapy should be noted. Patients proceeding to alternative therapy will be discontinued from study treatment but will be followed for investigator-reported disease status (eg, relapse from CR) and survival until the patient's death or the patient withdraws from the study (Section 9.8).

[e] Transplant follow-up: Patients who proceed to HSCT will be discontinued from study treatment and the date that the patient receives HSCT should be noted. These patients will, however, continue in the study to be followed additionally every 3 months until the patient's death or the patient withdraws from the study (Section 9.8). Every effort should be made to capture transplant-related procedures, investigator-reported disease status (eg, relapse from CR), survival, and the use of post-transplant treatment (chemotherapy, TKI).

[f] Visit windows: Tests and procedures should be performed on schedule, but occasional changes are allowable within a window (±3 days for Day 7 of Cycle 10; ±4 days for Day 1 of Cycles 10-20, during single agent treatment) for holidays, vacations, and other administrative reasons. See footnote b for additional guidance on the permitted window for EOT visit; and, see x and z for additional guidance on the permitted windows for the bone marrow aspirate and peripheral blood sample, respectively.

[g] Vital signs will be performed at every visit before dosing, including during the single-agent therapy phase and EOT, and will include systolic and diastolic BP, heart rate, respiratory rate, and body temperature. All BP measurements should be assessed in a seated position after the patient has been sitting quietly for 5 minutes, performed 3 times with 2-minute intervals between BP assessments. BP can be measured manually or with an automated device, but must be done using a consistent method for all patients at a given site. Monitor and manage BP elevations during the study and treat hypertension to normalize BP.

[h] Physical examinations will include a complete physical (including weight) performed before dosing on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle in the single-agent therapy phase (eg, Day 1 of Cycles 21, 24, 27, and so on) to be consistent with the visit schedule, and at the EOT Visit. The weight assessments will be documented in the electronic case report form without the need to calculate the BSA. The extent of the physical examination should be consistent with the medical history and the patient's underlying disease. All physical examinations should address the presence or absence of hepatomegaly and splenomegaly, and all findings should be recorded in the eCRF. ECOG performance status should be evaluated during physical examination at Day 1 every third cycle after Cycle 7 (ie, Day 1 of Cycles 10, 13, 16, 19), and then on Day 1 of Cycle 21 and then at least every 6 cycles (eg, Day 1 of Cycles 21, 27, and so on) to be consistent with the visit schedule, and EOT. Height measurement is not required.

[i] ECGs must all be 12-lead ECGs, performed before dosing on Day 1 of every third cycle after Cycle 7 (ie, Day 1 of Cycles 10, 13, 16, 19), and then on Day 1 of Cycle 21 and then at least every 6 cycles (eg, Day 1 of Cycles 21, 27, and so on) to be consistent with the visit schedule, and at the EOT visit; ECGs may be performed at other times as clinically indicated. Ventricular rate (or heart rate in case ventricular rate is not available), PR interval, RR interval, QRS duration, QT interval, and QTcF interval must be documented in the eCRF. ECGs are to be interpreted by a local cardiologist in cases where there are significant findings or when the investigator cannot interpret the findings. If medications known to prolong the QTcF interval are used while a patient is on study, then additional ECG monitoring should be performed as clinically indicated.

[j] PROs include both the EQ-5D-5L instrument from the EuroQOL group and the FACT-Leu instrument, used to collect patient-assessed quality-of-life and health outcomes measures, respectively. The instruments will be implemented at Day 1 every third cycle after Cycle 7 (ie, Day 1 of Cycles 10, 13, 16, 19), and then on Day 1 of Cycle 21 and then

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at least every 6 cycles (eg, Day 1 of Cycles 21, 27, and so on) to be consistent with the visit schedule, and EOT. All instruments will be administered to patients when they arrive for their scheduled visits, before any clinical measurements, assessments, evaluations, or procedures. Patients are required to complete the instruments if there is a validated translation available in a language in which they are fluent. At the survival follow-up assessments, only the EQ-5D-5L should be administered (at least once in 6 months) if telephone contact with the patient or caregiver is feasible.

[k] MRU: All medical care encounters will be collected each time an AE or unscheduled physician visit occurs. Examples of data to be collected are the number of medical care encounters, such as hospital admissions or major diagnostic procedures.

[l] Diary review will continue at every visit, including during the single-agent therapy phase and at the EOT visit.

[m] Concomitant medications include all medications/therapies that are ongoing as of or started on Cycle 10 Day 1.

[n] Monthly urine pregnancy testing will be performed during the study (through Cycle 20); subsequently, urine pregnancy test to be performed quarterly (at every scheduled patient visit which occurs every 3 months) (serum pregnancy test may be performed instead at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations). If the pregnancy test was deemed necessary at screening, it must be performed again at the EOT visit. For EOT visit, a serum β-HCG test must be performed. Women who are not of childbearing potential (status posthysterectomy, status post-bilateral oophorectomy, or postmenopausal [defined as amenorrhea for at least 12 months]) do not need to have the test performed. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of an IEC/IRB, or if required by local regulations.

[o] ABI will be repeated at the EOT visit and as clinically indicated to assess patients for the risk of peripheral arterial disease. In a supine position, the patient's BP will be assessed in both arms and again in both ankles with BP measured three times at each side. A hand-held Doppler ultrasound may be used to confirm the diastolic pressure in the arms and ankles. Instructions for scoring the ABI will be provided in the site operations manual, however, local standard of care process may be used.

[p] Framingham Score will be done at the EOT visit to assess patients who may be at risk for cardiovascular events.

[q] ECHO for assessment of LVEF should be performed at the EOT and need only be repeated if clinically indicated. As deemed appropriate by the investigator, ECHO could be substituted with multigated acquisition (MUGA) scan.

[r] Eye examinations should be repeated at the EOT visit and as clinically indicated. It is recommended to use Ophthalmoscopy to perform the eye examination (additional tests may be used as clinically indicated or as per physician discretion). The eye examinations should test the retinal vasculature and clinically significant abnormalities should be noted in the CRF.

[s] Predose plasma sample for PK: Patients should be instructed to not take their dose of ponatinib on Cycle 12 Day 1. Patients will be administered ponatinib at the site that day within 1 hour after the predose sample is obtained. Note: An unscheduled trough (predose) sample will be collected at the first scheduled visit following a dose reduction of at least 7 days duration before the visit. The date and exact time of dosing of the 2 preceding doses of ponatinib before all PK sample collections, and the date and exact time of collection of all the PK samples should be recorded in the eCRF.

[t] CBC with differential assessments will be performed centrally and will continue on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle during single-agent therapy, and at the EOT visit. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Dose modifications for hematologic adverse drug reactions (see Table 8.e for ponatinib and Section 8.4.2.2 for imatinib) could be based on local laboratory results. CBC with differential is defined as peripheral blood total WBC count, hemoglobin, hematocrit, platelet count, ANC, and WBC differential, reported individually for each cell type. Cell types required for diagnosis and response assessment (including basophils, myelocytes, metamyelocytes, promyelocytes, and blasts, when present) must be quantified. Additionally, tests related to CR or relapse from CR assessments should be performed locally at these visits, and at other times when clinically indicated. Results from local laboratory hematology testing (including CR or relapse from CR assessments), whether scheduled or unscheduled, must be entered in the patient's eCRF.

[u] Serum chemistry assessments will be performed centrally and will continue on Day 1 and Day 7 of Cycle 10, Day 1 of every subsequent cycle, Day 1 of every third cycle during single-agent therapy, and at the EOT visit. Testing should be completed within 24 hours before dosing in all cycles; however, every effort should be made to perform the test on the day of dosing. Dose modifications for nonhematologic adverse drug reactions related to serum chemistry (see Table 8.d for ponatinib and Section 8.4.2.1 for imatinib) could be based on local laboratory results. Serum chemistry consists of a peripheral blood draw with the following assessments: sodium; potassium; chloride; bicarbonate (or total CO_2);

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BUN (or urea); uric acid; albumin; creatinine; total, direct, and indirect bilirubin; AST; ALT; ALP; LDH; magnesium; phosphorous; calcium; amylase; and lipase. In case of a suspicion for disseminated intravascular coagulation (DIC), sites should perform tests at a local laboratory according to the applicable local guidelines. Results from any local laboratory chemistry testing, whether scheduled or unscheduled, must be entered in the patient's eCRF (local laboratory results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions).

[v] Fasting glucose, cholesterol, lipids, and HbA1c should be included on Day 1 of every third cycle starting with Cycle 10 (eg, Cycle 10, Cycle 13, Cycle 16), including during single-agent therapy and at the EOT visit, or more frequently as clinically indicated.

[w] CRP, cTnI assessments, and NT-proBNP or BNP assessments must be included with every blood draw (except Cycle 10, Day 7) to assess CV risks or more frequently as clinically indicated. In patients with persistent elevation of cTnI or NT-proBNP/BNP, performing an ECHO and/or consulting a cardiologist should be considered.

[x] BM aspirate must occur within ±7 days of the scheduled assessments. BM aspirates will continue on Day 1 of every sixth cycle starting with Cycle 10 (ie, Day 1 of Cycles 10 and 16). During the single-agent therapy phase, sampling will start on Day 1 of Cycle 21 and then at least annually (eg, Day 1 of Cycles 21, 33, and so on) to be consistent with the visit schedule. BM aspirates may be performed at other times as per SOC or when clinically indicated. Tests related to CR and relapse from CR assessments should be performed locally. A portion of BM aspirate sample will be sent to a local laboratory for CR and relapse from CR assessments. At any point that a BM aspirate is collected for tests related to CR and relapse from CR assessments, a portion of BM aspirate sample should also be sent to central laboratory for molecular assessment. In instances where a BM aspirate is a dry tap, BM biopsy could be used (any BM biopsy sample, if collected, will be evaluated locally). Results from local laboratory testing of any BM aspirate (or biopsy, if performed), whether scheduled or unscheduled, must be recorded in the patient's eCRF (local BCR-ABL1 results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions).

[y] Confirmation of loss of MRD negativity: In the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks at the central laboratory, with either a BM aspirate (optional) or peripheral blood, unless associated with loss of MR3 or relapse from CR.

[z] BM aspirate to be collected at EOT visit with the exception of not being required if BM was collected through C4D1 and the EOT visit date is less than 4 weeks from last BM collection.

[aa] Peripheral blood samples for molecular response assessment must occur within 7 days of the scheduled assessments. Samples will be obtained on Day 1 of every third cycle starting with Cycle 10 (eg, Cycles 10, 13, 16, 19). During the single-agent therapy phase, sampling will start on Day 1 of Cycle 21 (eg, Cycles 21, 24, 27) to be consistent with the visit schedule. A portion of the sample collected for molecular response assessment may also be used for exploratory biomarker assessment; which will include analysis of molecular determinants of response or resistance to ponatinib or imatinib, including BCR-ABL1 mutation analysis and/or biomarkers affecting ponatinib efficacy or safety. Specific instructions for collection of peripheral blood for molecular response and exploratory assessments will be provided in the laboratory manual. In the event that a patient had achieved MRD negativity at the previous assessment and subsequently no longer meets the criteria for achievement, MRD status should be assessed again within 4 weeks, with either a BM aspirate (optional) or peripheral blood.

[bb] Hepatitis B serology will be performed as clinically indicated for hepatitis B surface antigen, hepatitis B core antibody, and hepatitis B surface antibody, at minimum. Note: Patients who are chronic carriers of hepatitis B virus and receive a BCR-ABL1 TKI therapy may have a reactivation of hepatitis B. For patients with evidence of prior or current hepatitis B infection, please refer to Section 8.8 and the investigator's brochure.

[cc] Extramedullary assessments will be performed locally as clinically indicated and will include lumbar punctures to test CSF for CNS disease at the EOT visit and as clinically indicated during the maintenance phase and the single-agent therapy phase. Additional assessments for other extramedullary involvement (ie, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass) should be performed as clinically indicated throughout the study. When imaging studies have been used to assess extramedullary involvement, the same imaging methods should be used consistently throughout the study for individual patients. Results from local laboratory testing, whether scheduled or unscheduled, must be recorded in the patient's eCRF.

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Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50 ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should

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contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor. *This responsibility lies on the appropriate individual, designated by the site in Japan.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other identifying personal information. In addition, the investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the UK, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

The investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

The investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

The investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

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Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am Jf Clin Oncol. 1982; 5(6):649-55.

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Appendix E Drugs With a Risk of TdP

Four categories of QT-prolonging drugs that may be used as a guide for this protocol can be accessed at crediblemeds.org. This website identifies drugs with known risk of TdP, drugs with possible risk of TdP, drugs with conditional risk of TdP (ie, can cause TdP under certain conditions), and drugs to be avoided by congenital long QT patients. The investigator site should register (under the "For Healthcare Providers" tab) to access these categories. If the investigator site does not wish to register, a composite list, including all categories, is available.

A subset of drugs categorized in crediblemeds.org as having a known risk, a possible risk, and a conditional risk of TdP that are often used to treat patients including those with hematologic cancer are listed in Table 1; drugs with a known risk are presented in **bold** font and should be avoided.

Note: The website and table are only to be used as a guideline and are not comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as causing TdP.

Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Aclarubicin	**Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin**	Anti-cancer	**KR**
Alimemazine (Trimeprazine)	Nedeltran, Panectyl, Repeltin, Therafene, Theraligene, Theralen, Theralene, Vallergan, Vanectyl, Temaril	Antihistamine	PR
Amantadine	Symmetrel, Symadine	Antiviral	CR
Amiodarone	**Cordarone, Pacerone, Nexterone**	Antiarrhytmic	**KR**
Amisulpride	Barhemsys, Solian, Supitac, Soltus, Amitrex, Amazeo	Antiemetic, Antipsychotic	CR
Amitriptyline	Tryptomer, Tryptizol, Laroxyl, Saroten, Sarotex, Lentizol, Endep	Antidepressant	CR
Amphotericin B	Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, amphocil	Antifungal	CR
Amsacrine	Amsidine	Antineoplastic agent	CR
Anagrelide	**Agrylin, Xagrid**	Phospodiesterase 3 inhibitor	**KR**
Aripiprazole	Ability, Aripiprex	Antipsychotic, atypical	PR
Arsenic trioxide	**Trisenox**	Anti-cancer	**KR**
Asenapine	Saphris, Sycrest	Antipsychotic, atypical	PR
Astemizole	**Hismanal**	Antihistamine	**KR**
Atomoxetine	Strattera	CNS stimulant	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Azithromycin	**Zithromax, Zmax**	Antibiotic	**KR**
Bedaquiline	Sirturo	Antibiotic	PR
Bendamustine	Treanda, Treakisym, Ribomustin, Levact	Anti-cancer	PR
Bendroflumethiazide	Aprinox, Corzide	Diuretic thiazide	CR
Benperidol	Anquil, Glianimon	Antipsychotic	PR
Bepridil	**Vascor**	Antianginal	**KR**
Betrixaban	Bevyxxa	Anticoagulant	PR
Bortezomib	Velcade, Bortecad	Proteasome inhibitor	PR
Bosutinib	Bosulif	Anticancer	PR
Buprenorphine	Butrans, Belbuca, Bunavail, Buprenex, Subutex, Suboxone, Zubsolv	Opioid agonist	PR
Cabozantinib	Cometriq	Anticancer	PR
Capecitabine	Xeloda	Anticancer	PR
Carbetocin	Pabal, Lonactene, Duratocin	Uteotonic	PR
Ceritinib	Zykadia	Anticancer	PR
Cesium Chloride	**Energy Catalyst**	Toxin	**KR**
Chloral hydrate	Aquachloral, Novo-Chlorhydrate, Somnos, Noctec, Somnote	Sedative	CR
Chloroquine	**Aralen**	Antimalarial	**KR**
Chlorpromazine	**Thorazine, Largactil, Megaphen**	Antipsychotic/ Antiemetic	**KR**
Chlorprothixene	**Truxal**	Antipsychotic	**KR**
Cilostazol	**Pletal**	Phosphodiesterase 3 inhibitor	**KR**
Cimetidine	Tagamet	Antacid	CR
Ciprofloxacin	**Cipro, Cipro-XR, Neofloxin**	Antibiotic	**KR**
Cisapride	**Propulsid**	GI stimulant	**KR**
Citalopram	**Celexa, Cipramil**	Antidepressant, SSRI	**KR**
Clarithromycin	**Biaxin, Prevpac**	Antibiotic	**KR**
Clofazimine	Lamprene	Antibiotic	PR
Clomipramine	Anafranil	Antidepressant, tricyclic	CR
Clotiapine	Entumine	Antipsychotic, atypical	PR
Clozapine	Clozaril, Fazaclo, Versacloz	Antipsychotic, atypical	PR
Cobimetinib	Cotellic	Anticancer	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Cocaine	**Cocaine**	Local anesthetic	**KR**
Crizotinib	Xalkori	Anticancer	PR
Cyamemazine (Cyamepromazine)	Tercian	Antipsychotic	PR
Dabrafenib	Tafinlar	Anticancer	PR
Dasatinib	Sprycel	Anticancer	PR
Degarelix	Firmagon, Ferring	Anti-androgen	PR
Delamanid	Deltyba	Antibiotic	PR
Desipramine	Pertofrane, Norpramin	Antidepressant, tricyclic	PR
Dexmedetomidine	Precedex, Dexdor, Dexdomitor	Sedative	PR
Dextromethorphan (Quinidine)	Neudexta	Unknown	PR
Diphenhydramine	Benadryl, Nytol, Unisom, Sominex, Dimedrol, Daedalon, Banophen	Antihistamine	CR
Disopyramide	**Norpace**	Antiarrhythmic	**KR**
Dofetilide	**Tikosyn**	Antiarrhythmic	**KR**
Dolasetron	Anzemet	Antiemetic	PR
Domperidone	**Motilium, Motillium, motinorm Costi, Nomit for complete list see: *drugs.com/international/domperidone.html***	Antiemetic	**KR**
Donepezil	**Aricept**	Cholinesterase inhibitor	**KR**
Doxepin	Silenor, Sinequa, Aponal, Adapine, Doxal, Deptran, Sinquan	Antidepressant	CR
Dronedarone	**Multaq**	Antiarrhythmic	**KR**
Droperidol	**Droleptan, Dridol, Inapsine, Xomolix**	Antipsychotic / Antiemetic	**KR**
Encorafenib	Braftovi	BRAF inhibitor	PR
Eperisone	Myonal Epry	Antispasmodic	CR
Epirubicin	Ellence, Pharmorubicin, Epirubicin Ebewe	Anticancer	PR
Eribulin mesylate	Halaven	Anticancer	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Erythromycin	**E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Sterate Filmtab, Erythrocot, e-Base, Erythroped, Elosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth**	Antibiotic	**KR**
Escitalopram	**Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil**	Antidepressant, SSRI	**KR**
Esomeprazole	Nexium, Nexum, Inexium	Proton Pump Inhibitor	CR
Ezogabine (Retigabine)	Potiga, Trobalt	Anticonvulsant	PR
Famotidine	Pepci, Fluxid, Quamatel	H2-receptor antagonist	CR
Felbamate	Felbatol	Anticonvulsant	PR
Flecainide	**Tambocor, Almarytm, Apocard, Ecrinal, Flécaine**	Antiarrhythmic	**KR**
Fluconazole	**Diflucan, Trican**	Antifungal	**KR**
Fluorouracil (5-FU)	Adrucil, Carac, Efudex, Efudix	Anticancer	CR
Fluoxetine	Prozac, Sarafem, Fontex	Antidepressant	CR
Fluvoxamine [b]	Luvox, Luvox CR	Antidepressant, SSRI	CR
Flupentixol	Depixol, Fluanxol	Antipsychotic	PR
Fluvoxamine	Faverin, Fevarin, Floxyfral, Dumyrox, Luvox	SSRI	CR
Furosemide	Lasix, Fusid, Frumex, Lasilix	Diuretic	CR
Garenoxacin	Geninax	Antibiotic	CR
Gatifloxacin	**Tequin**	Antibiotic	**KR**
Gemifloxacin	Factive	Antibiotic	PR
Gilteritinib	Xospata	Antineoplastic	PR
Glasdegib	Daurismo	Anticancer	PR
Granisetron	Granisol, Kytril, Sancuso	Antiemetic	PR
Grepafloxacin	**Raxar**	Antibiotic	**KR**
Haloperidol	**Haldol, Aloperidin, Biperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol**	Antipsychotic	**KR**
Hydrochlorothiazide	Apo-Hydro, Aquazide H, BP Zide, Dichlotride, Hydrodiuril, Hydrosaluric, Microzide, Esidrex, Oretic	Diuretic	CR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Hydrocodone-ER	Hysingla™ ER, Zohydro ER	Analgesic	PR
Hydroquinidine	**Serecor**	Antiarrhythmic	**KR**
Hydoxychloroquine	**Plaquenil, Quineprox**	Anti-inflammatory, antimalarial	**KR**
Hydroxyzine	Atarax, Vistaril, Aterax, Alamon, Durrax, Equipose, Masmoran, Orgatrax, Paxistil Quiess, Tran-Q, tranquizine	Antihistamine	CR
Ibutilide	**Corvert**	Antiarrhytmic	**KR**
Iloperidone	Fanapt, Fanapta, zomaril	Antipsychotic, atypical	PR
Imipramine (melipramine)	Tofranil	Antidepressant	PR
Indapamide	Lozol, Natrilix, Insig	Diuretic	CR
Inotuzumab ozogamicin	Besponsa	Anti-cancer	PR
Isradipine	Dynacirc	Antihypertensive	PR
Itraconazole	Spranox, Onmel	Antifungal	CR
Iabradine	Procoralan, Coralan, Corlentor, Coraxan, Ivabid, Bradia	Antianginal	CR
Ivosidenib	Tibsovo	IDH1 inhibitor	PR
Ketanserin	Sufrexal	Antihypertensive	PR
Ketoconazole	Nizoral, Sebizole, Ketomed, Keton	Antifungal	CR
Lacidipine	Lacipil, Motens	Calcium channel blocker	PR
Lansoprazole	Prevacid, Ogast	Proton Pump Inhibitor	CR
Lapatinib	Tykerb, Tyverb	Anticancer	PR
Lefamulin	Xenleta	Antibiotic	PR
Lenvatinib	Lenvima	Anticancer	PR
Leuprolide	Eligard, Lupron, Viadur, Carcinil, Enanton, Leuplin, Lucrin, Procren, Prostap	Anticancer	PR
Levetiracetam	Keppra	Anti-seizure	PR
Levofloxacin	**Levaquin, Tavanic**	Antibiotic	**KR**
Levomepromazine (Methotrimeprazine)	**Nosinan, Nozinan, Levoprome**	Antipsychotic	**KR**
Levosulpiride	**Lesuride, Levazeo, Enliva**	Antipsychotic	**KR**
Linezolid	Zyvox, Zyvoxam, Zyvoxid	Antibiotic	PR
Lithium	Eskaith, Lithobid	Antimanic	PR
Loperamide	Imodium	Opioid agonist	CR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Lumateperone	Caplyta	Antipsychotic, atypical	PR
Lurasidone	Latuda	Antipsychotic, atypical	PR
Maprotiline	Ludiomil	Anti-depressant, tetracyclic	PR
Melperone	Bunil, Buronil, Eunerpan	Antipsychotic, atypical	PR
Mesoridazine	**Serentil**	Antipsychotic	**KR**
Methadone	**Dolohine, Symoron, Amidone, Methadose, Physeptone, Heptadon**	Opioid agonist	**KR**
Metoclopramide	Gimoti, Afipran, Maxolon, Cerucal, Clopamon, Clopra, Maxeran, Metozolv, Reglan, Plasil, Pramin, Primperan, Perinorm	Antiemetic	CR
Metolazone	Zytanix, Zaroxolyn, Mykrox	Diuretic	CR
Metronidazole	Flagyl, Helidac	Antibiotic	CR
Mianserin	Tolvon	Antidepressant	PR
Midostaurin	Rydapt	Anticancer	PR
Mifepristone	Korlym, Mifeprex	Progesterone antagonist	PR
Mirabegron	Myrbetriq	Beta3 adrenergic antagonist	PR
Mirtazapine	Remeron	Antidepressant, tetracyclic	PR
Moxifloxacin	**Avelox, Avalox, Avelon**	Antibiotic	**KR**
Necitumumab	Portrazza	Anticancer	PR
Nicardipine	Cardene	Antihypertensive	PR
Nifekalant	**Shinbit**	Antiarrhythmic	**KR**
Nilotinib	Tasigna	Anticancer	PR
Norfloxacin	Noroxin, Ambigram	Antibiotic	PR
Nortriptyline	Aventyl, Pamelor, Sensova, Norpress, Allegron, Noritren, Nortilen	Antidepressant, tricyclic	PR
Nusinersen	Spinraza	Antisense oligonucleotide	PR
Ofloxacin	Floxin	Antibiotic	PR
Olanzapine	Zyprexa, Zydis, Relprevv	Antipsychotic, atypical	CR
Oliceridine	Olinvyk	Analgesia	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Omeprazole	Losec, Prilosec, Zegerid, Mopral	Proton Pump Inhibitor	CR
Ondansetron	**Zofran, Anset, Emeset, Emetron, Ondavell, Ondemet, Ondisolv, Setronax, Zuplenz**	Antiemetic	**KR**
Osimertinib	Tagrisso	Anticancer	PR
Oxaliplatin	**Eloxatin**	Anticancer	**KR**
Paliperidone	Invega, Xepilon	Antipsychotic, atypical	PR
Palonosetron	Aloxi	Antiemetic	PR
Pantoprazole	Protonix, Inipomp, Eupantol	Proton Pump Inhibitor	CR
Papaverine HCl		Vasodilator, coronary	**KR**
Paroxetine	Aropax, Paxil, Pexeva, Seroxat, Sereupin, Deroxat	Antidepressant, SSRI	CR
Pazopanib	Votrient	Anticancer	PR
Pentamidine	**Pentam**	Antifungal	**KR**
Perphenazine	Trilafon, Etrafone/Triavil, Decentran	Antipsychotic	PR
Pilsicainide	Sunrythm	Antiarrhythmic	PR
Pimvanserin	Nuplazid	Antipsychotic, atypical	PR
Pimozide	**Orap**	Antipsychotic	**KR**
Pipamperone	Dipiperon, Propitan, Diperperal, Piperonil, Piperonyl	Antipsychotic	PR
Piperacillin/Tazobactam	Tazosyn, Zosyn	Antibiotic	CR
Pitolisant	Wakix	Histamine 3 antagonist/ inverse agonist	PR
Posaconazole	Noxafil, Posamol	Antifungal	CR
Pretomanid		Antitubercular	PR
Probucol	**Lorelco**	Antilipemic	**KR**
Procainamide	**Pronestyl, Procan**	Antiarrhythmic	**KR**
Promethazine	Phenergan	Antiemetic	PR
Propafenone	Rythmol SR Rytmonorm	Sodium channel blocker	CR
Propofol	**Diprivan, Propoven**	Anesthetic	**KR**
Prothipendyl	Domminal, Largophren, Timoval, Timovan, Tumovan	Antipsychotic	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Quetiapine	Seroquel	Antipsychotic, atypical	CR
Quinidine	**Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora**	Antiarrhytmic	**KR**
Ranolazine	Ranexa, Ranozex	Antianginal	CR
Remimazolam	Byfavo	Sedative	PR
Ribociclib	Kisqali	Anticancer	PR
Risperidone	Risperdal	Antipsychotic, atypical	CR
Roxithromycin	**Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin**	Antibiotic	**KR**
Sertindole	**Sedolect, Serlect**	Antipsychotic, atypical	**KR**
Sertraline	Zoloft, Lustral	Antidepressant, SSRI	CR
Sevoflurane	**Ulane, Sojourn**	Anesthetic	**KR**
Solifenacin	Vesicare	Muscle relaxant	CR
Sorafenib	Nexavar	Anticancer	PR
Sotalol	**Betapace, Sotalex, Sotacor, Sotalol-AF**	Antiarrhythmic	**KR**
Sparfloxacin	**Zagam**	Antibiotic	**KR**
Sulpiride	**Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor**	Antipsychotic, atypical	**KR**
Sultopride	**Barnetil, Barnotil, Topral**	Antipsychotic, atypical	**KR**
Sunitinib	Sutent	Anticancer	PR
Tacrolimus	Prograf, Advagraf, Protopic	Immunosuppressant	PR
Tamoxifen	Nolvadex, Istubal	Anticancer	PR
Telaprevir	Incivo, Incivek	Antiviral	CR
Telavancin	Vibativ	Antibiotic	PR
Telithromycin	Ketek	Antibiotic	PR
Terfenadine	**Seldane**	Antihistamine	**KR**
Terlipressin	**Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss**	Vasoconstrictor	**KR**
Terodiline	**Micturin, Mictrol**	Muscle relaxant	**KR**
Thioridazine	**Mellaril, Novoridazine, Thioril**	Antipsychotic	**KR**
Tipiracil / Trifluridine	Lonsurf	Anticancer	PR
Tizanidine	Zanaflex, Sirdalud	Muscle relaxant	PR
Tolterodine	Detrol, Detrusitol	Muscle relaxant	PR

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Table 1 Drugs Listed as Having a Known, Possible, or Conditional Risk of TdP

Generic Name	Brand Name	Class	Risk Category [a]
Toremifene	Fareston	Estrogen agonist/ antagonist	PR
Torsemide (Torasemide)	Demadex, Diuver, Examide	Diuretic	CR
Tramadol	Crispin, Ralivia ER, Ralivia, Flashtab, Tramadolum, Tramal, Tramodol, Tridural, Ultram, Ultram ER, Zydol, Ixprim, Zaldiar, Topalgic	Analgesic	PR
Trazodone	Desyrel, Desirel, Oleptro, Beneficat, Deprax, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, Mesyrel	Antidepressant, SARI	CR
Trimipramine	Surmontil, Rhotrimine, Stangyl	Antidepressant, tricyclic	PR
Tropisetron	Navoban, Setrovel	Antiemetic	PR
Valbenazine	Ingrezza	Vesicluar monamine transporter 2 inhibitor	PR
Vandetanib	**Caprelsa**	Anticancer	**KR**
Vardenafil	Levitra	Phosphodiesterase 5 inbibitor	PR
Vemurafenib	Zelboraf	Anticancer	PR
Venlafaxine	Effexor, Efexor	Antidepressant, SNRI	PR
Voclosporin	Lupkynis	Immunosupressant	PR
Voriconazole	VFend	Antifungal	CR
Vorinostat	Zolinza	Anticancer	PR
Ziprasidone	Geodon, Zeldox	Antipsychotic, atypical	CR
Zotepine	Losizopilon, Lodopin Setous, Zoleptil	Antipsychotic, atypical	PR
Zuclopenthixol (Zuclopentixol)	Cisordinol, Clopixol, Acuphase	Antipsychotic	PR

Source: crediblemeds.org; QTDrugs List, revision date 03 May 2021.

Abbreviation: CR, conditional risk; KR, known risk; PR, possible risk; TdP, torsades de pointes.

[a] KR of TdP: Substantial evidence supports the conclusion that these drugs prolong the QT interval *and* are clearly associated with a risk of TdP, even when taken as directed in official labeling.

[b] CR of TdP: Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP *but* only under certain conditions (eg, excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation).

[c] PR of TdP: Substantial evidence supports the conclusion that these drugs can cause QT prolongation *but* there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

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Appendix F Drugs That Inhibit or Induce CYP3A

The list of drugs that inhibit or induce CYP3A can be found online at fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm [Accessed 07 February 2018]. Drugs listed as strong inhibitors and inducers of CYP3A should be avoided, if possible. See Section 8.5, for dose reduction recommendations if medications that are strong CYP3A inhibitors are required and a suitable alternative cannot be identified.

Note: The website should be used as a guideline and is not necessarily comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as strong CYP3A4/5 inhibitors or inducers.

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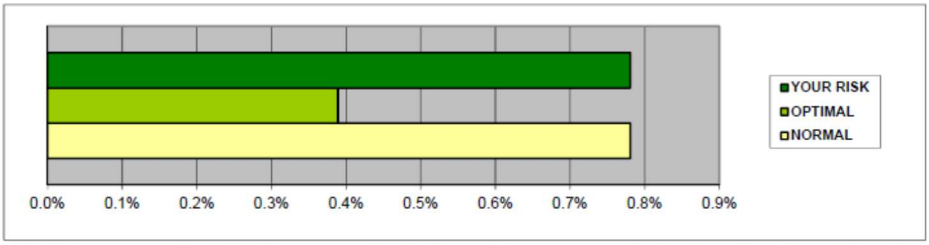
Appendix G Copy of Framingham Score

The following is a sample screenshot of the Framingham score; the Framingham score tool will be supplied in the site operations manual.

From The Framingham Heart Study	Enter Values Here		
General CVD Risk Prediction			
Risk Factor	**Units**	**(Type Over Placeholder Values in Each Cell)**	**Notes**
Sex	male (m) or female (f)	f	
Age	years	24	Enter a Value Between 30-74
Systolic Blood Pressure	mmHg	125.0	
Treatment for Hypertension	yes (y) or no (n)	n	
Smoking	yes (y) or no (n)	n	
Diabetes	yes (y) or no (n)	n	
HDL	mg/dL	45	
Total Cholesterol	mg/dL	180	
Your 10-Year Risk (The risk score shown is derived on the basis of an equation. Other print products, use a point-based system to calculate a risk score that approximates the equation-based one.)		0.8%	*If value is < the minimum for the field, enter the minimum value. If value is > the maximum for the field, enter the maximum value.*
Your Heart/Vascular Age		24	



Calculator prepared by R.B. D'Agostino and M.J. Pencina based on a publication by D'Agostino et al. in Circulation

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Appendix H EQ-5D-5L

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

SAMPLE

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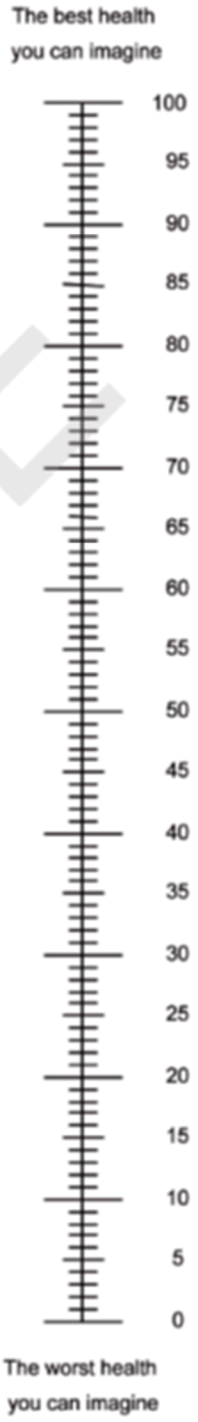
- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



SAMPLE

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Appendix I FACT-Leu

FACT-Leu (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

English (Universal)
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FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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FACT-Leu (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
BRM2	I am bothered by the chills	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
TH1	I bleed easily	0	1	2	3	4
TH2	I bruise easily	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
BMT9	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU5	I feel uncertain about my future health	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4

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Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate

Loading dose:	
Leucovorin 50 mg IV or PO (× 1 dose)	Starting 12 (±2) h after completion of methotrexate infusion
Additional:	
Leucovorin 15 mg IV or PO q6 h (× 8 doses) until serum methotrexate level is <0.1 µM/L (if the methotrexate level is <0.1 µM/L with fewer than 8 doses of leucovorin, then leucovorin can be discontinued).	Starting 6 h after completion of loading dose
Note:	
Increase leucovorin rescue to 50 mg IV or PO q6 h until serum methotrexate level is <0.1 µM/L	If methotrexate level is >20 µM/L at time "0" (first assessment) OR If methotrexate is >1 µM/L at 24 h OR If methotrexate is >0.1 µM/L at 48 h

Abbreviations: IV, intravenous; PO, by mouth; q, every.

Alternative dose modifications/schedules may be recommended after discussion with the investigator and sponsor's medical monitor/designee to maximize exposure of study treatment while protecting patient safety. Sites can implement an alternative rescue therapy for methotrexate as per their standard of care.

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Appendix K Cytarabine Dose Adjustments for Creatinine Clearance Values

Serum Creatinine Clearance (CrCl) Value	Cytarabine Dose Adjustment
89-60 mL/min	1000 mg/m^2 q12 h on Days 1, 3, and 5
59-30 mL/min	500 mg/m^2 q12 h on Days 1, 3, and 5
29-15 mL/min	500 mg/m^2 q24 h on Days 1, 3, and 5 OR Option to stop
<15 mL/min or hemodialysis	Stop cytarabine.

Abbreviations: CrCl, creatinine clearance; q, every.

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Appendix L Management of Tumor Lysis Syndrome

Patients at risk for TLS should receive prophylaxis consistent with local guidelines. Prophylaxis may include hydration with diuresis, alkalinization of the urine, and treatment with allopurinol or other approved uric acid lowering agents.

If TLS occurs, patients should receive treatment and supportive care consistent with local guidelines. The management for TLS includes adequate hydration, management of hyperuricemia, management of electrolyte abnormalities, and additional supportive care including monitoring of renal function and fluid balance, as clinically indicated. General guidelines for management of electrolyte abnormalities with TLS are presented in the table below [42]. Management of hyperuricemia should be done per best local practice. Rasburicase is indicated in cases where uric acid remains elevated despite treatment with allopurinol or in patients with renal insufficiency [43].

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Table 1 Management of Electrolyte Abnormalities for TLS

Abnormality	Management Recommendation
Hyperphosphatemia	
Moderate, ≥2.1 mmol/L	Avoid IV phosphate administration Administration of phosphate binder
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia, ≤1.75 mmol/L	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate 50-100 mg/kg IV administered slowly with ECG monitoring
Hyperkalemia	
Moderate and asymptomatic, ≥6.0 mmol/L	Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate
Severe (>7.0 mmol/L) and/or symptomatic	Same as above, plus: Calcium gluconate 100-200 mg/kg by slow IV infusion for life-threatening arrhythmias Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV Sodium bicarbonate (1-2 mEq/kg IV push) can be given to induce influx of potassium into cells. However, sodium bicarbonate and calcium should not be administered through the same line Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemo- or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)

Source: Coiffier B et al, 2008.

Abbreviations: CAVH, continuous arterial-venous hemodialysis; CAVHD, continuous arterial-venous hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; ECG, electrocardiogram; IV, intravenous; TLS, tumor lysis syndrome.

Alterations per local guidelines are acceptable.

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Appendix M Enrollment Projections at Primary Endpoint Analyses

Table 1 Enrollment Projections at Primary Endpoint Analyses

Analyses	Time Point From FPI	Time Point From Last Patient In for This Analysis	Enrollment Percentage at the Time of Data Cutoff Date	Enrollment Percentage at the Time of Topline Data Report	Additional Comments
MRD-negative CR IA	FPI + 2 years	Approximately 3.5 months after 115 patients enrolled	57%-63%	66%-83%	
MRD-negative CR FA if MRD-negative CR IA is not statistically significant	FPI + 3 years	Approximately 3.5 months after 230 patients enrolled	100%	100%	120-day safety data will include a minimum of 12 months of follow up for the final analysis on the primary endpoint

Abbreviations: CR, complete remission; FA, final analysis; FPI, first patient in; IA, interim analysis; MRD, minimal residual disease.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	29-Oct-2021 20:07 UTC
	Clinical Pharmacology Approval	29-Oct-2021 21:04 UTC
	Biostatistics Approval	29-Oct-2021 22:11 UTC

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Appendix N Amendment History

Date	Amendment Number	Amendment Type	Region
20 October 2021	10	Substantial	Global
07 May 2021	9	Substantial	Global
10 February 2021	8	Substantial	Global
13 August 2019	7	Substantial	Japan
29 July 2019	6	Substantial	Argentina
23 July 2019	5	Substantial	South Korea
09 May 2019	4	Substantial	Global
06 December 2018	3	Substantial	South Korea
08 Nov 2018	2	Substantial	Global
22 May 2018	1	Nonsubstantial	Global
12 March 2018	Initial Protocol	Not applicable	Global

Rationale for Amendment 9

This section describes the changes to the protocol incorporating Amendment 9. The primary reason for this amendment is to:

- Clarify that the breakpoint cluster region-Abelson (BCR-ABL1)/ABL1 minimal residual disease (MRD) assessment will be conducted using the same methodology in more than 1 central laboratory due to local regulations that prohibit shipping of biological samples.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included in this amendment for clarification and administrative purposes only and are not listed in the summary of changes below.

Protocol Amendment 9			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	**Description**	**Rationale**
21.	Section 2.0 Study Summary Section 6.1 Overview of Study Design	Clarified that the BCR-ABL1/ABL1 MRD assessment will be conducted using the same methodology in more than 1 central laboratory.	Due to local regulations that prohibit shipping of biological samples, more than 1 central laboratory is required.
22.	Section 9.1 Study Personnel and Organizations	Updated "central laboratory" to "central laboratories" and deleted "any additional clinical laboratories" to reflect the use of more than 1 central laboratory.	More than 1 central laboratory is being used in the study.
23.	Appendix A Schedule of Events Table 1, Footnote y	Deleted from Footnote y: (which is required as per the study inclusion criteria 3)	Correction; inclusion criterion 3 was deleted in Amendment 8.

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Rationale for Amendment 8

This section describes the changes to the protocol incorporating Amendment 8. The primary reasons for this amendment are to:

- Change the study design:
  - From an adaptive design to a group sequential design for the primary endpoint of minimal residual disease (MRD)-negative complete remission/response (CR) at the end of induction (CR and breakpoint cluster region-Abelson [BCR ABL1]/ABL1 ≤0.01%).
  - To add an interim analysis for event-free survival (EFS).
- Update the definition for EFS.
- Provide guidance for collecting data, conducting study procedures, and managing investigational product(s) to maintain patient safety, confidentiality, and study integrity during unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included in this amendment for clarification and administrative purposes only and are not listed in the summary of changes below.

Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Global Protocol			
Sections Affected by Change		**Description of Each Change and Rationale**	
Location		**Description**	**Rationale**
1.	Title Page Section 2.0 Study Summary Section 3.4 Corporate Identification	Replaced sponsor information for Millennium Pharmaceuticals with sponsor information for Takeda Development Center Americas.	Administrative change.
2.	Section 2.0 Study Summary	Clarified that study data will be evaluated for approximately 3-6 years rather than 5 years after enrollment of the last patient.	Clarification.
3.	Section 2.0 Study Summary Section 5.1.2 Secondary Objectives	Removed "the rate of" from the key secondary objective to clarify that the comparison of event-free survival (EFS) is the objective rather than rate of EFS. Removed "To compare the rate of MR4.5 (including best response) between the 2 cohorts, at multiple intervals including the end of induction, the end of consolidation, and prior to HSCT." from Secondary Objectives.	Clarification.

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Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Global Protocol			
Sections Affected by Change		**Description of Each Change and Rationale**	
Location		**Description**	**Rationale**
4.	Section 5.2.2.1 Key Secondary Endpoints Section 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures (Table 6.a) Section 13.1.3.2 Key Secondary Efficacy Endpoint Assessment Section 13.1.3.4 Definitions of Response Criteria	Removed "minimum residual disease (MRD)-negative" from the definition of EFS.	Updated the definition for EFS so that one of the events for EFS is based on failure to achieve CR by the end of induction instead of failure to achieve MRD-negative CR by the end of induction.
5.	Section 2.0 Study Summary Section 5.2.2.2 Other Secondary Endpoints Section 6.1 Overview of Study Design Section 13.1.3.3 Other Secondary Efficacy Endpoint Assessments	Removed "Rates of molecular response (MR)4.5 (including best response) at multiple intervals including the end of induction, the end of consolidation, and prior to hematopoietic stem cell transplantation (HSCT)" from the Other Secondary Endpoints. Clarified that overall survival (OS) and rate of relapse from CR are the only analyses to be conducted specifically for on-study patients with and without HSCT.	Clarification.
6.	Section 2.0 Study Summary Section 6.1 Overview of Study Design	Clarified that for patients in the ponatinib cohort who achieve CR but do not achieve the primary endpoint at the end of induction and who continue in the study at the investigator's discretion, the dose of ponatinib "will be" reduced at any time when the patient achieves MRD-negative CR and re-escalated upon loss of response.	Clarification on ponatinib dose modification for patients who achieve MRD-negative CR anytime during the study.
7.	Section 2.0 Study Summary Section 6.2 Number of Patients Section 13.3 Determination of Sample Size	Clarified that the number of patients enrolled in the study is to be approximately 230 and increased the number of study sites from 110 to 120.	Increased the number of study sites to meet accrual goals.

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Protocol Amendment 8			
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Sections Affected by Change		**Description of Each Change and Rationale**	
Location		**Description**	**Rationale**
8.	Section 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures Section 13.1.3.4 Definitions of Response Criteria	Replaced the definition of relapse from CR with a link to the definition in Table 13a. Clarified that overall survival (OS) and rate of relapse from CR are the only analyses to be conducted specifically for on-study patients with and without HSCT. Revised the interval for OS to begin at "randomization" rather than "the first dose date of study drug".	Updated to reference the definition of relapse from CR through a link to Table 13a and to accurately reflect the interval for OS.
9.	Section 6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures	Updated the maximum time frame for the key secondary endpoint of EFS from approximately 3 years to approximately 3-6 years. Revised the maximum time frame for several key secondary endpoints from "up to approximately 3 years" or "updated annually after year 3" to "up to approximately 3-6 years".	Revised based on the change in study design and projected timing of EFS based on the interim analysis (IA) for EFS.
10.	Section 6.3.4 Total Study Duration	Clarified the duration of the study will be approximately 6 to 9 years, including approximately 36 months for enrollment and approximately 3-6 years of follow-up from the date that the last patient enrolled.	Revised based on the change in study design and projected timing of EFS based on the IA for EFS.
11.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria	Deleted inclusion criterion 3.	Stratification based on transcript type was removed from the study.
12.	Section 2.0 Study Summary Section 7.1 Inclusion Criteria	Removed "and amylase" from inclusion criterion 4 d (formerly 5 d).	Serum lipase is more specific than amylase for pancreatic abnormalities.
13.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Revised exclusion criterion 13 to allow the enrollment of patients with lymphadenopathy or hepatosplenomegaly.	Most patients with acute lymphoblastic leukemia have lymphadenopathy or hepatosplenomegaly.
14.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Revised exclusion criterion 16 e to clarify that isolated elevation(s) of systolic and/or diastolic BP during screening are not exclusionary.	Clarification to ensure true cases of hypertension are excluded.

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Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Global Protocol			
Sections Affected by Change		**Description of Each Change and Rationale**	
Location		**Description**	**Rationale**
15.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Revised exclusion criterion 16 f to clarify that patients will be excluded due to *any* history of myocardial infarction (MI), unstable angina, coronary artery disease (CAD), cerebrovascular accident (CVA), ischemic stroke, or transient ischemic attack (TIA), whether considered clinically significant or not.	Clarification
16.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Revised exclusion criterion 16.k to clarify that "patients with catheter-associated deep vein thrombosis (DVTs) which are considered to be resolved/controlled may be included after discussion with the sponsor's medical monitor/designee."	DVT is common in patients with Philadelphia chromosome–positive acute lymphoblastic leukemia; most events are catheter-related and easy to manage.
17.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Removed definition for poorly controlled diabetes from exclusion criterion 17.	Revised to allow clinical judgment for guiding eligibility of patients with diabetes mellitus.
18.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Deleted exclusion criteria 20 and 21.	These criteria are not relevant for this study.
19.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria Appendix A Table 1, Footnote d	Revised exclusion criterion 22 (formerly 24) to allow enrollment of female patients with a positive serum pregnancy test who have undergone a complete abortion in the last 4-6 weeks after discussion with the sponsor's medical monitor/designee.	Clarification.
20.	Section 2.0 Study Summary Section 8.1.2 Induction Phase (Cycles 1 Through 3) Section 8.1.3 Consolidation Phase (Cycles 4 Through 9)	Updated lumbar puncture assessment be performed to test CSF for CNS disease "as clinically indicated" in addition to Day 1 and Day 14 of the 3 induction phase cycles and the first 3 consolidation phase cycles (total: 6 cycles, 12 samples).	Clarification.
21.	Section 2.0 Study Summary Section 8.1.3 Consolidation Phase (Cycles 4 Through 9)	Updated methotrexate and cytarabine dosing information to revise age ranges from ≤ and > 60 years to < and ≥ 60 years. Removed an additional slash in the cytarabine dosing information to clarify that the dose is to be administered every 12 hours and not split into 2 doses.	Correction.

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Protocol Amendment 8			
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Location		**Description**	**Rationale**
22.	Section 2.0 Study Summary Section 8.1.3 Consolidation Phase (Cycles 4 Through 9)	Moved reference to Appendix K (cytarabine dose adjustment by creatinine clearance) to the <60 age group. Added that the cytarabine dose should be reduced or possibly discontinued for patients ≥60 years with impaired renal function.	Correction.
23.	Section 8.4.1.1 Dose Reduction for Drug-Related Adverse Events	Updated definitions for Grade 3 and Grade 4 events of pancreatitis and elevation of lipase leading to dose modification.	Updated to expand list of drug-related adverse events (AEs) of serum lipase and pancreatitis leading to dose modification.
24.	Section 8.4.1.2.2 VTEs	Removed the word "arterial" from "arterial venous thrombotic/embolic events (VTEs)".	Correction.
25.	Section 8.5 Excluded Concomitant Medications and Procedures	Clarified wording around medication that should be avoided. Corrected the following statement to read "Elective surgery requiring inpatient care that *can* be postponed until study completion."	Clarification and correction.
26.	Section 8.10.2 Imatinib	Revised the description of imatinib tablets to include generic imatinib.	Imatinib is available as a generic tablet, and both brand-name and generic forms could be used in the study.
27.	Section 8.13.2 Handling and Accountability Section 9.4.19 Changes to Study Procedures Due to COVID 19 Pandemic Section 13.1 Statistical and Analytical Plans Section 14.1 Study Site Monitoring Visits Section 14.2 Protocol Deviations Appendix A Schedule of Events	Added information about study procedure flexibility permitted in extenuating circumstances such as the coronavirus disease 2019 (COVID-19) pandemic. In the Schedule of Events all 2-day visit windows were changed to 3 days.	Revised to ensure the safety of patients participating in the study and the integrity of data collected during the course of the study during COVID-19 pandemic.
28.	Section 9.4.15.3 Appendix A Schedule of Events Table 2, footnote bb	Added that extramedullary assessments will be performed locally "as clinically indicated."	Clarification.

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Protocol Amendment 8			
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Location		**Description**	**Rationale**
29.	Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Updated procedures for recording and reporting AEs and serious adverse events (SAEs).	Updated to incorporate the sponsor's current procedures.
30.	Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Updated procedures for reporting drug exposure during pregnancy. Added that study drug must be discontinued immediately for patients who become pregnant.	Updated to incorporate the sponsor's current procedures and revised to ensure the safety of patients who may become pregnant during the study.
31.	Section 10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)	Updated procedures for reporting product complaints or medication errors (including overdose).	Updated to incorporate the sponsor's current procedures.
32.	Section 11.2 Independent Data Monitoring Committee	Added that "The independent data monitoring committee (IDMC) will review the outcomes at the interim and final analyses for MRD-negative CR, EFS, and the futility analysis for OS."	Updated to support the change in study design.
33.	Section 13.1.1.2 Per-Protocol Population Section 13.1.3.1 Primary Efficacy Endpoint Assessment	Added that a sensitivity analysis of the intent-to-treat (ITT) population for the primary efficacy endpoint, MRD negative CR, may be performed in the per-protocol (PP) population, if needed.	Clarification.
34.	Section 2.0 Study Summary Section 13.1.3 Efficacy Analysis Section 13.3 Determination of Sample Size	Revised the efficacy analysis and determination of sample size to reflect the change in study design from an adaptive design to a group sequential design.	Updated to incorporate the change in study design.
35.	Section 2.0 Study Summary Section 13.1.3 Efficacy Analysis Section 13.2 IA and Criteria for Early Termination	Revised text regarding the IA and criteria for early termination to reflect the change in study design.	Updated to incorporate the change in study design.

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Protocol Amendment 8			
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Location		**Description**	**Rationale**
36.	Section 13.1.3.4 Definitions of Response Criteria	Corrected the definition for loss of MR4.5 to state: "This result must be confirmed at the subsequent visit, unless it is associated with loss of MR3 or relapse from CR" rather than a loss of MR 4.5.	Correction.
37.	Section 13.1.7 Safety Analysis	Added that "a descriptive safety analyses of OS will be conducted at the IA (or FA, as applicable) for MRD-negative CR if there are a sufficient number of deaths to perform such an analysis."	Update.
38.	Section 13.2 IA and Criteria for Early Termination	Added a reference to Appendix M: Enrollment Projections at Primary Endpoint Analyses	Updated to incorporate the change in study design.
39.	Section 13.4 Blinding of Trial Management Team for Data Review	Revised study team blinding requirements to state that: the study team "will be blinded to treatment assignment for aggregate efficacy-related data, unless publicly released, as well as individual patient-level data (except a few members who are included in patient management and monitoring of the study; however, generation of any aggregate summary of efficacy data by treatment arm is not allowed)."	Update.
40.	Section 16.0 REFERENCES	The following citations/references were removed in this amendment: Mehta 2011, Hung 2006, Fielding 2010, Pfeifer 2010, Mizuta 2011, and Cui 1999. Hwang et al 1990 and Lan K, DeMets DL 1983 reference was added.	Adjusted to reflect text changes.
41.	Appendix A Schedule of Events Table 1, Footnote b	Clarified the use of local laboratory results during screening. Added that an Eligibility Verification Form and required supporting documentation, as allowed by local regulations, should be sent to the sponsor's medical monitor or designee as soon as the screening procedures are completed for confirmation of patient eligibility (specific instructions for randomization will be supplied in the site operations manual).	Updated to provide flexibility in obtaining laboratory results when screening patients for eligibility.
42.	Appendix A Schedule of Events Table 1, Footnotes f, g, j, u, and v	Updated "before dosing" to "before intravenous (IV) chemotherapy dosing".	Clarification.

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Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Global Protocol			
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Location		**Description**	**Rationale**
43.	Appendix A Schedule of Events Table 1, Footnotes h and j Appendix A Schedule of Events Table 2, Footnotes i and o	Clarified instructions for performing and recording blood pressure and electrocardiogram (ECG) assessments. Added to Table 1, footnote j and Table 2, footnote i that ECGs are to be interpreted by a local cardiologist "in cases where there are significant findings or when the investigator cannot interpret the findings."	Update and clarification. Revised to reduce the burden of having the local cardiologist interpret all ECGs.
44.	Appendix A Schedule of Events Table 1, Footnote v; Table 2, Footnote u.	Added to Table 1, footnote v and Table 2, footnote u: "local laboratory results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions."	Clarification.
45.	Appendix A Schedule of Events Table 1, Footnote x	Deleted from Table 1, Footnote x: "C-reactive protein (CRP), cardiac troponin-I (cTnI), and N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP assessments must also be included with blood draws Days 1, 7, 14, and 21 of Cycles 1-3 and Day 1 of Cycles 4-9 to assess cardiovascular (CV) risks," Added to Table 1, Footnote x: "For maintenance phase, CRP, cTnI assessments and NT-proBNP or BNP testing must be included with every blood draw (except Cycle 10, Day 7)."	Correction.
46.	Appendix A Schedule of Events Table 1, Footnote bb	Added to Table 1, Footnote bb: "Cycle 1 Day 1 molecular response assessments need not be repeated if the screening assessment was within 7 days before Cycle 1 Day 1."	Clarification.
47.	Appendix A Schedule of Events Table 2, Footnote w	Added to Table 2, Footnote w: performing an ECHO "and/or consulting a cardiologist" should be considered	Update.
48.	Appendix A Schedule of Events Table 1, Footnote y and Table 2, Footnote x	Deleted from Table 1, Footnote y: BM aspirate must occur within 28 days before enrollment. Added to Table 1, Footnote y and Table 2, Footnote x: " (local BCR-ABL1 results should only be entered if the local laboratory results and required supporting documentation are used for treatment-related decisions)."	Clarification.
49.	Appendix A Schedule of Events Table 2, footnote b	Revised one of the end-of-treatment (EOT) visit specifications from "the decision to discontinue treatment" to "30 days after a patient has discontinued the study drug".	Clarification.

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Protocol Amendment 8			
Summary of Changes Since the Last Version of the Approved Global Protocol			
Sections Affected by Change		**Description of Each Change and Rationale**	
Location		**Description**	**Rationale**
50.	Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate	Added the following for clarification: "if the methotrexate level is <0.1 μM/L with fewer than 8 doses of leucovorin, then leucovorin can be discontinued."	Clarification.
51.	Appendix K Cytarabine Dose Adjustments for Creatinine Clearance	Updated the serum creatinine clearance values for cytarabine dose adjustments: **From** **To** 90-60 mL/min 89-60 mL/min 60-30 mL/min 59-30 mL/min 30-15 mL/min 29-15 mL/min	Correction of overlapping serum creatinine clearance values.
52.	Appendix M Enrollment Projections at Primary Endpoint Analyses	Added Appendix M to present the enrollment projections for the primary endpoint analyses.	Updated to incorporate the change in study design.

Rationale for Amendment 07

This section describes the changes to the protocol incorporating Amendment 07. The primary reason for this amendment is to allow Japanese sites to enroll patients into cohort A (ponatinib) without any randomization.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Protocol Amendment 07		
Summary of Changes Since the Last Version of the Approved Protocol		
	Description of Each Change and Rationale	
Location	**Description**	**Rationale**
Section 9.4.3 Section 2.0 Study Summary, Section 6.1 Overview of Study Design, Section 7.1 Inclusion Criteria, Section 7.2 Exclusion Criteria, Section 8.9 Blinding and Unblinding, Section 9.3 Treatment Group Assignments, Section 9.4.1 Screening Period Procedures, Section 9.4.18 PK Measurements: Ponatinib, Section 13.1.1.1 Intent-to-Treat Population, Section 13.1.1.3 Safety Population, Section 13.1.3.1 Primary Efficacy Endpoint Assessment Section 13.1.3.4 Definitions of Response Criteria, Section 13.1.5.1 Time-to-Next-Treatment and Time-to-HSCT Analyses, Appendix A, Table 1, Footnotes b and y.	Clarified that patients enrolled at Japanese sites will be assigned (not randomized) only to cohort A (ponatinib).	"Enrollment" used to include both assignment (Japan) and randomization (rest of world) to cohorts.
Section 13.3.1 Rationale for Sample Size Selection in Japan. Section 2.0 Study Summary, Section 6.1 Overview of Study Design, Section 6.2 Number of Patients.	Added rationale for sample size selection for Japanese patients.	To provide rationale for the addition of 10 Japanese patients.
Section 13.1.3.1 Primary Efficacy Endpoint Assessment	Clarified that minimal residual disease-negative patients will be analyzed in the safety population	To include patients with MRD-negative CR in the safety population.
Section 13.1.3.2 Key Secondary Efficacy Endpoint Assessment	Clarified that event-free survival will be analyzed in the safety population	To include EFS analysis in the safety population.

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Rationale for Amendment 06

This section describes the changes to the protocol incorporating Amendment 06, this amendment applies only to Argentina. The primary reason for this amendment is to incorporate advice from the National Administration of Drugs, Food and Medical Technology.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 06		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 7.1 Inclusion Criteria Section 2.0 STUDY SUMMARY, Section 6.1 Overview of Study Design, Section 7.0 STUDY POPULATION.	Raised the minimum age for participation in this study from 18 years to 40 years	Raised the minimum age of study participants in order to comply with local laws.

Rationale for Amendment 05

This section describes the changes to the protocol incorporating Amendment 05; this amendment applies only to South Korea. The primary reasons for this amendment are to incorporate changes from global Amendment 04 including updating the stratification of randomization criteria to allow for patients to be randomized more proficiently, to revise exclusion criteria to be less restrictive, and to modify assessments on the schedule of events to be less of a burden on patients.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 2.0 Study Summary	Removed stratification factor 2 (Transcript 190 versus 210) from stratification of randomization.	Decrease frequency of ECOG assessments beginning at Cycle 10 from once per cycle to once every 3 cycles.
Section 6.1 Overview of Study Design	Added text to use blood samples if bone marrow (BM) samples are not evaluable or not available.	Decrease frequency of ECOG assessments beginning at Cycle 10 from once per cycle to once every 3 cycles.

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Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 7.1 Inclusion Criteria Section 2.0 STUDY SUMMARY. Section 6.1 Overview of Study Design. Section 7.0 STUDY POPULATION. Appendix A, Table 1 Schedule of Events: Screening, Induction Phase, and Consolidation Phases, footnote c.	Added upper limit to age for patients with comorbidities and/or poor functional status.	Added upper limit for clarification purposes.
Section 7.1 Inclusion Criteria Section 2.0 Study Summary	Revised inclusion criterion number 5.	Updated to align with other clinical studies within the ponatinib clinical program.
Section 7.1 Inclusion Criteria Section 2.0 Study Summary	Revised inclusion criterion number 7.	Text revised for clarification to allow for compliance with any local regulations.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 2.	Updated to allow usage of some chemotherapy before randomization, based on feedback received from study sites.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 6.	Revised exclusion criterion to be less restrictive.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 8.	Revised exclusion criterion to be less restrictive.
Section 7.2 Exclusion Criteria	Revised exclusion criterion number 11.	Revised exclusion criterion for clarification.
Section 7.2 Exclusion Criteria	Revised exclusion criterion number 13.	Removed requirement for mandatory CSF analysis at screening
Section 8.4 Dose Modification Guidelines for Safety	Added text clarifying time frame for sites to communicate any variation of dose modification guidelines.	Text added to provide a time frame for sites to communicate to the sponsor any variation from dose reduction guidelines for safety.
Table 8.f Dose Modifications for AOEs: Ponatinib	Updated table detailing ponatinib dose modification strategy in response to Grade 2 arterial occlusion (cardiovascular [CV] and cerebrovascular events).	To align with the guidelines for other safety events.

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Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 8.8 Management of Clinical Events Appendix A Schedule of Events Table 1	Added text to provide additional guidance in managing persistent elevation of cardiac troponin-I (cTnI) or N-terminal pro-brain natriuretic peptide (NT proBNP)/B-type natriuretic peptide (BNP).	Guidance was added for monitoring/managing persistent elevation of CTnI or NT-proBNP/BNP.
Sections 9.4.6 Pregnancy Test Appendix A Schedule of Events	Added text regarding country-specific requirements for serum pregnancy test.	Updated text to address country-specific requirements.
Section 9.4.9 Vital Signs Appendix A Schedule of Events	Removed requirement that body temperature must be measured orally.	Removed the word “oral” to generalize the way body temperature is measured.
Section 9.4.14.2 Serum Analysis Appendix A Schedule of Events	Added NT-proBNP/BNP testing to required serum analyses.	Added guidance for monitoring/managing persistent elevation of CTnI or NT-proBNP/BNP.
Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Revised text regarding discontinuation of a patient who becomes pregnant.	Revised wording to align with other clinical studies within the ponatinib clinical program.
Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement.	Clarified wording for study discontinuation.	To clarify permanent discontinuation on study drug.
Section 9.10 Post-treatment Follow-Up Assessments.	Deleted incorrect text regarding study termination.	Deleted text was here by error as nothing more is collected once the study is terminated.
Section 11.3 Cardiovascular Endpoint Adjudication Committee.	Generalized documentation requirement for the cardiovascular endpoint adjudication committee’s assessment of each potential CV endpoint.	Removed clinical database language because the independent cardiovascular adjudication does not occur in the sponsor’s clinical database to ensure the independence of the committee’s decision-making.
Section 13.1.5.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib.	Added text to clarify that mutation analysis will be done as clinically needed.	Added text for clarification and consistency throughout protocol.
Section 13.2 IA and Criteria for Early Termination.	Added text regarding interim analysis to clarify timing.	Added text inserted for consistency and clarification.

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Protocol Amendment 05		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Appendix A Schedule of Events Section 9.4.15.1 BM Aspirate	Added text to revise BM aspirate schedule, and clarify collection and assessment procedures.	Changes made to reduce sample collection burden on patients and clarify BM aspirate collections.
Appendix A Schedule of Events	Removed requirement that all electrocardiograms (ECGs) are to be signed by a local cardiologist.	Change made to reduce the burden of getting signature of a cardiologist.
Appendix A Schedule of Events	Added text for clarification of complete blood count with differential testing.	Added text for clarification of CBC and differential testing.
Appendix A Schedule of Events	Clarified text for serum chemistry testing and total, indirect, and direct bilirubin testing.	Change made to clarify serum chemistry testing and total, direct, and indirect bilirubin test needed.
Appendix A Schedule of Events	Revised Schedule of Events (SOE) footnote for single-agent therapy sample collection.	Revised footnotes to be consistent with the visit schedule.
Appendix A Schedule of Events Table 2.	Added text to SOE to clarify that end-of-treatment visit should occur within 30 days after last dose or discontinuation.	This change was made to clarify timing of the EOT visit.
Appendix A Schedule of Events Table 2 footnotes and corresponding table row. Appendix A Schedule of Events, Table 1, footnote cc	Updated maintenance phase SOE footnotes for vital signs, physical exams, ECGs, and patient-reported outcomes for consistency	Revised footnotes to be consistent with the visit schedule.
Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate.	Updated Appendix J footnote for clarification of leucovorin (folinic acid) rescue therapy for methotrexate.	To clarify that sites may use alternative rescue therapy for methotrexate.
Appendix A, Table 2.	Decrease frequency of ECOG assessments beginning at Cycle 10 from once per cycle to once every 3 cycles.	To align with ECOG assessment frequency in the induction and consolidation phases of the study.

Rationale for Amendment 04

This section describes the changes to the protocol incorporating Amendment 04. The primary reasons for this amendment are to update the stratification of randomization criteria to allow for patients to be randomized more proficiently, to revise exclusion criteria to be less restrictive, and to modify assessments on the schedule of events to be less of a burden on patients.

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Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 2.0 Study Summary	Removed stratification factor 2 (Transcript 190 versus 210) from stratification of randomization	Update allows for patients to be randomized more proficiently. The SAP specifies that stratification based on transcript type will be used for post hoc analysis of efficacy and safety, and it will balance for any differences in the safety or efficacy outcomes between the 2 transcript types
Section 6.1 Overview of Study Design	Added text to use blood samples if bone marrow (BM) samples are not evaluable or not available	Added text to address instances where BM samples will not be evaluable or not available.
Section 7.1 Inclusion Criteria Section 2.0 Study Summary	Revised inclusion criterion number 5.	Updated to align with other clinical studies within the ponatinib clinical program.
Section 7.1 Inclusion Criteria Section 2.0 Study Summary	Revised inclusion criterion number 7.	Text revised for clarification to allow for compliance with any local regulations.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 2.	Updated to allow usage of some chemotherapy before randomization, based on feedback received from study sites.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 6.	Revised exclusion criterion to be less restrictive
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Revised exclusion criterion number 8.	Revised exclusion criterion to be less restrictive
Section 8.4 Dose Modification Guidelines for Safety	Added text clarifying time frame for sites to communicate any variation of dose modification guidelines.	Text added to provide a time frame for sites to communicate to the sponsor any variation from dose reduction guidelines for safety.
Table 8.f Dose Modifications for AOEs: Ponatinib	Updated table detailing ponatinib dose modification strategy in response to Grade 2 arterial occlusion (cardiovascular [CV] and cerebrovascular events).	To align with the guidelines for other safety events.

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Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 8.8 Management of Clinical Events	Added text to provide additional guidance in managing persistent elevation of cardiac troponin-I (cTnI) or N-terminal pro-brain natriuretic peptide (NT-proBNP)/B-type natriuretic peptide (BNP).	Guidance was added for monitoring/managing persistent elevation of CTnI or NT-proBNP/BNP.
Section 9.4.6 Pregnancy Test Appendix A Schedule of Events	Added text regarding country-specific requirements for serum pregnancy test	Updated text to address country-specific requirements
Section 9.4.9 Vital Signs	Removed requirement that body temperature must be measured orally	Removed the word "oral" to generalize the way body temperature is measured.
Section 9.4.14.2 Serum Analysis Appendix A Schedule of Events	Added NT-proBNP/BNP testing to required serum analyses.	Added guidance for monitoring/managing persistent elevation of CTnI or NT-proBNP/BNP
Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement Section 10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events	Revised text regarding discontinuation of a patient who becomes pregnant.	Revised wording to align with other clinical studies within the ponatinib clinical program
Section 9.7 Discontinuation of Treatment With Study Drug and Patient Replacement	Clarified wording for study discontinuation.	To clarify permanent discontinuation on study drug
Section 9.10 Post-treatment Follow-Up Assessments	Deleted incorrect text regarding study termination.	Deleted text was here by error as nothing more is collected once the study is terminated
Section 11.3 Cardiovascular Endpoint Adjudication Committee	Generalized documentation requirement for the cardiovascular endpoint adjudication committee's assessment of each potential CV endpoint.	Removed clinical database language because the independent cardiovascular adjudication does not occur in the sponsor's clinical database to ensure the independence of the committee's decision-making
Section 13.1.5.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib	Added text to clarify that mutation analysis will be done as clinically needed.	Added text for clarification and consistency throughout protocol
Section 13.2 IA and Criteria for Early Termination	Added text regarding interim analysis to clarify timing.	Added text inserted for consistency and clarification

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Protocol Amendment 04		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Appendix A Schedule of Events Section 9.4.15.1 BM Aspirate	Added text to revise BM aspirate schedule, and clarify collection and assessment procedures.	Changes made to reduce sample collection burden on patients and clarify BM aspirate collections
Appendix A Schedule of Events	Removed requirement that all electrocardiograms (ECGs) are to be signed by a local cardiologist.	Change made to reduce the burden of getting signature of a cardiologist
Appendix A Schedule of Events.	Added text for clarification of complete blood count with differential testing.	Added text for clarification of CBC and differential testing
Appendix A Schedule of Events	Clarified text for serum chemistry testing and total, indirect, and direct bilirubin testing.	Change made to clarify serum chemistry testing and total, direct, and indirect bilirubin test needed
Appendix A Schedule of Events	Revised Schedule of Events (SOE) footnote for single-agent therapy sample collection.	Revised footnotes to be consistent with the visit schedule
Appendix A Schedule of Events	Added text to SOE to clarify end-of-treatment visit should occur within 30 days after last dose or discontinuation.	This change was made to clarify timing of the EOT visit
Appendix A Schedule of Events Table 2 footnotes and corresponding table row	Updated maintenance phase SOE footnote for vital signs, physical exams, ECGs, and patient-reported outcomes for consistency.	Revised footnotes to be consistent with the visit schedule
Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate	Updated Appendix J footnote for clarification of leucovorin (folinic acid) rescue therapy for methotrexate.	To clarify that sites may use alternative rescue therapy for methotrexate

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Rationale for Amendment 03

This section describes the changes to the protocol incorporating Amendment 03; this amendment applies only to South Korea. The primary reason for this amendment is to incorporate advice from South Korea Ministry of Health.

Protocol Amendment 03		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 7.0 Study Population Section 2.0 Study Summary (Study Design, Patient Population, Main Criteria for Inclusion [1]) Section 6.1 Overview of Study Design Appendix A, Table 1, Footnote c.	Revised age/health status inclusion criterion for patients in South Korea only to include patients aged ≥65 years, or aged ≥18 years with comorbidities and/or poor functional status that, after discussion/agreement with the sponsor's medical monitor/designee, are considered to make the patient unfit for any intensive therapy.	Incorporate advice from South Korea Ministry of Health

Rationale for Amendment 02

This section describes the changes to the protocol incorporating Amendment 02. The primary reasons for this amendment are to incorporate advice from regulatory agencies including United States (US) Food and Drug Administration (FDA) and Spain Ministry of Health (MoH), to revise text to reflect inclusion of Japan in the study, and to update text based on recent updates to the Takeda Oncology Protocol template. Changes made based on advice from FDA include the addition of an endpoint to assess minimal residual disease (MRD)-negative complete remission (CR) at multiple intervals after the end of induction and the addition of timepoints for some other secondary endpoints; corresponding objectives were revised accordingly. Based on recommendations from Spain MoH, guidance was added regarding monitoring patients with evidence of prior hepatitis B infections for clinical and laboratory signs of hepatitis B virus reactivation or hepatitis during study treatment as well as the addition of monthly pregnancy testing during study treatment. Given a recent decision to implement this study in Japan, operational text specific to Japan has been added from the Takeda oncology protocol template. In addition, a posttrial access section is now included based on an update to the Takeda oncology template.

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Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 4.1.1.1 Ph+ ALL	Delete inaccurate statement regarding incidence of Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL)	This statement was incorrect as the reference describes incidence of ALL, not Ph+ ALL; thus, the statement is not needed
Section 5.1.2 Secondary Objectives Section 2.0 Study Summary	Add new secondary efficacy objective and add additional timepoints to secondary efficacy endpoints that have specific timepoints	Revise exploratory objective regarding biomarkers
Section 5.1.4 Exploratory Objectives	Revise exploratory objective regarding biomarkers	To expand exploratory objective to include biomarkers affecting ponatinib efficacy or safety
Section 5.2.2.2 Other Secondary Endpoints Section 2.0 Study Summary. Section 6.1 Overview of Study Design. Section 13.1.3.3 Other Secondary Efficacy Endpoint Assessments	Add new secondary efficacy endpoint and add timepoints to secondary efficacy endpoints that have specific timepoints	Changes to secondary endpoints were made based on advice from FDA
Section 5.2.5 Exploratory Endpoints Section 2.0 Study Summary. Section 6.1 Overview of Study Design. Section 13.1.5 Exploratory Endpoints	Revise exploratory endpoint regarding biomarkers	To expand exploratory endpoint to include the exploration of biomarkers affecting ponatinib efficacy or safety
Section 6.3.1 Duration of an Individual Patient's Study Participation Section 2.0 Study Summary. Section 8.1.5 Postcycle 20 Therapy. Section 9.5 Completion of Study Treatment (for Individual Patients)	Add clarification to description of duration of individual patient participation	Text added for clarification of duration of individual patient participation
Section 6.3.5 Posttrial Access	Add posttrial access section	This section was added to conform to updates to the Takeda Oncology Protocol Template in compliance with the posttrial access initiative
Section 7.2 Exclusion Criteria	Add exclusion criterion #11 regarding previous malignancy diagnosis	Revision made for guidance regarding exclusion based on previous malignancy diagnosis.

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Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 7.2 Exclusion Criteria	Revise exclusion criterion #13 regarding patients with central nervous system (CNS) or extramedullary involvement	Revision made for clarity
Section 7.2 Exclusion Criteria	Revise exclusion criterion #16.j. regarding patients with pleural or pericardial effusions	Revision made for clarity
Table 8.a Induction Phase Treatment footnotes Section 2.0 Study Summary Table 8.b Consolidation Phase Treatment Table 8.c Maintenance Phase Treatment Appendix J Leucovorin (Folinic Acid) Rescue Therapy for Methotrexate	Add guidance regarding alternative dose modifications/schedules during study	To provide guidance regarding procedure for potential use of alternative dose modifications/schedules
Section 8.0 Study Drug	Correct error regarding number of cycles in maintenance phase	Correction was made for consistency with other sections
Table 8.c Maintenance Phase Treatment Section 2.0 Study Summary	Add guidance regarding use of prednisolone if prednisone is not available	Footnote added as clarification and additional guidance for sites
Section 8.3.1 Mandatory Dose Reduction for Response	Clarify guidance regarding timing of dose reduction for response	Text was added as guidance for sites based on FDA advice
Section 8.4.1.1 Dose Reduction for Drug-Related AEs	Clarify guidance regarding dose reduction for drug-related adverse events (AEs)	Text was added as guidance for sites based on FDA advice
Section 8.4.1.2 Dose Modifications for AOEs and VTEs	Revise text related to dose modifications for arterial occlusive events (AOEs) and venous thrombotic/embolic events (VTEs)	Text was added as guidance for sites based on FDA advice
Section 8.5 Excluded Concomitant Medications and Procedures	Clarify definition of “other anticancer therapies” that are considered excluded concomitant medications	Text was added to clarify which anticancer therapies are considered exclusionary
Section 8.8 Management of Clinical Events Section 9.4.14.2 Serum Analysis Appendix A Schedule of Events	Add guidance regarding monitoring of patients with evidence of prior hepatitis B infection	Text added per Spain MoH advice

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Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 8.8 Management of Clinical Events Appendix A Schedule of Events, Table 1, footnote f and Table 2, footnote g	Add guidance for monitoring/managing any blood pressure (BP) elevations during ponatinib use	Text was added to provide guidance for sites in monitoring and managing any BP elevations during ponatinib treatment
Section 9.4.6 Pregnancy Test Appendix A, Table 1 and Table 2	Increase frequency of pregnancy testing	Add monthly pregnancy testing per Spain MoH advice
Section 9.4.7 Physical Examination and ECOG Performance Status Appendix A Schedule of Events	Replace calculation of body mass index (BMI) with calculation of body surface area (BSA) at baseline	BSA is needed for dosing some of the study drugs and, therefore, BMI was changed to BSA
Section 9.4.15.1 BM Aspirate	Add guidance regarding shipment of bone marrow (BM) samples	Text added as guidance/clarification for sites and consistency with SOE
Section 9.4.15.2 Peripheral Blood Samples for Molecular Response, CR and Exploratory Biomarker Assessments	Add clarification regarding collection and analysis of peripheral blood samples	Text added as guidance/clarification for sites
Section 10.1.4 AEs of Special Interest Definitions	Clarify definition of adverse events of special interest (AESIs)	Revisions to this section clarify the definition of AESIs
Section 10.1.4 AEs of Special Interest Definitions	Correct definition of myocardial infarction (MI)	MI definition was incorrect; added text based on source for MI definition
Section 10.1.4. AEs of Special Interest Definitions	Add guidance regarding sponsor monitoring of AESIs	Text added as guidance for sites regarding sponsor monitoring of AESIs
Section 10.2 Procedures for Recording and Reporting AEs and SAEs	Clarify guidance for reporting SAEs to local health authorities	The amended wording provides guidance and clarifies sponsor responsibilities for reporting of SAEs to local health authorities
Section 12.2.1 Japan Record Retention	Add section for Japan record retention	Text added per decision to implement study in Japan
Table 13.a Definitions of Efficacy Response Criteria	Add footnote to Table 13.a. Definitions of Efficacy Response Criteria to clarify definition of CNS-3	Footnote added to clarify definition of CNS-3
Figure 13.a Statistical Design: Alpha Spending Plan	Revise Figure 13.a Statistical Design: Alpha Spending Plan	The revision to the figure is intended to provide a more accurate plan for regulatory strategy
Section 14.2.1 Japan Protocol Deviations	Add section for Japan protocol deviations	Section added per decision to implement study in Japan

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Protocol Amendment 02		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Appendix A, Table 1 and Table 2	Revisions to Schedule of Events table include: a) Change in duration of windows for specific visits b) Increase frequency of pregnancy testing (also see Change 20) c) Add guidance for monitoring/managing BP elevations during ponatinib use (also see Change 19) d) Reduce frequency of Eastern Cooperative Oncology Group (ECOG) assessments e) Add guidance regarding monitoring of patients with evidence of prior hepatitis B infection (also see Change 18) f) Reduce frequency of C-reactive protein (CRP) and cardiac troponin-I (cTnI) assessments	Increasing the duration of windows for visits that include certain assessments (BM aspirate, peripheral blood sample, and extramedullary assessments) and reducing the frequency of other assessments (ECOG, chemistry, CRP and cTnI) eliminates unnecessary testing and reduces the burden on patients and their families
Appendix A, Table 1. Schedule of Events	Revise guidance regarding eye examinations in the Schedule of Events	The SOE footnote was revised to provide guidance regarding the timing and type of eye examination(s) to be performed
Appendix B Investigator Responsibilities	Add clarification specific to Japan to Appendix B, Investigator Responsibilities	Section added per decision to implement study in Japan

Rationale for Amendment 01

This document describes the changes in reference to the protocol incorporating Amendment 01.

The primary reason for this amendment is to provide guidance on imatinib dose modifications for adverse drug reactions, guidance on the prevention and management of tumor lysis syndrome, and to allow patients with complete remission (CR) who have not achieved minimal residual disease (MRD)-negative CR at the end of induction to remain on study treatment at the investigator' discretion. Additional updates include increasing the planned number of sites because of updated recruitment forecasts, clarifying the follow-up of patients who discontinue study treatment, and clarifying the requirements for patient rescreening.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

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Changes in Amendment 1

Protocol Amendment 01		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 8.4 Dose Modification Guidelines for Adverse Drug Reactions Section 2.0 Study Summary	Add guidance on imatinib dose modifications for adverse drug reactions	Dose modification guidelines for imatinib are added to help investigators make dosing decisions on the basis of safety events
Section 8.8 Management of Clinical Events	Add discussion of tumor lysis syndrome (TLS) risk factors	This information was added as TLS is a risk factor in this patient population
Appendix L Management of Tumor Lysis Syndrome	Add guidance on the prophylaxis and management of TLS	This information was added as TLS is a risk factor in this patient population
Section 6.1 Overview of Study Design Section 2.0 Study Summary Section 6.3.1 Duration of an Individual Patient's Study Participation Section 8.3.1 Mandatory Dose Reduction for Response Section 9.4.15.1 BM Aspirate Section 9.5 Completion of Study Treatment (for Individual Patients) Section 9.10 Post-treatment Follow-Up Assessments	Allow patients who have achieved CR to remain on study treatment at the investigator's discretion	To clarify the possibility of further continuation in the study for patients achieving CR at the end of induction
Section 6.3.1 Duration of an Individual Patient's Study Participation Section 2.0 Study Summary Section 8.1.5 Postcycle 20 Therapy Section 9.10 Post-treatment Follow-Up Assessments Table 2 Schedule of Events: Maintenance Phase, Single-Agent Therapy, End-of-Treatment, and Follow-up, footnote e	Clarify how patients discontinuing study treatment, including patients proceeding to hematopoietic stem cell transplant (HSCT) or alternative therapy, will be followed in the study	To clarify post-treatment data collection
Section 2.0 Study Summary Section 6.2 Number of Patients	Increase number of planned sites	Revised recruitment projections suggested that more sites may be necessary
Section 2.0 Study Summary	Add a range to the number of patients to be randomized in each arm	The protocol uses an adaptive design that provides variable numbers of patients, dependent on conditional power. The study summary was modified to show the

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Protocol Amendment 01		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by the Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
		expected range of numbers of patients, rather than the expected maximum number of patients. The power calculations and study design were not changed.
Section 8.7 Precautions and Restrictions	Add guidance regarding patient counseling on pre-study sperm and egg storage	Updated per protocol template changes
Section 9.4.15.1 BM Aspirate Section 9.4.15.3 Extramedullary Disease	Clarify tests to be conducted at central and local laboratories	To provide clarification regarding location of tests related to the CR component of the study
Section 10.2 Procedures for Recording and Reporting AEs, SAEs, and AESIs	Update SAE reporting process per updated pharmacovigilance procedure	Updated per protocol template changes with respect to updated pharmacovigilance procedures
Section 10.3 Monitoring of AEs and Period of Observation	Update language on monitoring of adverse events (AEs) per updated pharmacovigilance procedure	Updated per protocol template changes with respect to updated pharmacovigilance procedures
Section 13.1.3.3 Other Secondary Efficacy Endpoint Assessments	Add details on post-transplantation competing risk analysis	To clarify that additional competing risk analysis will be carried out in patients' post-transplantation as a part of study evaluation
Section 13.4 Blinding of Trial Management Team for Data Review Section 8.9 Blinding and Unblinding Section 9.4.3 Enrollment and Randomization	Add description of blinding of study management team to study data	To clarify steps taken to avoid bias during data review
Section 8.13.1 Storage	Clarify the storage conditions for ponatinib and imatinib	To clarify storage conditions for study drug for sites globally
Section 8.10.1 Ponatinib Section 8.1.1 Investigational Therapy: Ponatinib	Update information on ponatinib tablets	To update information on how ponatinib will be supplied
Section 8.10.2 Imatinib	Update information on imatinib tablets	To update information on how imatinib will be supplied
Section 9.4.1 Screening Period Procedures	Clarify procedures for rescreening of patients	To define when procedures must be repeated in re-screening

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1.1.1 Protocol Changes

At the time of the FA for the primary endpoint of MRD-negative CR, this protocol had 6 amendments (excluding country-specific amendments), producing 7 versions of the protocol. Protocol Amendment 10 was in effect at the data cutoff date for the FA of the primary endpoint. Key changes to each version are summarized below.

Protocol Amendment 1 (Dated 22 May 2018)

This amendment served the following purposes:

- Provided guidance on imatinib dose modifications for adverse drug reactions.
- Provided guidance on the prevention and management of tumor lysis syndrome.
- Allowed patients with CR who had not achieved MRD-negative CR at the end of induction to remain on study treatment at the investigator's discretion.
- Increased the planned number of sites because of updated recruitment forecasts.
- Clarified the follow-up of patients who discontinued study treatment.
- Clarified the requirements for patient rescreening.
- Update SAE reporting process and language on monitoring of AEs per updated pharmacovigilance procedure.

Protocol Amendment 2 (Dated 08 November 2018)

This amendment served the following purposes:

- Incorporated advice from the US FDA, including the addition of an endpoint to assess MRD-negative CR at multiple intervals after the end of induction and the addition of timepoints for some other secondary endpoints; corresponding objectives were revised accordingly.
- Incorporated advice from the Spain Ministry of Health (MoH), including the addition of guidance regarding monitoring patients with evidence of prior hepatitis B infections for clinical and laboratory signs of hepatitis B virus reactivation or hepatitis during study treatment as well as the addition of monthly pregnancy testing during study treatment.
- Revised text to reflect inclusion of Japan in the study.
- Updated text based on recent updates to the Takeda Oncology Protocol template, including addition of a posttrial access section.

Protocol Amendment 4 (Dated 09 May 2019)

The amendment served the following purposes:

- Updated the stratification of randomization criteria to allow for patients to be randomized more proficiently.
- Revised exclusion criteria to be less restrictive.

- Modified assessments on the schedule of events to be less of a burden on patients.

Protocol Amendment 8 (Dated 10 February 2021)

The amendment served the following purposes:

- Changed the study design:
  - From an adaptive design to a group sequential design for the primary endpoint of MRD-negative CR at the end of induction (CR and BCR-ABL1/ABL1 ≤0.01%).
  - To add an interim analysis for event-free survival (EFS).
- Updated the definition for EFS.
- Provided guidance for collecting data, conducting study procedures, and managing investigational product(s) to maintain patient safety, confidentiality, and study integrity during unavoidable circumstances such as the coronavirus disease 2019 (COVID-19) pandemic.

Protocol Amendment 9 (Dated 07 May 2021)

The amendment served the following purpose:

- Clarified that the BCR-ABL1/ABL1 MRD assessment was to be conducted using the same methodology in more than 1 central laboratory due to local regulations that prohibit shipping of biological samples.

Protocol Amendment 10 (Dated 20 October 2021)

The amendment served the following purpose:

- Updated the efficacy analysis to reflect a change in the sample size for the FA from 150 patients to 230 patients.

In addition, the amendment:

- Clarified that patients who achieved MRD-negative status with CRi at the end of induction could remain on study drug treatment, at the investigator's discretion.
- Clarified that for MRD-negative CR, the analysis would be based on the ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210.
- Provided additional guidance to sites regarding survival follow up assessments, timing for EOT, reporting of mutation status if available at time of relapse, and the time period for requiring BM at EOT.

1.1.1.1 Country-specific amendments

Country-specific amendments for the P-3001 study included:

- Five amendments for South Korea (Amendment 3, dated 06 December 2018; Amendment 5, dated 23 July 2019; Amendment 8 KR v1, dated 09 March 2021; Amendment 9 KR v1, dated 07 May 2021; Amendment 10 KR v1, dated 10 November 2021).

- Four amendments for Argentina (Amendment 6, dated 29 July 2019; Amendment 8 AR v1, dated 04 March 2021; Amendment 9 AR v1, dated 07 May 2021; Amendment 10 AR v1 dated 10 November 2021).
- Four amendments for Japan (Amendment 7, dated 13 August 2019; Amendment 8 JP v1, dated 17 March 2021; Amendment 9 JP v1, dated 07 May 2021; Amendment 10 JP v1, dated 11 November 2021).

Refer to Appendix 16.1.1 for full versions of the protocols and more details on the summary of changes.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Ponatinib-3001

A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination with Reduced-Intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

PHASE 3

Version**: Final 1.0**

Date**:** 07 May 2021

Prepared by:

PPD

Based on:

Protocol Version: Amendment 08

Protocol Date: 10 Feb 2021

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1.1 Approval Signatures

Study Title: A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination with Reduced-Intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Approvals:

PPD

Date

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2.0 TABLE OF CONTENTS

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ABI	ankle-brachial index
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALL	chromosome-positive acute lymphoblastic leukemia
ALP	albumin, alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AOE(s)	arterial occlusive event(s)
AST	aspartate aminotransferase
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BP	blood pressure
BSA	body surface area
CI(s)	confidence intervals
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete remission (complete response)
Cri	incomplete complete remission
EAIR	Exposure-adjusted incidence rates
ECG(s)	Electrocardiogram(s)
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EQ-5D-5L	EuroQOL-5 Dimension-5 Level
EOT	end of treatment
FA	final analysis
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
HR	hazard ratio
HLT	High Level Term
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
IDMC	independent data monitoring committee
IPCW	Inverse Probability Censoring Weighting
IS	International Scale
IXRS	interactive voice/web response system
ITT	intent-to-treat

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Abbreviation	Term
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR3	molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%)
MR4	molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%)
MR4.5	molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%)
MRD	minimal residual disease
MRU	medical resource utilization
MSM	Marginal Structural Model
MUGA	Multiple-Gated Acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
Ph+ ALL	Philadelphia chromosome–positive acute lymphoblastic leukemia
PIF	primary induction failure
PK	Pharmacokinetic
PP	per-protocol
PT	Preferred Term
QD	once daily
QTcF	QT interval corrected per Fridericia method
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD(s)	standard deviation(s)
SOC	System Organ Class
TEAE(s)	treatment-emergent adverse event(s)
TKI	tyrosine kinase inhibitor
VTE(s)	venous thrombotic/embolic event(s)
WHO	World Health Organization

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4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction (see Table 5.a for the definitions of MRD negativity and CR).

4.2 Secondary Objectives

4.2.1 Key Secondary Objectives

The key secondary objective is to compare event-free survival (EFS) between the 2 cohorts.

4.2.2 Other Secondary Objectives

Other secondary objectives are:

- To compare the rates of CR and incomplete CR (CRi) between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of MR3, MR4, and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of primary induction failure (PIF) and overall response rate (ORR) between the 2 cohorts, at the end of induction.
- To compare rates of MRD-negative CR at multiple intervals after the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare OS between the 2 cohorts.
- To collect plasma concentration-time data to contribute to population pharmacokinetic (PK) and exposure-response analyses of ponatinib.

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4.3 Safety Objectives

The safety objectives are:

- To characterize the rates of AEs/SAEs, AOEs, venous thrombotic/embolic events (VTEs), and other safety outcomes of interest in the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

4.4 Exploratory Objectives

The exploratory objectives are:

- To compare patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]) results between the 2 cohorts.
- To compare medical resource utilization (MRU) results between the 2 cohorts.
- To compare the time to start of alternative therapy between the 2 cohorts.
- To compare the time to HSCT between the 2 cohorts.
- To explore biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

4.5 Study Design

4.5.1 Study Design

This phase 3 study is designed as an open-label, multicenter, randomized comparison of the TKIs ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced-intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously. Patients will remain on study treatment until they are deceased, have failed to achieve the primary endpoint at the end of induction (patients who do not achieve the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

The primary endpoint of this study is MRD-negative CR at the end of induction (defined in Table 5.a). Patients who achieve the primary endpoint will continue in the study in the consolidation and maintenance phases followed by a single-agent therapy phase. Patients who achieve CR but do not achieve the primary endpoint at the end of induction may, at the investigator's discretion, continue on study treatment. All patients who do not achieve CR at the

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end of induction will be discontinued from study drug. For all discontinued patients, the patient's treating physician should consider alternative therapy options.

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib QD, which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Protocol Section 8.4.1). For patients in the ponatinib cohort who achieve CR but do not achieve the primary endpoint at the end of induction and who continue in the study at the investigator's discretion, the dose of ponatinib will be reduced, as described above, at any time when the patient achieves MRD-negative CR and re-escalated, as described above, upon loss of response. Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for central nervous system (CNS) disease prophylaxis. At the end of the 20 cycles, all patients remaining on study will remain on ponatinib or imatinib (administered as a single agent).

MRD status will be measured using qPCR-based tests validated for the ability to detect breakpoint cluster region-Abelson (BCR-ABL1)/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as <0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Protocol Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale (IS) with traceability to the World Health Organization (WHO) first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported.

The key secondary endpoint for this study is EFS. Other secondary endpoints will include rates of CR and CRi at the end of Cycle 1, Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MR3, MR4, and MR4.5 at the end of Cycle 1, the end of Cycle 2, the end of induction and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MRD-negative CR at multiple intervals after the end of induction; rates of PIF and ORR at the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; duration of MR4.5 in patients who achieved MR4.5; OS and rate of relapse from CR for on-study patients with and without HSCT, and OS.

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all AEs, SAEs, AOEs, and VTEs; rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

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Exploratory endpoints will include change from baseline in patient-reported quality-of-life; MRU assessments; time to start of alternative therapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

4.5.2 Randomization and Stratification

The randomization scheme will be generated by an independent statistician who is not on the study team. Before dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive voice/web response system (IXRS).

Eligible patients will be randomized in a 2:1 ratio to receive ponatinib or imatinib treatment arms, stratified by ages: 18 through <45 years; ≥45 through <60 years; and ≥60 years.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints:

The primary endpoint is MRD-negative CR at the end of induction (see Table 5.a for the definitions of MRD negativity and CR).

5.2 Secondary Endpoints:

5.2.1 Key Secondary Endpoints

The key secondary endpoint is:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve CR by the end of induction.
  - Relapse from CR.

5.2.2 Other Secondary Endpoints

Other secondary endpoints (defined in Table 5.a) are:

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.
- Rates of MRD-negative CR at multiple intervals after the end of induction.

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- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.
- OS and rate of relapse from CR for on-study patients with and without HSCT.
- OS.

Table 5.a Definitions of Efficacy Response Criteria

Term	Definition
CNS-1	CNS-1: No lymphoblasts in the CSF regardless of WBC count.
CNS-2	WBC count <5 leukocytes/µl in the CSF with the presence of blasts.
CNS-3 [a]	WBC count of ≥5 leukocytes/µl with the presence of blasts.
CNS disease remission	No lymphoblasts in CSF regardless of WBC count in a patient with CNS-2 or CNS-3 at diagnosis.
CNS relapse	Development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).
CR	Complete remission; meeting all the following for at least 4 weeks (ie, no recurrence): • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass). • ANC >1000/µl (or >1.0 × 10^9/L). • Platelets >100,000/µl (or >100 × 10^9/L).
CRi	Hematologic complete remission with incomplete hematologic recovery. Meets all criteria for CR except platelet count and/or ANC.
Duration of CR	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.
Duration of MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.
Duration of MRD negativity	The interval between the first assessment at which the criteria for MRD negativity are met until the earliest date at which loss of MRD negativity occurs or relapse from CR occurs.
Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.
EFS	Event-free survival (EFS), defined as the dates of randomization until: • Death due to any cause. • Failure to achieve CR by the end of induction. • Relapse from CR.

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Table 5.a Definitions of Efficacy Response Criteria

Term	Definition
Loss of MR3	An increase to >0.1% BCR-ABL1/ABL1.
Loss of MR4.5	An increase to >0.0032% BCR-ABL1/ABL1. This result must be confirmed at the subsequent visit, unless it is associated with loss of MR3 or relapse from CR.
Loss of MRD negativity	An increase to ≥0.01% BCR-ABL1/ABL1. This result must be confirmed within 4 weeks with either a BM aspirate (optional) or peripheral blood, unless it is associated with loss of MR3 or relapse from CR.
MR3	Molecular response 3-log reduction (≤0.1% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts.
MR4.5	Molecular response 4.5-log reduction (≤0.0032% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.
MRD-negative CR	Meeting the criteria for both MRD negativity and CR.
MRD negativity (MR4)	≤0.01% BCR-ABL1/ABL1, or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. Also referred to as MR4.
ORR	Overall response rate: CR + CRi.
OS	Overall survival. The interval between randomization and death due to any cause.
PD	Progressive disease. Increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease.
PIF	Primary induction failure: Patients who received treatment for ALL but never achieved CR or CRi by the end of induction. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi.
Relapse from CR	Reappearance of blasts in the blood or BM (≥5%) or in any extramedullary site after a CR.
Time to treatment failure	Time to end of study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or efficacy reasons.

Abbreviations: ANC, absolute neutrophil count; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; CR, complete remission; CRi, incomplete blood count recovery; CSF, cerebrospinal fluid; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MR4, molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%); MR4.5, molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%); MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; RBC, red blood cell; WBC, white blood cell.

[a] If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥5/μL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

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5.3 Safety Endpoints:

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP, and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

5.4 Pharmacokinetic Endpoint

The PK endpoint is plasma concentration-time data to contribute to population PK and exposure-response analyses of ponatinib.

5.5 Exploratory Endpoints

The exploratory endpoints are (see Table 5.a for the definitions):

- Change from baseline in patient-reported quality of life (FACT-Leu and EQ-5D-5L).
- MRU assessments.
- Time to start of alternative therapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

6.0 DETERMINATION OF SAMPLE SIZE

The study employed group sequential design for the primary endpoint MRD-negative CR and the key secondary endpoint EFS.

Assuming an effect size of 28% (48% and 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of approximately 150 patients (approximately 100 vs 50 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 95% power for MRD-negative CR, with 82% power at IA (performed after the end of induction phase data have been collected for 115 patients) using the group sequential testing procedure. The O'Brien-Fleming alpha spending function (the Lan-DeMets method [1]) will be implemented to determine the significance level at IA and FA for the primary endpoint, with an overall type I error rate at a 2-sided 0.05 level.

Inference for the key secondary endpoint of EFS will be conducted at $\alpha = 5\%$ level only if the primary endpoint is met either at IA or FA for the MRD-negative CR (Figure 6.a). Based on

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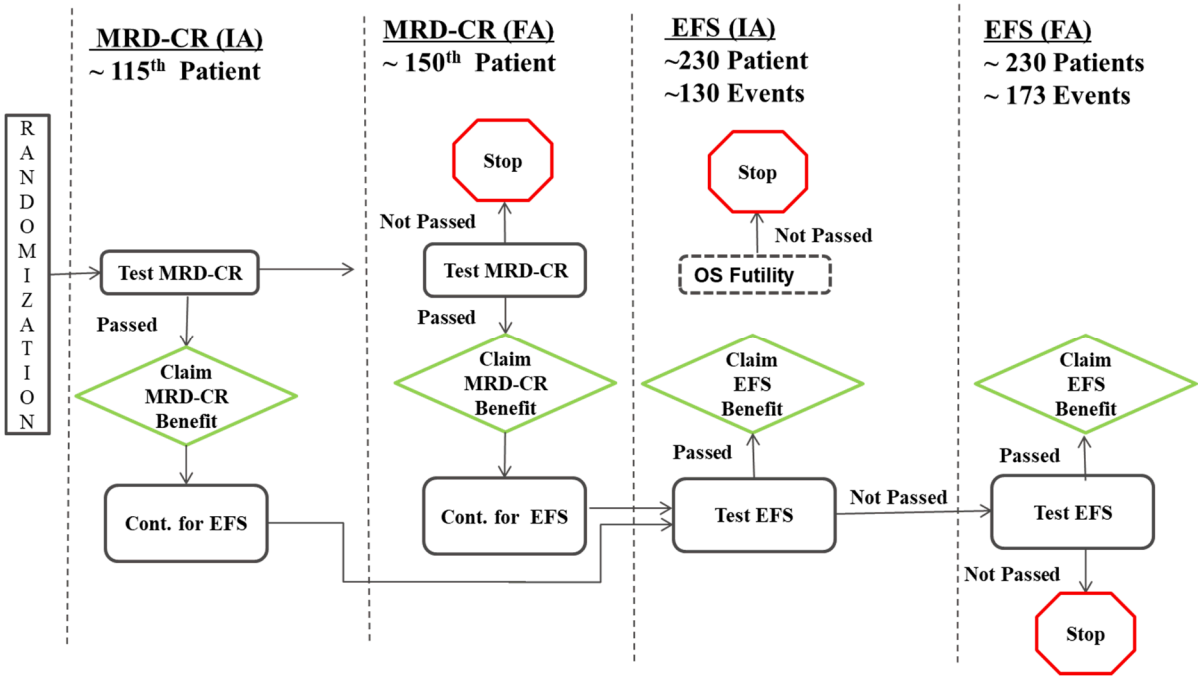
3-year EFS data observed from various phase 2 studies [2, 3], effect size is assumed as 67% vs 46% for EFS at year 3 for the active and control arms, respectively, or HR = 0.516 for non-HSCT patients. The effect size is assumed as 53% and 40% for EFS at year 3 for active and control arms, respectively, or HR = 0.693 for patients who are undertaking HSCT. Also, it is assumed that 50% and 45% of patients from active and control arms will undertake HSCT, respectively. Based on simulation studies, approximately 230 patients will be enrolled to collect long-term EFS data. Among these 230 patients, approximately 173 events need to be accumulated at FA so that the power will be approximately 80% for the EFS endpoint. It is expected that the time of EFS will be approximately 8.5 years after first patient has been enrolled.

Figure 6.a Statistical Analysis Schema



Abbreviations: Cont., continue; CP, conditional probability; CR, complete response; EFS, event-free survival; FA, final analysis; IA, interim analysis; LPI, last patient in; MRD, minimal residual disease.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will be presented by treatment arm, and will be displayed by the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

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Where appropriate, variables will be summarized descriptively by study visit. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses.

All available efficacy and safety data will be included in data listings and tabulations as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Baseline values are defined as the last observed value before the first dose of study medication.

Screen failure subjects will be presented.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Definition of Study Days

- Study Day 1 is defined as the date on which a subject is administered with their first dose of the medication. After Study Day 1, Study Day = Date of event - Date of the first dose + 1 day.
- Prior to Study Day 1, Study Day = Date of the first dose - Date of event.

7.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

7.1.3 Conventions for Missing Adverse Event Dates

AEs with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then impute to first dose date.
  - If month and year are different than month and year of first dose date, then impute to first date of the month.

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- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be used instead.
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then it is imputed with 1st dose date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

AEs with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed.
  - If YYYY = year of last dose, then 31st of December will be imputed.
  - If YYYY > year of last dose, then 1st of January will be imputed.
- If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

7.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
  - If year is known, but day and month are missing, then 1st of January of the year will be imputed.
- If all is missing, then impute date to Date of Birth (DOB)
  - If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB).

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.

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- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, then impute date to 31st of December in the year of last dose

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

7.1.5 Conventions for Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.
- When only a year is present,
  - If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.
- If no components of the onset date are present the date of last dose + 1 will be imputed.

7.2 Analysis Populations

The Analysis Populations will include the following.

7.2.1 Intent-to-Treat Analysis Population

The intent-to-treat (ITT) analysis set is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

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7.2.2 Per-Protocol Analysis Population

The per-protocol (PP) population is a subset of the ITT population. The PP population consists of all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the sponsor's medical monitor/designee. All decisions to exclude patients from the PP population will be made before the database lock for the analyses.

The PP population will be used as a sensitivity analysis of the ITT population for the efficacy endpoints as needed if more than 5% of patients from the ITT population are excluded from this analysis.

7.2.3 Safety Analysis Population

The safety population is defined as all patients who receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, patients who receive any dose of ponatinib arm will be included in the ponatinib arm, and patients who receive any dose of imatinib will be included in the imatinib arm, regardless of their randomized treatment.

7.3 Disposition of Subjects

Dispositions of patients will be summarized using number and percentage of patients based on the ITT analysis set by each treatment cohort and all patients combined for the following patient disposition data. All percentages will be based on the number of patients in the ITT analysis set.

- Patients who are in the PP analysis population.
- Patients who are in the safety analysis population.
- Patients who are on study treatment.
- Patients who discontinued from study treatment.
- Primary reason for discontinuing study treatment.
- Patients who are on study.
- Follow-up status.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions (ie, number and percentage of patients) for categorical data and summary descriptive statistics (ie, n, mean, SD, median, minimum, and maximum) for continuous data, based on the ITT analysis set for each treatment cohort and for all patients combined.

Demographic data will also be presented in a by-patient listing. Baseline demographic data to be evaluated will include age at informed consent, age category (ie, 18≤age<45 years, 45≤age<60 years, and age≥60 years), sex, race, ethnicity, height, weight, body surface area (BSA), and other parameters as appropriate. No inferential statistics will be generated.

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Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Baseline characteristics include Eastern Cooperative Oncology Group (ECOG) score, time from initial diagnosis of PH+ ALL to first dose date prior anti-cancer regimen, Framingham Score, BCR-ABL transcript type, baseline white blood count, baseline homoglobin, baseline platelet, and other parameters as appropriate.

7.5 Medical and Surgical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by MedDRA System Organ Class (SOC), and Preferred Term (PT) using number and percentage of patients based on the ITT analysis set for each treatment cohort. Patients with the same medical history more than once will have that medical history counted only once within each SOC, and once within each PT.

Surgical history will not be coded. Surgical history will be summarized using number and percentage of patients based on the ITT analysis set for each treatment cohort, as approximate.

Medical and surgical history will be presented in a by-patient listing.

Family medical history will also be presented in a by-patient listing.

7.6 Prior and Concomitant Medications and Concomitant Procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior and concomitant medications will be summarized by WHO therapeutic class and standard drug names using number and percentage of patients based on the ITT analysis set for prior medications and the safety analysis set for concomitant medications for each treatment cohort.

Prior and concomitant medications will also be presented in a by-patient listing.

Prior radiation, and prior anticancer therapy will be summarized using number and percentage of patients based on the ITT analysis set for each treatment cohort, as appropriate.

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

7.7 Study Drug Exposure and Compliance

Extent of Exposure:

Parameters pertaining to study drug exposure (ie, duration of exposure, number of days dosed, number of cycles dosed, dose intensity, relative dose intensity, total cumulative dose) will be summarized separately by treatment cohort and overall treatment period. Duration of treatment exposure is defined as the time interval from the first dose to the last dose of study treatment (last dose date – first dose date +1).

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Dose intensity in mg/day is calculated as total cumulative dose in mg divided by duration of treatment exposure in day. Relative dose intensity is calculated as total cumulative dose in mg divided by expected total dose × 100%.

The drug exposure will be listed and summarized for the following drugs.

- Ponatinib
- Imatinib
- Vincristine
- Dexamethasone
- Methotrexate
- Cytarabine
- Prednisone
- Intrathecal therapy for CNS disease prophylaxis

Dose adjustment:

Dose adjustment and dose adjustment due to adverse event (AE) will be summarized by treatment cohort for each treatment phase and overall treatment period.

A by-patient listing including extent of exposure and dose adjustment will be presented.

7.8 Efficacy Analysis

The standard *closed* sequential testing procedure will be used for testing the primary endpoint of MRD-negative CR and the key secondary endpoint of EFS with one planned IA and one final analysis (FA) for each. Only if the hypothesis test on the primary endpoint of MRD-negative CR is statistically significant at either the IA or FA for MRD-negative CR, the test for EFS will be conducted. Both MRD-negative CR and EFS will be tested at a 2-sided alpha level of 0.05. To maintain the type I error family wise at 2-sided 0.05 level, the O'Brien-Fleming alpha spending function (the Lan-DeMets method [1]) will be used to determine the significance level at the IA or FA for MRD-negative CR; the Gamma Family (-1) alpha spending function will be used to determine the significance level at IA and FA for EFS [4]. By employing such closed sequential testing procedure, the type I error for the primary endpoint MRD-negative CR and the key secondary endpoint (EFS) are strongly controlled.

If the analysis of MRD-negative CR achieves statistical significance at the IA or FA for MRD-negative CR, then EFS will be tested at the IA or FA for EFS. The study will continue to enroll patients to achieve the accrual target of 230 patients for the EFS test.

The hypothesis test for the primary and key secondary endpoints will be grouped and ordered as:

1. MRD-negative CR rate: At the IA (alpha = 0.021 with an efficacy boundary of 0.021) and FA (alpha = 0.029 with an efficacy boundary of 0.043) for MRD-negative CR if number of patients used for IA and FA are 115 and 150, respectively.

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2. EFS: At the IA (alpha = 0.033 with an efficacy boundary of 0.033) and FA (alpha = 0.017 with an efficacy boundary of 0.034) for EFS if observed number of events at IA and FA are 130 and 173, respectively.

Therefore, the overall type I error rate for these 2 endpoints is strongly controlled at a 2-sided 0.05 alpha level.

The boundaries for hypotheses testing in MRD-negative CR and EFS will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

All other efficacy endpoints, if tested, will be at a 2-sided alpha level of 0.05.

Efficacy analyses will be conducted in the ITT population, unless otherwise specified.

MRD negativity will be based on the central laboratory results, and CR status will be based on the investigator's assessment.

7.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is defined as achievement of MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 5.a for endpoint definitions). The analysis of the primary efficacy endpoint will test for differences comparing the proportion of patients who achieve the primary endpoint at the end of induction in the ponatinib arm versus the imatinib arm. The patients who achieve MRD-negative CR at baseline or early terminate the study treatment prior to the end of induction will be considered as non-responders.

There will be one IA and possibly an FA in the study for the primary endpoint of MRD-negative CR in ITT population who have BCR-ABL1 dominant variants of p190 or p210 at screening and who have the opportunity to and be followed up to end of induction.

If the MRD-negative CR does not achieve the significance boundary at the IA, the study will continue and the FA will be triggered after the end of induction phase data have been collected for approximately 150 patients.

The primary analysis for MRD-negative CR will be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square p-value and the relative risk along with its 95% 2-sided CI will be provided.

Sensitivity analyses for the primary endpoint will include:

1. MRD-negative CR will be analyzed in the PP analysis set if more than 5% of patients are excluded from this analysis.
2. MRD-negative CR will be analyzed with non-missing observed cases.

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3. MRD-negative CR will be analyzed for patients who don't have extramedullary disease at baseline.

Subgroup analyses will be performed for the primary endpoint relative to the baseline randomization stratification factor (age); additional age category (18 through <60 years; ≥60 years), demographic data, such as gender (male, female), race (white; non-white), region (north America; south America; Europe; APAC); and baseline disease characteristics including BCR-ABL1 Transcript Type (P190; P210) and ECOG status (0; 1 or 2), as appropriate. The absolute treatment difference will also be provided along with the 95% 2-sided CI estimate.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Key Secondary Efficacy Endpoint

The key secondary endpoint is EFS, defined as the dates of randomization until:

- Death due to any cause.
- Failure to achieve CR by the end of induction.
- Relapse from CR.

EFS will be tested only if the primary endpoint comparison achieves statistical significance at the IA or FA for MRD-negative CR. EFS endpoint will be tested at the 5% level at IA or FA for EFS, per the closed sequential testing procedure, to maintain the family-wise type I error rate at 5% level.

One IA and one FA will be planned for EFS. When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The FA will be performed when approximately 173 EFS events have been observed. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05 for ITT population. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factor. The K-M survival curves and K-M median PFS (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group. The test significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary of 0.033 at IA. The final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

The primary analysis for EFS will be based on time-to-event analysis. Since it is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT, the number of events needed for EFS analysis may change depending on how HSCT cases are handled in the EFS. The primary analysis of EFS will not consider censoring at the time of HSCT. Other details regarding the handling of missing assessments and censoring for EFS analysis are presented in Table 7.a.

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Table 7.a Censoring Rules for EFS Primary Analysis Based on FDA Guidance

Situation	Date of Progression or Censoring	Outcome
Death due to any cause	Date of death	Event
Failure to achieve CR by the end of induction	Day 1	Event
Relapse from CR	Date of documented relapse from CR	Event
No documented death or relapse	Date of last adequate assessment*	Censored
Not reached the end of induction	Date of last adequate assessment*	Censored
Lost to follow-up, withdraw consent before any documented death or relapse	Date of last adequate assessment*	Censored
No randomization and/or no post randomization assessment, no subsequent anticancer therapy after study treatment, no death	Date of randomization	Censored
Alternate antineoplastic therapy started prior to relapse**	Date of last adequate assessment* prior to starting alternate antineoplastic therapy	Censored

* Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.
** Alternate antineoplastic therapy does not include HSCT.

Sensitivity analyses for EFS will include:

1. EFS will be analyzed in the PP analysis set if more than 5% of patients will be excluded in this analysis.
2. PFS will be analyzed using the missing assessment and censoring rules based on EMA guidance from FDA guidance as presented in Table 7.b.

Table 7.b Handling of missing assessment and censoring for PFS Sensitivity Analysis based on EMA guidance

Situation	Date of Progression or Censoring	Outcome
Alternate antineoplastic therapy started prior to disease progression	Date of documented disease progression	Event

1. If there exists time depended confounding factors caused by informative censoring from imbalance in the proportion of HSCT events between the 2 cohorts, Marginal Structural Model (MSM) [5] and Inverse Probability of Censoring Weighted (IPCW) [6] analysis of the EFS endpoint will be considered.
2. If the propotional hazard assumption is violated, non-propotional hazard Cox models will be applied to evaluate HR using piecewise expotential model.

In the MSM and IPCW analyses, in order to derive weights adjusting for the time-fixed and time-varying confounding effects due to taking HSCT, the covariates affecting EFS endpoint will be used. Potential time-fixed covariates and time-varying covariates include demographic data, such as age (18 through <45 years; 45 -<60 years; ≥60 years), gender (male, female), race

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(white; non-white), region (north America; south America; Europe; APAC); and baseline disease characteristics including BCR-ABL1 dominant transcript (P190; P210) and ECOG status (0; 1 or 2); baseline laboratory parameters such as white blood count, homoglobin, platelet, LDH, peripheral blood blast, bone marrow blast; and time-dependent covariates including SCT status, duration of exposure, relapse status at each study visit, initiation of alternative therapy, and other perimeters as appropriate. The final criteria for selected covariates would need to be statistically have a p-value of less than or equal to 0.15 in the multivariate logistic regression models for weight calculations. If there are more than 5% missing in the baseline covariate, then this covariate will be dropped from the weighting calculation and final model. For both MSM and IPCW analyses, logistic regression models on repeated measurements will be used to approximate the Cox models in the weight derivations from which stabilized weights will be derived per subject per observation. Adjusted K-M curves will also be presented along with hazard ratios (HRs), 95% confidence intervals for HRs, and adjusted p-values based on MSM and IPCW approaches. SAS proc PHREG procedure with counting process type of data input, which takes multiple observations per subject, will be used as the final Cox model for both MSM and IPCW approaches, where robust variance will be used to accommodate covariance introduced by correlated longitudinal observations within each subjects and other extra variabilities due to departure from model assumptions.

Additional sensitivity analysis for EFS might be conducted as appropriate.

Subgroup analyses will be performed for EFS relative to baseline stratification factor, demographic data listed in Section 7.4.

7.8.2.2 Other Secondary Efficacy Endpoints

The following other secondary endpoints will be analyzed (see Table 5.a for endpoint definitions):

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Molecular response rates (MR3/MMR(Major Molecular Response), MR4/CMR(Complete Molecular Response), and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.
- Rates of MRD-negative CR at multiple intervals after the end of induction.
- Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.

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- OS and rate of relapse from CR for on-study patients with and without HSCT.
- OS.

The other secondary efficacy endpoints will be tested at $\alpha = 0.05$ level in a nonhierarchical fashion without adjustments for multiplicity.

For analysis of time-to-event endpoints (eg, time to treatment failure, OS), 2-sided, stratified log-rank tests will be used to compare the treatment groups with respect to the endpoints. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio (HR) and its 95% CIs for the treatment effect using the stratification factors. K-M survival curves and K-M medians (if appropriate and estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

For the secondary endpoint of OS, a futility analysis with be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

OS results are expected to be confounded by alternative therapies after patients discontinue from the study assigned drug. Thus, sensitivity analyses, such as Marginal Structural Models (MSM) and Inverse Probability Censoring Weighting (IPCW), will be conducted for OS analysis adjusting for time depending on confounding factors occurring due to taking alternative therapies. With IPCW and MSM analyses, to reduce bias, the following settings will be similar with the EFS analysis including: 1) the list of potential confounders, both baseline and time-dependent, which may impact both OS and censoring outcome, and thus will be included in the initial weighting models; 2) the p-value cut off for confounders remain in the final weighting models will be at 0.15 level; and 3) SAS procedure.

The primary analysis for duration of MRD-negative CR will be based on time-to-event analysis and will not consider censoring at the time of HSCT.

The proportion-based other secondary endpoints (eg, CR and CRi rates, proportion of patients received HSCT) will be analyzed in the same fashion as the primary endpoint. The CMH chi-square p-value and the odds ratio, along with its 95% 2-sided CI, will be provided.

7.8.3 Additional Efficacy Endpoint(s)

The exploratory endpoints are:

- Time to HSCT.
- Time to start of alternative chemotherapy.
- Change from baseline in patient-reported HRQOL (FACT-Leu and EQ-5D-5L).
- MRU assessments.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

Further details on the exploratory endpoint analyses will be discussed in the following.

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7.8.3.1 Time-to-Next-Treatment and Time-to-HSCT Analyses

Time to subsequent antineoplastic therapy will be defined as the time from randomization to the date of first documentation of subsequent antineoplastic therapy or the last contact date for subjects who never received subsequent antineoplastic therapy.

Likewise, time to HSCT will be defined as the time from randomization to the date of first documentation of HSCT or the last contact date for subjects who did not receive an HSCT.

A Cox regression model with treatment as explanatory variable will be used for the time-to-event analyses. Median will be calculated by K-M method.

7.8.3.2 Patient-Reported Outcomes Analysis

Quality of life and health outcomes measures are being collected using the EQ-5D-5L and FACT-Leu instruments. Means and medians of scores of these questionnaires will be summarized for each cohort by time point, overall, and for each domain. Assessments based on the FACT-Leu will be analyzed to determine if treatments affect all domains.

Analyses of HRQOL scores, including global health status, will be performed using longitudinal models for scores and change from baseline scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point.

The manuals published for FACT-Leu will be used for scoring and handling missing data.

EQ-5D-5L scores will be summarized in descriptive statistics for treatment groups. Both utility scores and change from baseline scores will be assessed across time using longitudinal models.

Compliance for EQ-5D-5L and FACT-Leu will also be summarized by number of expected and number and percentage of received by treatment group over time.

PROs by proportion of patients that achieved or did not achieve MRD-negative CR at end of induction will be summarized by treatment group as appropriate.

Patient-reported outcome analysis will use safety population.

7.8.3.3 Health Economics Analysis Using Medical Resource Utilization

Medical resource utilization data will be summarized in descriptive statistics for safety population hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities, by patient and caregiver, and by treatment group.

7.8.3.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib

The mutation status of BCR-ABL1 and other genes implicated in tumor biology and/or drug metabolism will be determined, as clinically needed, through analyses of tumor cells collected at study entry, on study, and/or at EOT. Analysis methodologies include, but are not limited to, DNA sequencing, digital PCR, and mass spectrometry.

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7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The PK data collected in this study are intended to contribute to future population PK analyses of ponatinib. These population PK analyses may additionally include data collected in other ponatinib clinical studies. The analysis plan for the population PK analysis will be defined separately and the results of these analyses will be reported separately.

Ponatinib plasma concentration-time data will be listed and summarized by time point.

7.9.2 Pharmacodynamic Analysis

Not Applicable.

7.10 Other Analysis

In general, missing or partial dates due to COVID-19 will follow the convention without special handling. COVID-19 impact on the study visit and dosing/laboratory schedule will be tabulated and listed.

7.11 Safety Analysis

The safety analysis will be carried out at interim and final analyses. In addition, an extended safety analysis for the study will be carried out at study completion.

Safety analyses will be based on the safety analysis set. Descriptive statistics (ie, n, mean, SD, median, minimum and maximum for continuous variables, and frequency and percentage of patients for categorical variables) will be used to summarize the safety parameters.

Safety evaluations will be based on incidence, severity, and type of AEs; clinically significant changes or abnormalities in the patient's physical or neurological examinations; vital signs; ECG; ECOG performance status; clinical laboratory test results and other safety parameters.

7.11.1 Adverse Event

7.11.1.1 Adverse Events

AEs will be coded using MedDRA. All AEs will be presented in a by-patient listing. Treatment-emergent adverse events (TEAEs) are defined as any AEs that occur after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

AEs will be tabulated according to MedDRA by SOC, HLT, and PT and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.

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- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs (related and regardless of relationship)
- TEAEs leading to study drug modification and discontinuation.
- TEAEs leading to hospitalization or prolonging hospitalization.
- TEAEs leading to death.
- Adverse events of special interest (AESIs) including Arterial Occlusive Events (AOEs) and Venous Thromboembolic Events (VTEs).

Patients with the same AE more than once will have that event counted only once within each SOC, once within each HLT, and once within each PT.

TEAEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Patients with the same AE more than once will have the maximum intensity of that event counted within each SOC, once within each HLT, and once within each PT.

The most commonly reported TEAEs (ie, those events reported by ≥10% of any treatment cohort) will be tabulated by PT. Patients with the same AE more than once will have that event counted only once within each PT.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation, and on-study deaths. On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

In addition, TEAEs will be summarized by each treatment cohort. Secondary malignancy will be tabulated and listed as appropriate.

By-patient listing of grade 3 or higher treatment-emergent AE will also be provided, where the cycle day information for the AE onset and end dates will be included in the listing.

Analysis of AOEs and VTEs

Arterial occlusive and venous thromboembolic events with an initial onset date on or after the first dose date will be considered treatment-emergent and summarized. Number and percentages of patients who developed AOEs and VTEs will be summarized for each cohort. These events will be categorized as follows:

- Arterial occlusive events
  - Cardiovascular occlusive events.
  - Cerebrovascular occlusive events.

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  - Peripheral vascular occlusive events.

- Venous thrombotic events.

Exposure-adjusted incidence rates (EAIR) of adjudicated AOEs and VTEs will be calculated for each cohort and for all patients. The 95% CI of the EAIR will be computed.

The following additional descriptive analyses will be performed to characterize AOEs and VTEs described above:

- Time to onset: Calculated as date of first event AE- first dose date + 1.
- Dose at onset: Dose of ponatinib/imatinib taken immediately prior to onset of first event.

7.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA primary system organ class, high level term, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).

7.11.1.3 Deaths

All deaths will be summarized by treatment arm, including deaths occurring on-study and death during follow-up separately.

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status).

7.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug regimen will be presented.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, absolute neutrophil count (ANC), platelets counts, WBC, lymphocytes and leukocytes

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- Serum chemistry: blood urea nitrogen (BUN), creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, corrected calcium, sodium, potassium, chloride, lipase and amylase

Shift tables will be constructed for laboratory parameters to tabulate changes from study entry to post study entry either by CTCAE toxicity grade or abnormality. Parameters to be tabulated will include, but not limited to:

- Hematology: ANC, hemoglobin, and platelets.
- Serum chemistry: ALT, AST, ALP, creatinine, total bilirubin, amylase and lipase.

Mean laboratory values and box plots over time for key lab parameters will be produced, including but not limited to ANC, platelets, and liver function tests (ALT/SGPT, AST/SGPT, alkaline phosphatase, and total bilirubin), and lipase.

By-patient listings to be presented include hematology, serum chemistry, urinalysis, urine total protein, and urine creatinine.

7.11.3 Vital Signs

The actual values of vital sign parameters (ie, systolic and diastolic BP, heart rate, respiratory rate, temperature, height, and weight) will be summarized at all planned timepoints by each treatment cohort using descriptive statistics (ie, n, mean, SD, median, minimum and maximum). Change of vital signs from baseline values will also be summarized at all planned timepoints. Vital sign values will also be presented in a by-patient listing.

7.11.4 12-Lead ECG

The absolute values and absolute change from baseline of electrocardiogram (ECG) parameters including ECG ventricular rate, PR interval, RR interval, QRS duration, QT interval, and QT interval corrected per Fridericia method (QTcF) interval will be summarized at each timepoint using descriptive statistics (ie, n, mean, SD, median, minimum and maximum).

QTc interval will be calculated using Fridericia correction, if necessary. The formulas are:

$$QTcF\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (<450 msec, 450-480 msec, >480-<500 msec, and ≥500msec) will be summarized at each time point. Categories of changes from baseline (≥30 msec and ≥60 msec) will be summarized as well. Maximum QTcF intervals and maximum changes from baseline will also be summarized similarly in a separate display.

ECG abnormalities will be presented in a data listing.

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7.11.5 ECOG Performance Status

ECOG performance status and shifts from baseline to post study entry assessment over time, and ECOG score frequency table over time will be summarized. Shifts from baseline to the worst post study entry score will be tabulated by each treatment cohort.

7.11.6 Other Observations Related to Safety

The ankle-brachial index (ABI), echocardiogram (ECHO) for assessment of left ventricular ejection fraction (LVEF) and Multiple-Gated Acquisition (MUGA) scan will be presented in a data listing.

7.12 Interim Analysis

MRD-negative CR

There will be one IA and possibly an FA in the study for the MRD-negative CR primary endpoint using a group sequential testing approach.

The IA will be performed after the end of induction phase data have been collected for 115 patients. The primary endpoint of MRD-negative CR will be first tested at IA with a 2-sided efficacy boundary of 0.021 if exactly 115 patients are used in the IA. Otherwise, the efficacy boundary will be calculated using the exact number of patients in IA with 150 patients in FA for the MRD-negative CR.

If the significance boundary is crossed, this will be the FA for MRD-negative CR for statistical testing purpose and, there will be a testing for EFS at a 2-sided alpha level of 0.05 using group sequential testing approach.

If MRD-negative CR does not achieve statistical significance at the IA, the study will continue and the FA will occur after the end of induction phase data have been collected for approximately 150 patients. The MRD-negative CR will be tested with a 2-sided efficacy boundary of 0.043.

The boundaries for hypotheses testing in MRD-negative CR will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

EFS

There will be one IA and possibly an FA in the study for the key secondary endpoint EFS using a group sequential testing approach.

When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The IA is expected to occur approximately 5.5 years after the first patient is enrolled. The FA is expected to be performed approximately 8.5 years after the first patient enrolled, when all approximately 173 EFS events have been observed.

The test significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary

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(p=0.033) at IA and this will be the FA for EFS for statistical testing purpose. If EFS does not achieve statistical significance at the IA, the final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

The boundaries for hypotheses testing in EFS will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

Overall Survival

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

The analyses for the IA will be carried out by an independent statistical team in a manner that maintains the blinding of the study results to the team (see Section 13.4). The IDMC will review both efficacy and safety data at the time of the IA, and will inform the sponsor's executive committee of their recommendation.

7.13 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol Ponatinib-3001 amendment 8 (Protocol amendment dated 10 February 2021).

8.0 REFERENCES

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	07-May-2021 20:53 UTC

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Ponatinib-3001

A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination with Reduced-Intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

PHASE 3

Version**: Final 3.0**

Date**:** 20 September 2022

Prepared by:

PPD

Based on:

Protocol Version: Amendment 10

Protocol Date: 20 October 2021

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1.1 Approval Signatures

Study Title: A Phase 3, Randomized, Open-label, Multicenter Study Comparing Ponatinib Versus Imatinib, Administered in Combination with Reduced-Intensity Chemotherapy, in Patients with Newly Diagnosed Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

Approvals:

PPD

Date

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

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3.0 LIST OF ABBREVIATIONS

Abbreviation	Term
ABI	ankle-brachial index
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALL	chromosome-positive acute lymphoblastic leukemia
ALP	albumin, alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AOE(s)	arterial occlusive event(s)
AST	aspartate aminotransferase
BCR	breakpoint cluster region
BCR-ABL	breakpoint cluster region-Abelson
BP	blood pressure
BSA	body surface area
CI(s)	confidence intervals
CMH	Cochran-Mantel-Haenszel
CML	chronic myeloid leukemia
CNS	central nervous system
CR	complete remission (complete response)
Cri	incomplete complete remission
EAIR	Exposure-adjusted incidence rates
ECG(s)	Electrocardiogram(s)
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EQ-5D-5L	EuroQOL-5 Dimension-5 Level
EOT	end of treatment
FA	final analysis
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia
HR	hazard ratio
HLT	High Level Term
HRQOL	health-related quality of life
HSCT	hematopoietic stem cell transplantation
IA	interim analysis
IDMC	independent data monitoring committee
IPCW	Inverse Probability Censoring Weighting
IS	International Scale
IXRS	interactive voice/web response system
ITT	intent-to-treat

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Abbreviation	Term
K-M	Kaplan-Meier
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MR3	molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%)
MR4	molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%)
MR4.5	molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%)
MRD	minimal residual disease
MRU	medical resource utilization
MSM	Marginal Structural Model
MUGA	Multiple-Gated Acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease (disease progression)
Ph+ ALL	Philadelphia chromosome–positive acute lymphoblastic leukemia
PIF	primary induction failure
PK	Pharmacokinetic
PP	per-protocol
PT	Preferred Term
QD	once daily
QTcF	QT interval corrected per Fridericia method
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD(s)	standard deviation(s)
SOC	System Organ Class
TEAE(s)	treatment-emergent adverse event(s)
TKI	tyrosine kinase inhibitor
VTE(s)	venous thrombotic/embolic event(s)
WHO	World Health Organization

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4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of the study is to compare the efficacy of ponatinib versus imatinib, administered as first-line therapy in combination with reduced-intensity chemotherapy, in patients with newly diagnosed Ph+ ALL, as measured by the MRD-negative CR rate at the end of induction (see Table 5.a for the definitions of MRD negativity and CR).

4.2 Secondary Objectives

4.2.1 Key Secondary Objectives

The key secondary objective is to compare event-free survival (EFS) between the 2 cohorts.

4.2.2 Other Secondary Objectives

Other secondary objectives are:

- To compare the rates of CR and incomplete CR (CRi) between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of MR3, MR4, and MR4.5 between the 2 cohorts, at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- To compare the rates of primary induction failure (PIF) and overall response rate (ORR) between the 2 cohorts, at the end of induction.
- To compare rates of MRD-negative CR at multiple intervals after the end of induction.
- To determine the duration of MRD-negative CR in each of the 2 cohorts.
- To determine the duration of CR in each of the 2 cohorts.
- To compare the time to treatment failure between the 2 cohorts.
- To compare the duration of MR4.5 between the 2 cohorts, in patients who achieved MR4.5.
- To compare outcomes in patients with and without HSCT, between the 2 cohorts.
- To compare OS between the 2 cohorts.
- To collect plasma concentration-time data to contribute to population pharmacokinetic (PK) and exposure-response analyses of ponatinib.

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4.3 Safety Objectives

The safety objectives are:

- To characterize the rates of AEs/SAEs, AOEs, venous thrombotic/embolic events (VTEs), and other safety outcomes of interest in the 2 cohorts, using multiple methods.
- To compare the tolerability between the 2 cohorts, including the rates of discontinuation, dose reductions, and dose interruptions due to AEs.

4.4 Exploratory Objectives

The exploratory objectives are:

- To compare patient-reported quality of life (Functional Assessment of Cancer Therapy – Leukemia [FACT-Leu] and EuroQOL-5 Dimension-5 Level [EQ-5D-5L]) results between the 2 cohorts.
- To compare medical resource utilization (MRU) results between the 2 cohorts.
- To compare the time to start of alternative therapy between the 2 cohorts.
- To compare the time to HSCT between the 2 cohorts.
- To explore biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

4.5 Study Design

4.5.1 Study Design

This phase 3 study is designed as an open-label, multicenter, randomized comparison of the TKIs ponatinib versus imatinib, when administered as first-line therapy in patients aged ≥18 years with newly diagnosed Ph+ ALL. The TKIs will be administered in combination with 20 cycles of a reduced-intensity chemotherapy regimen (including 3 cycles of induction therapy, 6 cycles of consolidation therapy, and 11 cycles of maintenance therapy), followed by single-agent therapy with ponatinib or imatinib, to be administered continuously. Patients will remain on study treatment until they are deceased, have failed to achieve the primary endpoint at the end of induction (patients who do not achieve the primary endpoint may remain on study drug, at the investigator's discretion, if they have achieved CR at the end of induction), have experienced relapse from CR or have progressive disease, have an unacceptable toxicity, have withdrawn consent, have proceeded to HSCT or alternative therapy, or until the sponsor terminates the study, whichever occurs first.

The primary endpoint of this study is MRD-negative CR at the end of induction (defined in Table 5.a). Patients who achieve the primary endpoint will continue in the study in the consolidation and maintenance phases followed by a single-agent therapy phase. Patients who achieve CR but do not achieve the primary endpoint at the end of induction may, at the investigator's discretion, continue on study treatment. All patients who do not achieve CR at the

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end of induction will be discontinued from study drug. For all discontinued patients, the patient's treating physician should consider alternative therapy options.

Upon enrollment, patients will be randomized in a 2:1 ratio of ponatinib:imatinib to be taken throughout the study, beginning on Cycle 1 Day 1. Patients randomized to Cohort A (ponatinib) will receive 30 mg of oral ponatinib QD, which will be reduced to 15 mg if MRD-negative CR is achieved at the end of induction. If a patient loses MRD negativity after dose reduction to 15 mg, re-escalation to 30 mg may be considered after discussion with the sponsor's medical monitor/designee. Dose reductions to 10 mg of ponatinib QD may be considered for safety reasons after discussion with the sponsor's medical monitor/designee (see Protocol Section 8.4.1). For patients in the ponatinib cohort who achieve CR but do not achieve the primary endpoint at the end of induction and who continue in the study at the investigator's discretion, the dose of ponatinib will be reduced, as described above, at any time when the patient achieves MRD-negative CR and re-escalated, as described above, upon loss of response. Patients randomized to Cohort B (imatinib) will receive 600 mg of oral imatinib QD. Intrathecal therapy will be performed twice per month for the first 6 cycles for central nervous system (CNS) disease prophylaxis. At the end of the 20 cycles, all patients remaining on study will remain on ponatinib or imatinib (administered as a single agent).

MRD status will be measured using qPCR-based tests validated for the ability to detect breakpoint cluster region-Abelson (BCR-ABL1)/ABL1 levels with a minimal sensitivity of 0.01%, with MRD negativity defined as ≤0.01% BCR-ABL1/ABL1. Separate tests will be used to assess the *p210* and *p190* variants of BCR-ABL1 (see Protocol Section 4.2.3), which comprise >95% of the variants present in adult patients with Ph+ ALL. For the p210 test, BCR-ABL1/ABL1 levels will be reported on the International Scale (IS) with traceability to the World Health Organization (WHO) first International Genetic Reference Panel. For the p190 test, for which there is no internationally available reference material, the raw ratio of BCR-ABL1/ABL1 levels will be reported.

The key secondary endpoint for this study is EFS. Other secondary endpoints will include rates of CR and CRi at the end of Cycle 1, Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MR3, MR4, and MR4.5 at the end of Cycle 1, the end of Cycle 2, the end of induction and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier); rates of MRD-negative CR at multiple intervals after the end of induction; rates of PIF and ORR at the end of induction; duration of MRD-negative CR; duration of CR; time to treatment failure; duration of MR4.5 in patients who achieved MR4.5; OS and rate of relapse from CR for on-study patients with and without HSCT, and OS.

Safety and tolerability parameters will be assessed in both cohorts, including incidence of all AEs, SAEs, AOEs, and VTEs; rates of discontinuation, dose reductions, and dose interruptions due to AEs; incidence of death while on treatment, and changes from baseline in vital signs and laboratory test results. Plasma concentration-time data will also be collected for patients receiving ponatinib.

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Exploratory endpoints will include change from baseline in patient-reported quality-of-life; MRU assessments; time to start of alternative therapy; time to HSCT; and biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

4.5.2 Randomization and Stratification

The randomization scheme will be generated by an independent statistician who is not on the study team. Before dosing, a randomization number will be assigned to each patient. The randomization assignment will be implemented by an interactive voice/web response system (IXRS).

Eligible patients will be randomized in a 2:1 ratio to receive ponatinib or imatinib treatment arms, stratified by ages: 18 through <45 years; ≥45 through <60 years; and ≥60 years.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints:

The primary endpoint is MRD-negative CR at the end of induction (see Table 5.a for the definitions of MRD negativity and CR).

5.2 Secondary Endpoints:

5.2.1 Key Secondary Endpoints

The key secondary endpoint is:

- EFS, defined as the dates of randomization until:
  - Death due to any cause.
  - Failure to achieve CR by the end of induction.
  - Relapse from CR.

5.2.2 Other Secondary Endpoints

Other secondary endpoints (defined in Table 5.a) are:

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.

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- Rates of MRD-negative CR at multiple intervals after the end of induction.Duration of MRD-negative CR.
- Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.
- OS and rate of relapse from CR for on-study patients with and without HSCT.
- OS.

Table 5.a Definitions of Efficacy Response Criteria

Term	Definition
CNS-1	CNS-1: No lymphoblasts in the CSF regardless of WBC count.
CNS-2	WBC count <5 leukocytes/µl in the CSF with the presence of blasts.
CNS-3 [a]	WBC count of ≥5 leukocytes/µl with the presence of blasts.
CNS disease remission	No lymphoblasts in CSF regardless of WBC count in a patient with CNS-2 or CNS-3 at diagnosis.
CNS relapse	Development of CNS-3 status or development of clinical signs of CNS leukemia (eg, facial nerve palsy, brain/eye involvement, hypothalamic syndrome).
CR	Complete remission; meeting all the following for at least 4 weeks (ie, no recurrence): • No circulating blasts and <5% blasts in the BM. • Normal maturation of all cellular components in the BM. • No extramedullary disease (CNS involvement, lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass). • ANC >1000/µl (or >1.0 × 10^9/L). • Platelets >100,000/µl (or >100 × 10^9/L).
CRi	Hematologic complete remission with incomplete hematologic recovery. Meets all criteria for CR except platelet count and/or ANC.
Duration of CR	The interval between the first assessment at which the criteria for CR are met until the time at which relapse from CR occurs.
Duration of MR4.5	The interval between the first assessment at which the criteria for MR4.5 are met until the earliest date at which loss of MR4.5 occurs.
Duration of MRD negativity	The interval between the first assessment at which the criteria for MRD negativity are met until the earliest date at which loss of MRD negativity occurs or relapse from CR occurs.
Duration of MRD-negative CR	The interval between the first assessment at which the criteria for MRD-negative CR are met until the earliest date at which loss of MRD negativity or relapse from CR occurs.

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Table 5.a Definitions of Efficacy Response Criteria

Term	Definition
EFS	Event-free survival (EFS), defined as the dates of randomization until: • Death due to any cause. • Failure to achieve CR by the end of induction. • Relapse from CR.
Loss of MR3	An increase to >0.1% BCR-ABL1/ABL1.
Loss of MR4.5	An increase to >0.0032% BCR-ABL1/ABL1. This result must be confirmed at the subsequent visit, unless it is associated with loss of MR3 or relapse from CR.
Loss of MRD negativity	An increase to ≥0.01% BCR-ABL1/ABL1. This result must be confirmed within 4 weeks with either a BM aspirate (optional) or peripheral blood, unless it is associated with loss of MR3 or relapse from CR.
MR3	Molecular response 3-log reduction (≤0.1% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥1000 ABL1 transcripts.
MR4.5	Molecular response 4.5-log reduction (≤0.0032% BCR-ABL1/ABL1), or undetectable BCR-ABL1 transcripts in cDNA with ≥32,000 ABL1 transcripts.
MRD-negative CR	Meeting the criteria for both MRD negativity and CR.
MRD negativity (MR4)	≤0.01% BCR-ABL1/ABL1, or undetectable BCR-ABL1 transcripts in cDNA with ≥10,000 ABL1 transcripts. Also referred to as MR4.
ORR	Overall response rate: CR + CRi.
OS	Overall survival. The interval between randomization and death due to any cause.
PD	Progressive disease. Increase of at least 25% in the absolute number of circulating or BM blasts or development of extramedullary disease.
PIF	Primary induction failure: Patients who received treatment for ALL but never achieved CR or CRi by the end of induction. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in CR or CRi.
Relapse from CR	Reappearance of blasts in the blood or BM (≥5%) or in any extramedullary site after a CR.
Time to treatment failure	Time to end of study-randomized treatment (except for HSCT without loss of MRD-negative CR) due to safety and/or efficacy reasons.

Abbreviations: ANC, absolute neutrophil count; BCR-ABL, breakpoint cluster region-Abelson; BM, bone marrow; CNS, central nervous system; CSF, cerebrospinal fluid; CR, complete remission; CRi, incomplete blood count recovery; HSCT, hematopoietic stem cell transplant; MR3, molecular response 3-log reduction (BCR-ABL1/ABL1 ≤0.1%); MR4, molecular response 4-log reduction (BCR-ABL1/ABL1 ≤0.01%); MR4.5, molecular response 4.5-log reduction (BCR-ABL1/ABL1 ≤0.0032%); MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; Ph+ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; RBC, red blood cell; WBC, white blood cell.

[a] If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and WBC ≥5/μL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least 2-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2.

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5.3 Safety Endpoints:

The safety endpoints are:

- Incidence and exposure-adjusted incidence rates of AOEs, VTEs, AEs, and SAEs, in each of the 2 cohorts.
- Incidence of dose reductions, interruptions, and discontinuations due to AEs, in each of the 2 cohorts.
- Incidence of death on treatment, in each of the 2 cohorts.
- Changes from baseline in vital signs (including systolic and diastolic BP, and heart rate) and clinical laboratory test results, in each of the 2 cohorts.

5.4 Pharmacokinetic Endpoint

The PK endpoint is plasma concentration-time data to contribute to population PK and exposure-response analyses of ponatinib.

5.5 Exploratory Endpoints

The exploratory endpoints are (see Table 5.a for the definitions):

- Change from baseline in patient-reported quality of life (FACT-Leu and EQ-5D-5L).
- MRU assessments.
- Time to start of alternative therapy.
- Time to start of HSCT.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib and/or biomarkers affecting ponatinib efficacy or safety.

6.0 DETERMINATION OF SAMPLE SIZE

The study employed group sequential design for the primary endpoint MRD-negative CR, the key secondary endpoint EFS, and other endpoints (Duration of CR, Duration of MRD-negative CR, ORR and OS).

Assuming an effect size ranging from 20% to 28% (40 - 48% vs. 20% MRD-negative CR rates for the active and control arms, respectively), an upfront committed sample size of approximately 230 patients (approximately 153vs 77 for the active and control arms, respectively, based on a 2:1 allocation ratio) will provide 84% to 98% power for MRD-negative CR final analysis using the efficacy boundary of 0.036 according to the the group sequential testing procedure with IA performed from 116 patients [7]. The O'Brien-Fleming alpha spending function (the Lan-DeMets method [1]) will be implemented to determine the significance level at IA and FA for the primary endpoint, with an overall type I error rate at a 2-sided 0.05 level.

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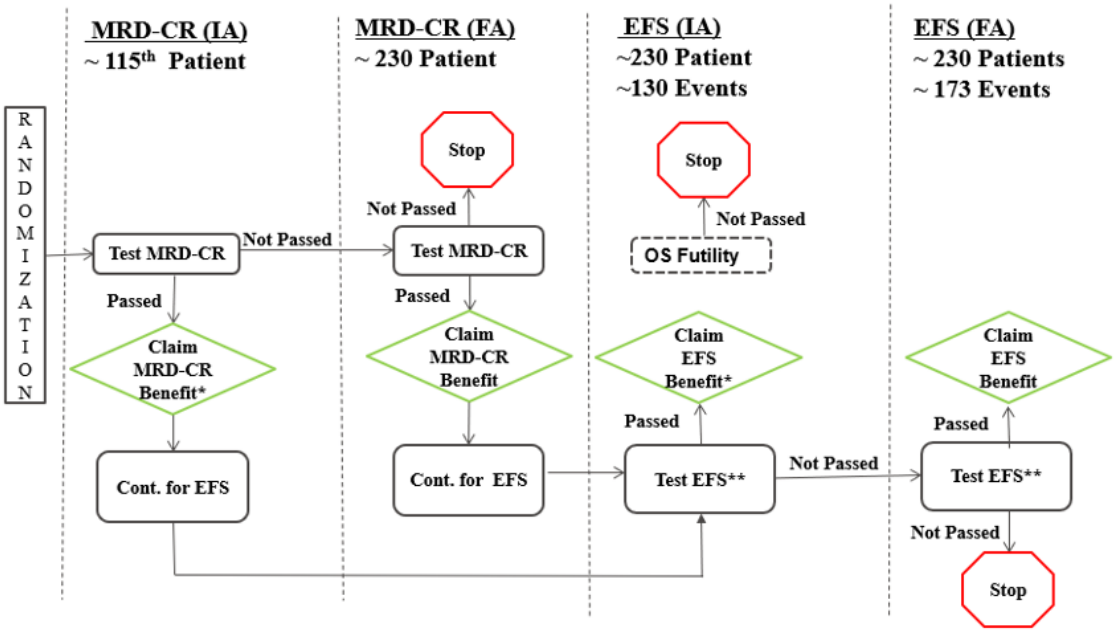
Inference for the key secondary endpoint of EFS will be conducted at α = 5% level only if the primary endpoint is met either at IA or FA for the MRD-negative CR (Figure 6.a). Based on 3-year EFS data observed from various phase 2 studies [2,3], effect size is assumed as 67% vs 46% for EFS at year 3 for the active and control arms, respectively, or HR = 0.516 for non-HSCT patients. The effect size is assumed as 53% and 40% for EFS at year 3 for active and control arms, respectively, or HR = 0.693 for patients who are undertaking HSCT. Also, it is assumed that 50% and 45% of patients from active and control arms will undertake HSCT, respectively. Based on simulation studies, approximately 230 patients will be enrolled to collect long-term EFS data. Among these 230 patients, approximately 173 events need to be accumulated at FA so that the power will be approximately 80% for the EFS endpoint. It is expected that the time of EFS will be approximately 8.5 years after first patient has been enrolled.

Figure 6.a Statistical Analysis Schema



*If efficacy boundary is crossed at IA, it is the final analysis and no formal hypothesis testing will be performed.
**If the efficacy boundary is crossed at either IA or FA for EFS, the following endpoints will be tested in the order using the same boundaries: a) Duration of CR; b) ORR; c) Duration of MRD-negative CR; d) OS.

Abbreviations: Cont., continue; CP, conditional probability; CR, complete response; EFS, event-free survival; FA, final analysis; IA, interim analysis; LPI, last patient in; MRD, minimal residual disease.

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7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will be presented by treatment arm, and will be displayed by the number of observations, mean, standard deviation (SD), median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data. The Kaplan-Meier (K-M) survival curves and 25th, 50th (median), and 75th percentiles will be provided along with their 2-sided 95% confidence intervals (CIs) for time-to-event data.

Where appropriate, variables will be summarized descriptively by study visit. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable.

A windowing convention will be used to determine the analysis value for a given study visit for observed data analyses.

All available efficacy and safety data will be included in data listings and tabulations as needed. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

Baseline values are defined as the last observed value before the first dose of study medication.

Screen failure subjects will be presented.

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

7.1.1 Definition of Study Days

- Study Day 1 is defined as the date on which a subject is administered with their first dose of the medication. After Study Day 1, Study Day = Date of event - Date of the first dose + 1 day.
- Prior to Study Day 1, Study Day = Date of the first dose - Date of event.

7.1.2 Conventions for Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded during the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the fifteenth will be used.
- If only the year is present, and it is the same as the year of the first dose of study drug, the fifteenth of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only the year is present, and it is not the same as the year of the first dose of study drug, the fifteenth of June will be used, unless other data indicates that the date is earlier.

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7.1.3 Conventions for Missing Adverse Event Dates

AEs with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known but day is missing
  - If month and year are the same as month and year of first dose date, then impute to first dose date.
  - If month and year are different than month and year of first dose date, then impute to first date of the month.
- If year is known but day and month are missing
  - If year is same as year of 1st dose date, then 1st dose date will be used instead.
  - If year is different than year of 1st dose date, then 1st of January of the year will be imputed.
- If all is missing, then it is imputed with 1st dose date.

Imputing missing AE start date is mandatory. After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

AEs with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed.
  - If YYYY = year of last dose, then 31st of December will be imputed.
  - If YYYY > year of last dose, then 1st of January will be imputed.
- If all are missing, then impute date to 31st of December, in the year of last dose.

Imputing missing AE stop date is not mandatory if AE is regarded as ongoing. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for AE stop date.

After the imputation, all imputed dates are checked against the start dates to ensure the stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date the same as the start date.

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7.1.4 Conventions for Missing Concomitant Medication/Therapy Dates

Concomitant medications/therapies with start dates that are completely or partially missing will be analyzed as follows:

- If month and year are known, but day is missing, then impute day to first of the month
  - If year is known, but day and month are missing, then 1st of January of the year will be imputed.
- If all is missing, then impute date to Date of Birth (DOB)
  - If DOB is not available but age is available, then estimate DOB by using screening date and age (age = screening date – DOB).

Concomitant therapies with stop dates that are completely or partially missing will be analyzed as follows:

- If "ongoing" is checked, no imputation is necessary.
- If month and year are known but day is missing, the last day of the month will be imputed
- If year is known, but day and month are missing,
  - If YYYY < year of last dose, then 31st of December will be imputed
  - If YYYY = year of last dose, then 31st of December will be imputed
  - If YYYY > year of last dose, then 1st of January will be imputed
- If all is missing, then impute date to 31st of December in the year of last dose

Imputing missing concomitant therapies is optional. However, if it is to be done, the rules are outlined above. If subject dies, then use death date for concomitant therapies stop date. After the imputation, all imputed dates are checked against the start dates to ensure stop date does not occur before start date. If the imputed stop date occurs prior to start date, then keep the imputed date same as the start date.

7.1.5 Conventions for Missing Subsequent Medication/Therapy Dates

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

- When month and year are present and the day of the month is missing,
  - If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
  - If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month is imputed.

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- When only a year is present,
  - If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
  - If the onset year is not the same as the year of last dose with study drug, the first day of the year is imputed.
- If no components of the onset date are present the date of last dose + 1 will be imputed.

7.2 Analysis Populations

The Analysis Populations will include the following.

7.2.1 Intent-to-Treat Analysis Population

The intent-to-treat (ITT) analysis set is defined as all patients who are randomized. Patients will be analyzed according to the treatment they were randomized to receive, regardless of any errors of dosing.

7.2.2 Per-Protocol Analysis Population

The per-protocol (PP) population is a subset of the ITT population. The PP population consists of all patients who do not violate the terms of the protocol in a way that would affect the study outcome significantly, as determined by the sponsor's medical monitor/designee. All decisions to exclude patients from the PP population will be made before the database lock for the analyses.

The PP population will be used as a sensitivity analysis of the ITT population for the efficacy endpoints as needed if more than 5% of patients from the ITT population are excluded from this analysis.

7.2.3 Safety Analysis Population

The safety population is defined as all patients who are randomized to the ponatinib or imatinib arm and receive at least 1 dose of any study drug. Patients will be analyzed according to the treatment actually received. That is, patients who receive any dose of ponatinib will be included in the ponatinib arm, and patients who receive any dose of imatinib will be included in the imatinib arm, regardless of their randomized treatment.

Patients at sites in Japan are assigned to the ponatinib arm only. These nonrandomized patients will be analyzed separately.

7.3 Disposition of Subjects

Dispositions of patients will be summarized using number and percentage of patients based on the ITT analysis set by each treatment cohort and all patients combined for the following patient disposition data. All percentages will be based on the number of patients in the ITT analysis set.

- Patients who are in the PP analysis population.

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- Patients who are in the safety analysis population.
- Patients who are on study treatment.
- Patients who discontinued from study treatment.
- Primary reason for discontinuing study treatment.
- Patients who are on study.
- Follow-up status.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized using frequency distributions (ie, number and percentage of patients) for categorical data and summary descriptive statistics (ie, n, mean, SD, median, minimum, and maximum) for continuous data, based on the ITT analysis set for each treatment cohort and for all patients combined.

Demographic data will also be presented in a by-patient listing. Baseline demographic data to be evaluated will include age at informed consent, age category (ie, 18≤age<45 years, 45≤age<60 years, and age≥60 years), sex, race, ethnicity, height, weight, body surface area (BSA), and other parameters as appropriate. No inferential statistics will be generated.

Throughout this study, baseline assessments are defined as those performed at the closest time before the start of study drug administration.

Baseline characteristics include Eastern Cooperative Oncology Group (ECOG) score, time from initial diagnosis of PH+ ALL to first dose date prior anti-cancer regimen, Framingham Score, BCR-ABL transcript type, baseline white blood count, baseline homoglobin, baseline platelet, baseline blast count, extramedullary disease and other parameters as appropriate.

7.5 Medical and Surgical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized by MedDRA System Organ Class (SOC), and Preferred Term (PT) using number and percentage of patients based on the ITT analysis set for each treatment cohort. Patients with the same medical history more than once will have that medical history counted only once within each SOC, and once within each PT.

Surgical history will not be coded. Surgical history will be summarized using number and percentage of patients based on the ITT analysis set for each treatment cohort, as approximate.

Medical and surgical history will be presented in a by-patient listing.

Family medical history will also be presented in a by-patient listing.

7.6 Prior and Concomitant Medications and Concomitant Procedures

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior and concomitant medications will be summarized by WHO therapeutic

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class and standard drug names using number and percentage of patients based on the ITT analysis set for prior medications and the safety analysis set for concomitant medications for each treatment cohort.

Prior and concomitant medications will also be presented in a by-patient listing.

Prior radiation, and prior anticancer therapy will be summarized using number and percentage of patients based on the ITT analysis set for each treatment cohort, as appropriate.

Concomitant procedures will not be coded, but will be presented in a by-patient listing.

7.7 Study Drug Exposure and Compliance

Extent of Exposure:

Parameters pertaining to study drug exposure (ie, duration of exposure, number of days dosed, number of cycles dosed, dose intensity, relative dose intensity, total cumulative dose) will be summarized separately by treatment cohort and overall treatment period. Duration of treatment exposure is defined as the time interval from the first dose to the last dose of study treatment (last dose date – first dose date +1).

Dose intensity in mg/day is calculated as total cumulative dose in mg divided by duration of treatment exposure in day. Relative dose intensity is calculated as total cumulative dose in mg divided by expected total dose × 100%.

The drug exposure will be listed and summarized for the following drugs.

- Ponatinib
- Imatinib
- Vincristine
- Dexamethasone
- Methotrexate
- Cytarabine
- Prednisone
- Intrathecal therapy for CNS disease prophylaxis

Dose adjustment:

Dose adjustment and dose adjustment due to adverse event (AE) will be summarized by treatment cohort for each treatment phase and overall treatment period.

A by-patient listing including extent of exposure and dose adjustment will be presented.

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7.8 Efficacy Analysis

The standard *closed* sequential testing procedure will be used for testing the selected efficacy endpoitns with the following testing order.

1. MRD-negative CR rate: it will be tested at the IA or FA at the significance level determined by the O'Brien-Fleming alpha spending function (the Lan-DeMets method [1]) using the group sequential testing approach. At the IA (alpha = 0.022 with an efficacy boundary of 0.022) given 116 patients have been observed, and FA (alpha = 0.028 with an efficacy boundary of 0.036) for MRD-negative CR if number of patients is 230 [7].
2. EFS: EFS will be tested at the IA or FA at the significance level determined by the Gamma Family (-1) alpha spending function using group sequential testing approach [4]. At the IA (alpha = 0.033 with an efficacy boundary of 0.033) and FA (alpha = 0.017 with an efficacy boundary of 0.034) for EFS if observed number of events at IA and FA are 130 and 173, respectively. If the efficacy boundary is crossed at either IA or FA for EFS, the following endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA) [8]:
   a) Duration of CR.
   b) ORR.
   c) Duration of MRD-negative CR.
   d) OS.

Therefore, the overall type I error rate for these selected efficacy endpoints is strongly controlled at a 2-sided 0.05 alpha level.

The boundaries for hypotheses testing will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

All other efficacy endpoints, if tested, will be at a 2-sided alpha level of 0.05.

For MRD-negative CR, the analysis will be based on ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210. Other efficacy analyses will be conducted in the ITT population, unless otherwise specified.

MRD negativity will be based on the central laboratory results, and CR status will be based on the investigator's assessment verified by the Sponsor that the data reported for bone marrow blast, platelets and neutrophil counts are consistent with the protocol definition for CR in Table 5.a.

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7.8.1 Primary Efficacy Endpoint(s)

The primary endpoint is defined as achievement of MRD-negative CR (BCR-ABL/ABL1 ≤0.01% and meeting criteria for CR) at the end of induction (see Table 5.a for endpoint definitions). The analysis of the primary efficacy endpoint will test for differences comparing the proportion of patients who achieve the primary endpoint at the end of induction in the ponatinib arm versus the imatinib arm. The patients who early terminate the study treatment prior to the end of induction will be considered as non-responders.

If a C4D1 visit or assessment is not done or not available (e.g. patient discontinues after C3D28 or has a C4D1 dry tap bone marrow at C4D1), then the next available assessment that is completed within 45 days of C3D1 or within 15 days of C4D1 (i.e. "EOT" or "Unscheduled" visit) will be used.

If a MRD assessment is not available for C4D1 (including above), and if the patient had at least one earlier sample assessed as MRD negative (e.g. C2D1 or C3D1), at least one later sample assessed as MRD negative up to and including C6D1 visit (+7 day window), and there are no intervening MRD positive results, then that patient will be considered to be MRD negative at C4D1. For all MRD analyses conducted in the study, only MRD assessments performed at central laboratories will be used and only from patients where a dominant p190 or p210 transcript was identified by central laboratories using baseline (Screening/C1D1) samples.

There will be one IA and possibly an FA in the study for the primary endpoint of MRD-negative CR in ITT population who have been identified with BCR-ABL1 dominant variants of p190 or p210.

If the MRD-negative CR does not achieve the significance boundary at the IA, the study will continue and the FA will be triggered after the end of induction phase data have been collected for approximately 230 patients.

The primary analysis for MRD-negative CR will be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square p-value on risk difference between treatment arms will be calculated. The risk difference and relative risk will be presented along with 95% 2-sided confidence intervals.

Sensitivity analyses for the primary endpoint will include:

1. MRD-negative CR will be analyzed in the PP analysis set if more than 5% of patients are excluded from this analysis.
2. After the FA for MRD-negative CR is conducted, an additional sensitivity analysis for the primary endpoint will be retrospectively performed for the first 150 patients who have been enrolled and treated at the end of induction phase.

Other sensitivity analyses will be considered as appropriate.

Subgroup analyses will be performed for the primary endpoint relative to the baseline randomization stratification factor (age); additional age category (18 through <60 years; ≥60 years), demographic data, such as gender (male, female), race (white; non-white), region (north

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America; south America; Europe; APAC); and baseline disease characteristics including BCR-ABL1 Transcript Type (P190; P210) and ECOG status (0; 1 or 2), as appropriate.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Key Secondary Efficacy Endpoint

The key secondary endpoint is EFS, defined as the dates of randomization until:

- Death due to any cause.
- Failure to achieve CR by the end of induction.
- Relapse from CR.

EFS will be tested only if the primary endpoint comparison achieves statistical significance at the IA or FA for MRD-negative CR. EFS endpoint will be tested at the 5% level at IA or FA for EFS, per the closed sequential testing procedure, to maintain the family-wise type I error rate at 5% level.

One IA and one FA will be planned for EFS. When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The FA will be performed when approximately 173 EFS events have been observed. A 2-sided, stratified log-rank test will be used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05 for ITT population. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio and its 95% CIs for the treatment effect using the stratification factor. The K-M survival curves and K-M median PFS (if estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group. The test significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary of 0.033 at IA. The final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

The primary analysis for EFS will be based on time-to-event analysis. Since it is expected that a subset of patients who achieve MRD-negative CR after the induction phase will proceed to HSCT, the number of events needed for EFS analysis may change depending on how HSCT cases are handled in the EFS. The primary analysis of EFS will not consider censoring at the time of HSCT or initiation of alternative therapy. Other details regarding the handling of missing assessments and censoring for EFS analysis are presented in Table 7.a.

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Table 7.a Censoring Rules for EFS Primary Analysis Based on FDA Recommendations

Situation	Date of Progression or Censoring	Outcome
Death due to any cause	Date of death	Event
Failure to achieve CR by the end of induction	Day 1	Event
Relapse from CR	Date of documented relapse from CR	Event
No post-randomization CR assessments	Day 1	Event
No documented death or relapse	Date of last adequate assessment*	Censored
Not reached the end of induction	Date of last adequate assessment*	Censored
Lost to follow-up, withdraw consent before any documented death or relapse	Date of last adequate assessment*	Censored

* Adequate disease assessment is defined as there is sufficient data to evaluate a patient's disease status.

Sensitivity analyses for EFS will include:

1. EFS will be analyzed in the PP analysis set if more than 5% of patients will be excluded in this analysis.
2. Considering that EFS may be influenced by subsequent therapies administered after failure to achieve or maintain remission, an additional sensitivity analysis that treats an alternative therapy as an event where the start date for the alternative therapy is the event date, will be conducted to obtain a more precise assessment of efficacy for EFS.
3. If there exists time depended confounding factors caused by informative censoring from imbalance in the proportion of HSCT events between the 2 cohorts, Marginal Structural Model (MSM) [5] and Inverse Probability of Censoring Weighted (IPCW) [6] analysis of the EFS endpoint will be considered.
4. If the propotional hazard assumption is violated, non-propotional hazard Cox models will be applied to evaluate HR using piecewise expotential model.

In the MSM and IPCW analyses, in order to derive weights adjusting for the time-fixed and time-varying confounding effects due to taking HSCT, the covariates affecting EFS endpoint will be used. Potential time-fixed covariates and time-varying covariates include demographic data, such as age (18 through <45 years; 45 -<60 years; ≥60 years), gender (male, female), race (white; non-white), region (north America; south America; Europe; APAC); and baseline disease characteristics including BCR-ABL1 dominant transcript (P190; P210) and ECOG status (0; 1 or 2); baseline laboratory parameters such as white blood count, homoglobin, platelet, LDH, peripheral blood blast, bone marrow blast; and time-dependent covariates including SCT status, duration of exposure, relapse status at each study visit, initiation of alternative therapy, and other perimeters as appropriate. The final criteria for selected covariates would need to be statistically have a p-value of less than or equal to 0.15 in the multivariate logistic regression models for weight calculations. If there are more than 5% missing in the baseline covariate, then this covariate will be dropped from the weighting calculation and final model. For both MSM and IPCW analyses, logistic regression models on repeated measurements will be used to

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approximate the Cox models in the weight derivations from which stabilized weights will be derived per subject per observation. Adjusted K-M curves will also be presented along with hazard ratios (HRs), 95% confidence intervals for HRs, and adjusted p-values based on MSM and IPCW approaches. SAS proc PHREG procedure with counting process type of data input, which takes multiple observations per subject, will be used as the final Cox model for both MSM and IPCW approaches, where robust variance will be used to accommodate covariance introduced by correlated longitudinal observations within each subjects and other extra variabilities due to departure from model assumptions.

Subgroup analyses will be performed for EFS similar to the primary endpoint.

7.8.2.2 Other Secondary Efficacy Endpoints

The following other secondary endpoints will be analyzed (see Table 5.a for endpoint definitions):

- CR and CRi rates at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Molecular response rates (MR3, MRD negativity [MR4], and MR4.5) at the end of Cycle 1, the end of Cycle 2, the end of induction, and during or at the end of consolidation (end of Cycle 9 or end of study treatment, whichever occurs earlier).
- Rates of PIF and ORR at the end of induction.
- Rates of MRD-negative CR at multiple intervals after the end of induction.
- Duration of MRD-negative CR.Duration of CR.
- Time to treatment failure.
- Duration of MR4.5 in patients who achieved MR4.5.
- OS and rate of relapse from CR for on-study patients with and without HSCT.
- OS.

If the efficacy boundary is crossed at either IA or FA for EFS, the following secondary endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA):

a) Duration of CR.

b) ORR.

c) Duration of MRD-negative CR.

d) OS.

The remaining secondary efficacy endpoints will be tested at $\alpha = 0.05$ level in a nonhierarchical fashion without adjustments for multiplicity.

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For analysis of time-to-event endpoints (eg, time to treatment failure, OS), 2-sided, stratified log-rank tests will be used to compare the treatment groups with respect to the endpoints. In addition, an unadjusted stratified Cox model will be used to estimate the hazard ratio (HR) and its 95% CIs for the treatment effect using the stratification factors. K-M survival curves and K-M medians (if appropriate and estimable), along with their 2-sided 95% CIs, will also be provided for each treatment group.

For the secondary endpoint of OS, a futility analysis with be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

OS results are expected to be confounded by alternative therapies after patients discontinue from the study assigned drug. Thus, sensitivity analyses, such as Marginal Structural Models (MSM) and Inverse Probability Censoring Weighting (IPCW), will be conducted for OS analysis adjusting for time depending on confounding factors occurring due to taking alternative therapies. With IPCW and MSM analyses, to reduce bias, the following settings will be similar with the EFS analysis including: 1) the list of potential confounders, both baseline and time-dependent, which may impact both OS and censoring outcome, and thus will be included in the initial weighting models; 2) the p-value cut off for confounders remain in the final weighting models will be at 0.15 level; and 3) SAS procedure.

Duration of MRD-negative CR is defined as the time from the date of first documentation of MRD-negativity or CR (whichever comes latest), to the date of first documentation of loss of MRD-negativity (BCR-ABL/ABL1 >0.01%) or relapse from CR, for patients who achieve MRD-negative CR. The primary analysis for duration of MRD-negative CR will be based on time-to-event analysis.

The primary analysis for duration MRD-negative CR will not consider censoring at the time of HSCT or initiation of alternative therapies.

Duration of CR is defined as the time from the date of first documentation of a CR to the date of first documentation of PD for patients who achieved CR. These patients without documentation of PD will be censored at the date of their last response assessment. The primary analysis for duration of CR will be based on time-to-event analysis.

Duration of MR4.5 is defined as the time from the date of first documentation of a MR4.5 to the date of first documentation of loss of MR4.5 for patients who achieved MR4.5. The analysis for duration of MR4.5 will be based on time-to-event analysis. Duration of MRD-negativity will be defined and explored in a similar manner, as appropriate.

The proportion-based other secondary endpoints (eg, CR and CRi rates, proportion of patients received HSCT) will be analyzed in the same fashion as the primary endpoint. The analyses will be conducted using a Cochran-Mantel-Haenszel (CMH) chi-square test. The CMH chi-square p-value on risk difference between treatment arms may be calculated. The risk difference and relative risk will be presented along with 95% 2-sided confidence intervals.

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7.8.3 Additional Efficacy Endpoint(s)

The exploratory endpoints are:

- Time to HSCT.
- Time to start of alternative chemotherapy.
- Change from baseline in patient-reported HRQOL (FACT-Leu and EQ-5D-5L).
- MRU assessments.
- Biomarkers of disease sensitivity and resistance to ponatinib and imatinib.

Further details on the exploratory endpoint analyses will be discussed in the following.

7.8.3.1 Time-to-Next-Treatment and Time-to-HSCT Analyses

Time to subsequent antineoplastic therapy will be defined as the time from randomization to the date of first documentation of subsequent antineoplastic therapy or the last contact date for subjects who never received subsequent antineoplastic therapy.

Likewise, time to HSCT will be defined as the time from randomization to the date of first documentation of HSCT or the last contact date for subjects who did not receive an HSCT.

A Cox regression model with treatment as explanatory variable will be used for the time-to-event analyses. Median will be calculated by K-M method.

7.8.3.2 Patient-Reported Outcomes Analysis

Quality of life and health outcomes measures are being collected using the EQ-5D-5L and FACT-Leu instruments. Means and medians of scores of these questionnaires will be summarized for each cohort by time point, overall, and for each domain. Assessments based on the FACT-Leu will be analyzed to determine if treatments affect all domains.

Analyses of HRQOL scores, including global health status, will be performed using longitudinal models for scores and change from baseline scores. All subscales and individual item scores will be tabulated. Descriptive summaries of observed data will be provided at each scheduled assessment time point.

The manuals published for FACT-Leu will be used for scoring and handling missing data.

EQ-5D-5L scores will be summarized in descriptive statistics for treatment groups. Both utility scores and change from baseline scores will be assessed across time using longitudinal models.

Compliance for EQ-5D-5L and FACT-Leu will also be summarized by number of expected and number and percentage of received by treatment group over time.

PROs by proportion of patients that achieved or did not achieve MRD-negative CR at end of induction will be summarized by treatment group as appropriate.

Patient-reported outcome analysis will use safety population.

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7.8.3.3 Health Economics Analysis Using Medical Resource Utilization

Medical resource utilization data will be summarized in descriptive statistics for safety population hospitalization (length of stay, inpatient, outpatient, and reason), number of missing days from work or other activities, by patient and caregiver, and by treatment group.

7.8.3.4 Biomarkers of Disease Sensitivity and Resistance to Ponatinib and Imatinib

The mutation status of BCR-ABL1 and other genes implicated in tumor biology and/or drug metabolism will be determined, as clinically needed, through analyses of tumor cells collected at study entry, on study, and/or at EOT. Analysis methodologies include, but are not limited to, DNA sequencing, digital PCR, and mass spectrometry.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

The PK data collected in this study are intended to contribute to future population PK analyses of ponatinib. These population PK analyses may additionally include data collected in other ponatinib clinical studies. The analysis plan for the population PK analysis will be defined separately and the results of these analyses will be reported separately.

Ponatinib plasma concentration-time data will be listed and summarized by time point.

7.9.2 Pharmacodynamic Analysis

Not Applicable.

7.10 Other Analysis

In general, missing or partial dates due to unexpected situations, such as COVID-19 or Ukraine Crisis, will follow the convention without special handling. COVID-19 or Ukraine Crisis impact on the study visit and dosing/laboratory schedule will be tabulated and listed. In addition, if missing data distribution is not balanced between the two arms, sensitivity analysis by excluding patients with missing data due to Covid/Crisis will be carried out.

In addition, the patients who received ponatinib alone post 20 cycles may be analyzed for efficacy and safety endpoints.

7.11 Safety Analysis

The safety analysis will be carried out at interim and final analyses. In addition, an extended safety analysis for the study will be carried out at study completion.

Safety analyses will be based on the safety analysis set. Descriptive statistics (ie, n, mean, SD, median, minimum and maximum for continuous variables, and frequency and percentage of patients for categorical variables) will be used to summarize the safety parameters.

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Safety evaluations will be based on incidence, severity, and type of AEs; clinically significant changes or abnormalities in the patient's physical or neurological examinations; vital signs; ECG; ECOG performance status; clinical laboratory test results and other safety parameters.

7.11.1 Adverse Event

7.11.1.1 Adverse Events

AEs will be coded using MedDRA. All AEs will be presented in a by-patient listing. Treatment-emergent adverse events (TEAEs) are defined as any AEs that occur on or after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.

AEs will be tabulated according to MedDRA by SOC and PT and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs (related and regardless of relationship)
- TEAEs leading to study drug modification and discontinuation.
- TEAEs leading to hospitalization or prolonging hospitalization.
- TEAEs leading to death.
- Adverse events of special interest (AESIs) including Arterial Occlusive Events (AOEs) and Venous Thromboembolic Events (VTEs); and Other AEs of Significance, as appropriate.

Patients with the same AE more than once will have that event counted only once within each SOC and once within each PT.

TEAEs will also be summarized by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. Patients with the same AE more than once will have the maximum intensity of that event counted within each SOC and once within each PT.

The most commonly reported TEAEs (ie, those events reported by ≥10% of any treatment cohort) will be tabulated by PT. Patients with the same AE more than once will have that event counted only once within each PT.

An overall summary treatment-emergent AE table will include numbers and percentages of patients who had any treatment-emergent AE, drug-related treatment-emergent AE, grade 3 or higher treatment-emergent AE, grade 3 or higher drug-related treatment-emergent AE, serious AE (SAE), drug-related SAE, treatment-emergent AE resulting in discontinuation, and on-study

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deaths. On-study death is defined as the death that occurs between the first dose of any study drug and within 30 days of the last dose of any study drug.

In addition, TEAEs will be summarized by each treatment cohort. Secondary malignancy will be tabulated and listed as appropriate.

By-patient listing of grade 3 or higher treatment-emergent AE will also be provided, where the cycle day information for the AE onset and end dates will be included in the listing.

Analysis of AOEs and VTEs

Arterial occlusive and venous thromboembolic events with an initial onset date on or after the first dose date will be considered treatment-emergent and summarized. Number and percentages of patients who developed AOEs and VTEs will be summarized for each cohort. These events will be categorized as follows:

- Arterial occlusive events
  - Cardiovascular occlusive events.
  - Cerebrovascular occlusive events.
  - Peripheral vascular occlusive events.
- Venous thrombotic events.

Exposure-adjusted incidence rates (EAIR) of adjudicated AOEs and VTEs will be calculated for each cohort and for all patients. The 95% CI of the EAIR will be computed.

The following additional descriptive analyses will be performed to characterize AOEs and VTEs described above:

- Time to onset: Calculated as date of first event AE- first dose date + 1.
- Dose at onset: Dose of ponatinib/imatinib taken immediately prior to onset of first event.

Analysis of Other AEs of Significance

Categories of AEs will be prospectively defined using Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or Modified MedDRA Queries based on SMQs and MedDRA System Organ Classes (SOCs). The AE crude rates, as well as the frequency of occurrence by overall toxicity—categorized by toxicity grades (severity)—will be described for each cohort. Events will also be characterized by time to onset, dose at onset, and duration, as described above. Categories of AEs will include but will not be limited to:

- Cardiac failure
- Arrhythmias including QT prolongation
- Pancreatitis and Amylase or Lipase elevations
- Hepatotoxicity
- Myelosuppression

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- Hemorrhage
- Fluid retention
- Hypertension

7.11.1.2 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA primary system organ class, and preferred term. Drug-related SAEs will be summarized similarly.

In addition, a by-patient listing of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status).

7.11.1.3 Deaths

All deaths will be summarized by treatment arm, including deaths occurring on-study and death during follow-up separately.

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment emergent AE status).

7.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

A by-patient listing of treatment-emergent AEs resulting in discontinuation of study drug regimen will be presented.

7.11.2 Clinical Laboratory Evaluations

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summary statistics, ignoring the non-numeric qualifier. If a patient has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Laboratory test results will be summarized according to the scheduled sample collection time point. Change from baseline will also be presented. Unscheduled laboratory test results will be listed and included in laboratory shift tables. The parameters to be analyzed are as follows:

- Hematology: hemoglobin, absolute neutrophil count (ANC), platelets counts, WBC, lymphocytes and leukocytes
- Serum chemistry: blood urea nitrogen (BUN), creatinine, total bilirubin, urate, lactate dehydrogenase (LDH), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, corrected calcium, sodium, potassium, chloride, lipase and amylase

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Shift tables will be constructed for laboratory parameters to tabulate changes from study entry to post study entry either by CTCAE toxicity grade or abnormality. Parameters to be tabulated will include, but not limited to:

- Hematology: ANC, hemoglobin, and platelets.
- Serum chemistry: ALT, AST, ALP, creatinine, total bilirubin, amylase and lipase.

Mean laboratory values and box plots over time for key lab parameters will be produced, including but not limited to ANC, platelets, and liver function tests (ALT/SGPT, AST/SGPT, alkaline phosphatase, and total bilirubin), lipase and amylase.

By-patient listings to be presented include hematology, serum chemistry, urinalysis, urine total protein, and urine creatinine.

7.11.3 Vital Signs

The actual values of vital sign parameters (ie, systolic and diastolic BP, heart rate, respiratory rate, temperature, height, and weight) will be summarized at all planned timepoints by each treatment cohort using descriptive statistics (ie, n, mean, SD, median, minimum and maximum). Change of vital signs from baseline values will also be summarized at all planned timepoints. Vital sign values will also be presented in a by-patient listing.

7.11.4 12-Lead ECG

The absolute values and absolute change from baseline of electrocardiogram (ECG) parameters including ECG ventricular rate, PR interval, RR interval, QRS duration, QT interval, and QT interval corrected per Fridericia method (QTcF) interval will be summarized at each timepoint using descriptive statistics (ie, n, mean, SD, median, minimum and maximum).

QTc interval will be calculated using Fridericia correction, if necessary. The formulas are:

$$QTcF\ (Fridericia) = QT / (RR^{0.33})$$

where RR = 60 / heart rate (bpm)

In addition, a categorical analysis of QTcF intervals will be performed for each time point. The number and percentage of patients in each QTcF interval (<450 msec, 450-480 msec, >480-<500 msec, and ≥500msec) will be summarized at each time point. Categories of changes from baseline (≥30 msec and ≥60 msec) will be summarized as well. Maximum QTcF intervals and maximum changes from baseline will also be summarized similarly in a separate display.

ECG abnormalities will be presented in a data listing.

7.11.5 ECOG Performance Status

ECOG performance status and shifts from baseline to post study entry assessment over time, and ECOG score frequency table over time will be summarized. Shifts from baseline to the worst post study entry score will be tabulated by each treatment cohort.

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7.11.6 Other Observations Related to Safety

The ankle-brachial index (ABI), echocardiogram (ECHO) for assessment of left ventricular ejection fraction (LVEF) and Multiple-Gated Acquisition (MUGA) scan will be presented in a data listing.

7.12 Interim Analysis

MRD-negative CR

There would be one IA and possibly an FA in the study for the MRD-negative CR primary endpoint using a group sequential testing approach.

The IA has been performed after the end of induction phase data had been collected for 116 patients. The primary endpoint of MRD-negative CR was first tested at IA with a 2-sided efficacy boundary of 0.022and will be tested at FA with a 2-sided efficacy boundary of 0.036 after the end of induction phase data have been collected for 230 patients.

If the significance boundary is crossed at the FA for MRD-negative CR, then there will be a testing for EFS and other secondary endpoints at a 2-sided alpha level of 0.05 using group sequential testing approach.

The boundaries for hypotheses testing in MRD-negative CR will be updated according to the observed data in the FA, using the prespecified alpha spending function.

EFS

There will be one IA and possibly an FA in the study for the key secondary endpoint EFS using a group sequential testing approach.

When approximately 130 EFS events are observed (75% of the total 173 expected EFS events), an IA will be performed. The IA is expected to occur approximately 5.5 years after the first patient is enrolled. The FA is expected to be performed approximately 8.5 years after the first patient enrolled, when all approximately 173 EFS events have been observed.

The test significance for the IA and FA of EFS will be determined using Gamma Family (-1) boundaries. Based on the projected number of EFS events, the formal hypothesis testing will be stopped for overwhelming efficacy if the 2-sided p-value crosses the efficacy boundary (p=0.033) at IA and this will be the FA for EFS for statistical testing purpose. If EFS does not achieve statistical significance at the IA, the final analysis will be tested at 2-sided alpha level of efficacy boundary 0.034 (corresponding to nominal alpha of 0.017).

If the efficacy boundary is crossed at either IA or FA for EFS, the following secondary endpoints will be tested in the order listed below using the same boundaries (0.033 for IA and 0.034 for FA):

a) Duration of CR.

b) ORR.

c) Duration of MRD-negative CR.

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d) OS.

The boundaries for hypotheses testing in EFS will be updated according to the observed data in the IA and FA, using the prespecified alpha spending function.

Overall Survival

For the secondary endpoint of OS, a futility analysis will be conducted at the time of the IA for EFS. The hazard ratio and corresponding 95% CI for the OS analysis will be calculated and reviewed by the IDMC. If the HR is >1.2, the IDMC will review the totality of the data and provide a recommendation to the sponsor's executive committee regarding study continuation.

The analyses for the IA and FA for MRD-negative CR and the IA for EFS will be carried out by an independent statistical team in a manner that maintains the blinding of the study results to the team (see Section 13.4). The IDMC will review both efficacy and safety data at the time of the IA, and will inform the sponsor's executive committee of their recommendation.

7.13 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol Ponatinib-3001 amendment 10 (Protocol amendment dated 20 October 2021). Additional major changes include:

- Furthe clarify the following order of secondary endpoints that will be tested at the time of IA for EFS: a) Duration of CR; b) ORR; c) Duration of MRD-negative CR; d) OS.

8.0 REFERENCES

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PPD	Biostatistics Approval	21-Sep-2022 14:05 UTC

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Ponatinib-3001 SAP Change Summary Version 3.0 vs. Version 1.0

Rationale for Version 3.0

This document describes the changes in reference to the statistical analysis plan (SAP) incorporating Version 3.0 based on the protocol amendment 10. The primary reason for this version is to revise the efficacy analysis of the primary end point (MRD-negative CR) to reflect a change in the sample size for the final analysis (FA) from 150 patients to 230 patients. According to this new sample size, the 2-sided efficacy boundary is updated for MRD-negative CR FA. In addition, the censoring rules of EFS per investigator assessment will be updated and statistical testing for selected secondary endpoints will be added at the time of EFS IA and FA depending upon FDA recommendation.

Minor grammatical, editorial, formatting, and administrative changes are included for clarification purposes only.

Changes in Version 3.0

1. Revised the sample size for the final analysis of MRD-negative CR from 150 patients to 230 patients
2. Updated the censoring rules of EFS per investigator assessment based on FDA recommendation
3. Added formal statistical testing for the following secondary endpoints by order
    a) Duration of CR.
    b) ORR.
    c) Duration of MRD-negative CR.
    d) OS.